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(71) Applicant: **MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH** [US/US]; 200 First Street S.W., Rochester, Minnesota 55905 (US).

(72) Inventors: **PITTOCK, Sean J.**; 1948 Westwood Court SW, Rochester, Minnesota 55902 (US). **KRYZER, Thomas J.**; 61075 260th Avenue, Mantorville, Minnesota 55955 (US). **GADOTH, Avi**; 3088 Avalon Cove Court NW, Rochester, Minnesota 55901-8497 (US). **MCKEON, Andrew**; 2901 Oakview Drive NE, Rochester, Minnesota 55906-7646 (US). **LENNON, Vanda A.**; 202 14th Street NE, Rochester, Minnesota 55906 (US). **FRYER, James P.**; 605 4th Avenue SE, Stewartville, Minnesota 55976 (US).

(74) Agent: **FINN III, J. Patrick**; Fish & Richardson P.C., PO Box 1022, Minneapolis, Minnesota 55440-1022 (US).

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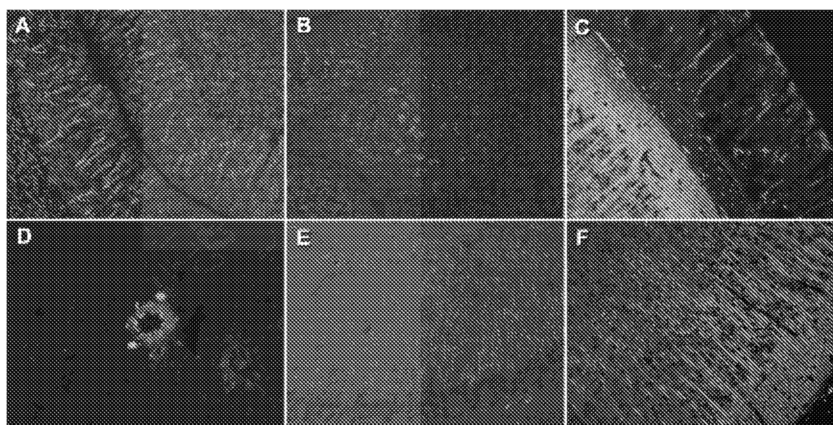
FIG. 1



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(57) **Abstract:** This document provides methods and materials for detecting PCA-2-specific autoantibodies, which can be associated with paraneoplastic neurological disorders and cancers associated with PCA-2-specific autoantibodies.

[Continued on next page]

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MATERIALS AND METHODS FOR EVALUATING AND TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application Serial No. 62/400,420, filed on September 27, 2016. The disclosure of the prior application is considered part of the
5 disclosure of this application, and is incorporated in its entirety into this application.

BACKGROUND

1. Technical Field

This document relates to methods and materials for evaluating and treating paraneoplastic neurological disorders and cancers associated with Purkinje cell antibody-
10 type 2 (PCA-2)-specific autoantibodies. For example, this document relates to methods and materials for using microtubule associated protein 1B (MAP1B) polypeptides and fragments thereof to detect the presence or absence of PCA-2-specific autoantibodies.

2. Background Information

Neural-restricted autoantibodies are emerging as serum biomarkers of acquired
15 neurological disorders, both idiopathic and paraneoplastic. PCA-2 was described in 2000 as an IgG biomarker of paraneoplastic neurologic autoimmunity initiated by small-cell lung carcinoma (SCLC), with an ~280-kDa onconeural cytoplasmic antigen expressed in central and peripheral neural tissues and SCLC cells (Vernino *et al.*, *Ann. Neurol.*, 47:297-305 (2000)). The autoantibody was named PCA-2 to distinguish it from a biomarker of
20 ovarian and breast cancer-related cerebellar degeneration, PCA-1 (AKA anti-Yo; Greenlee *et al.*, *Ann. Neurol.*, 14:609-13 (1983)).

SUMMARY

This document provides methods and materials for detecting paraneoplastic neurological disorders and/or cancers associated with PCA-2-specific autoantibodies as
25 well as methods and materials for treating paraneoplastic neurological disorders and/or cancers associated with PCA-2-specific autoantibodies (e.g., neuroendocrine tumors).

As described herein, MAP1B is the antigenic target of a paraneoplastic neurological disorders and/or cancers associated with PCA-2-specific autoantibodies, which serve as a strong positive predictor of small-cell lung carcinoma and a biomarker for paraneoplastic neurological disorders with a diversity of neurological manifestations. The detection of PCA-2-specific autoantibodies (also referred to as MAP1B-specific autoantibodies herein) can be used to support the diagnosis of a paraneoplastic neurological disorders and cancers associated with PCA-2-specific autoantibodies. MAP1B is highly expressed in both developing neurons and in neuroendocrine tumors (e.g., SCLC), and can be targeted for the treatment of paraneoplastic neurologic disorders.

In general, one aspect of this document features a method of detecting the presence or absence of a PCA-2-specific autoantibody in a biological sample from an individual. The method includes, or consists essentially of, contacting a biological sample from an individual with a MAP1B polypeptide or fragment thereof to form a MAP1B-PCA-2-specific autoantibody complex if the biological sample contains said PCA-2-specific autoantibody, and detecting the presence or absence of the complex. The presence of the PCA-2-specific autoantibody in the biological sample can be associated with a paraneoplastic neurological disorder or a cancer associated with PCA-2-specific autoantibodies in the individual. The paraneoplastic neurological disorder can be encephalitis/encephalopathy, seizures, sleep disorders, cerebellar dysfunction/cerebellar degeneration/cerebellar ataxia, optic neuropathy, retinopathy, movement disorders/non voluntary movements, eye movement abnormalities, peripheral neuropathy, autonomic dysfunction, neuromuscular junction syndromes, Lambert-Eaton myasthenic syndrome (LEMS), Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), paraneoplastic cerebellar degeneration, encephalomyelitis, limbic encephalitis, brainstem encephalitis, opsoclonus myoclonus ataxia syndrome, or polymyositis. In some embodiments, the paraneoplastic neurological disorder can be LEMS. The cancer can be small-cell lung cancer (SCLC), renal carcinoma, squamous cell skin carcinoma, extrapulmonary small-cell carcinoma (EPSCC), prostate adenocarcinoma, primary intrahepatic cholangiocarcinoma, Ewing sarcoma, nasopharyngeal carcinoma, lymphoma, large cell neuroendocrine carcinoma of the lung (LCNEC), gastroenteropancreatic neuroendocrine tumors (GEP-NET), pituitary tumors, thyroid tumors, or medullary carcinoma. In some embodiments, the cancer can be SCLC. The method also can include

performing a Western blot to detect the complex. The method also can include detecting the presence of the complex or detecting the absence of the complex. The biological sample can be serum, plasma, cerebrospinal fluid, or blood.

In another aspect, this document features a kit including a MAP1B polypeptide or fragment thereof and instructions for using the MAP1B polypeptide to detect a PCA-2-specific autoantibody in an individual. The kit can be used to diagnose the presence or absence of a paraneoplastic neurological disorder or a cancer associated with PCA-2-specific autoantibodies in an individual. The kit also can include a monoclonal antibody having specific binding affinity for a MAP1B polypeptide or fragment thereof. The kit also can include a PCA-2-specific autoantibody.

In another aspect, this document features a method of treating an individual having a paraneoplastic neurological disorder associated with PCA-2-specific autoantibodies. The method includes, or consists essentially of, identifying an individual as having a paraneoplastic neurological disorder associate with PCA-2-specific autoantibodies, and administering an immunomodulatory agent to said individual. The step of identifying an individual as having a paraneoplastic neurological disorder associate with PCA-2-specific autoantibodies can include contacting a biological sample from the individual with a MAP1B polypeptide or fragment thereof to form a MAP1B-PCA-2-specific autoantibody complex if said biological sample contains the PCA-2-specific autoantibody, and detecting the presence of the complex. The immunomodulatory agent can include a corticosteroid. The immunomodulatory agent can include cyclophosphamide. The immunomodulatory agent can include tacrolimus.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and

advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF THE DRAWINGS

Figure 1 is indirect immunofluorescence showing binding of patient's MAP1B (PCA-2) specific-IgG from serum (at 1:240 dilution) to a composite of mouse nervous system and other organ tissues. Panel A shows Purkinje cell cytoplasm and dendrites are brightly stained. Synaptic staining of the molecular layer (ML) and the granular layer (GL) are also seen. Panel B shows intense immunoreactivity in the cytoplasm of the cerebellar dentate neurons. Panel C shows ganglia within the myenteric plexus and nerve fibers within the smooth muscle of the stomach stain brightly. Nerves within the gastric mucosa are also stained. Panel D shows intense immunoreactivity of autonomic (sympathetic) nerves adjacent to a renal blood vessel. Panel E shows diffuse "synaptic" staining and staining of pyramidal cell cytoplasm and their dendrites in CA-1 region of the hippocampus. Panel F shows pyramidal cell' dendrites are stained in the cortex. The diffuse "synaptic" staining is also notable.

Figures 2A – 2B show that PCA-2 IgG binds to a native neural protein. A) A common band (~280 kDa by reference to molecular weight standards) was revealed by IgG (PCA-2) in patients' sera (lanes 1 and 2), but not by IgG in control human serum (lanes 3 and 4). To verify specificity, patient IgG was affinity purified on the putative antigenic band and a control band. B) Eluates from the putative antigenic band and control band were reapplied to the composite mouse tissue substrate slide, and compared to the original immunostaining pattern of whole patient serum IgG on the composite mouse tissue slides. The eluate from the putative antigenic band revealed an identical pattern of staining as shown in Figure 1. Panel A shows Purkinje cells' and their dendrites are brightly stained on a background of diffuse "synaptic" staining of the molecular layer (ML) and the granular layer (GL) and Panel B shows Ganglia within the myenteric plexus and nerve fibers within the smooth muscle of the stomach stain brightly.

Figures 3A – 3B show that patient IgG colocalizes with MAP1B immunoreactivity in mouse brain. Colocalization with MAP1A is also observed in some but not all regions. A) Top row: commercially available MAP1B autoantibodies; middle row: patient IgG; and bottom row, merged images. Column A shows cerebellar Purkinje cells and dendrites,

Column B shows dendrites in higher magnification, Column C shows neuronal cells in dentate nucleus of cerebellum, Column D shows autonomic (sympathetic) nerves adjacent to renal arterial vessels, and Column E shows myenteric plexus with nerve fibers in the stomach smooth muscle. B) Top row: commercially available MAP1A autoantibodies; middle row: patient IgG; and bottom row, merged images. Panel A shows myenteric plexus where colocalization not observed; some staining is observed but not as intense and diffused. Panel B shows dentate neuronal cells are not stained. Panel C shows staining within gastric mucosa. Panels D and E shows colocalization observed in cerebellar Purkinje cells and dendrites, respectively.

Figures 4A – 4B show that MAP1B antibodies (A) and patients' IgG (B) bind to proteins of similar molecular weight in western blot. Western blot of mouse brain proteins reveals binding of commercially available MAP1B antibodies and patient IgG to bands with similar molecular weights and staining pattern. The commercially available antibodies to MAP1A, MAP2 and MAP2B bind to proteins of different molecular weights. Section A was taken at a lower exposure to reduce extent of signal and allow comparison with patient signal in section B. Normal controls show no band.

Figures 5A – 5B shows recombinant western blot screening of sera for binding to different Map1B and MAP1A fragments. A) A common band (~110 kDa by reference to molecular weight standards) was revealed by IgG in patients' sera (lanes 1, 2 and 3), but not by IgG in control human sera (lanes 4 and 5) when screening MAP1B fragment 1 recombinant protein on western blot. B) Recombinant MAP1B and MAP1A protein fragments probed by western blot with sera of 40 individual PCA-2-positive patients. IgG in all were reactive with MAP1B fragment 1 (polypeptide 1-666); 50% bound to fragment 2. Green= positive; yellow= moderately reactive; orange= equivocally reactive; red= negative. Western blot with a synthetic peptide comprising the overlap region of MAP1B fragment 1 and MAP1B fragment 2, revealed that residues 540-693 constituted a major B cell epitope (bound IgG in 27 of 40 patients' sera).

Figure 6 shows elimination of patient IgG by MAP1B fragment 1 antigen. The characteristic staining pattern of patient IgG (pre absorption, top row) is eliminated after incubation of patient sera with recombinant MAP1B (post absorption, bottom row). Panel A shows cerebellar Purkinje cells and dendrites. Panel B shows autonomic (sympathetic) nerves adjacent to renal arterial vessels. Panel C shows myenteric plexus with nerve fibers

in the stomach smooth muscle. Panel D shows neuronal cells in dentate nucleus of cerebellum from an ANNA-1 positive patient with no loss of staining after absorption with MAP1B fragment 1.

Figure 7 shows that SCLC tumors express MAP1B. Lanes 1 – 3 are small cell lung tumors screened with MAP1B commercial antibody. Lane 1, Mayo Clinic Small Cell Cancer Cell line (SCC) – 81, positive; lane 2, SCC-117 negative; Lane 3, National cancer institute – 146 (SCLC cell line) positive. Lane 4 is a mouse brain screened with MAP1B as positive control. Neurological diagnosis of the small cell carcinoma patients from whom the tumors were resected from: SCC 2, 4, 17, 18, 24 (not shown) – Lamber eaton myasthenic syndrome (LEMS), SCC-21, 59 (not shown) – no neurologic symptoms, SCC 81 – sensory motor peripheral neuropathy, Scc 117 – ataxia and sensory neuropathy, NCI-146 – information not available.

Figure 8 shows the amino acid sequence (SEQ ID NO:1) of a human microtubule-associated protein 1B (MAP1B). Underlined and highlighted residues represent overlap between fragments. Highlighted residues represent regions of homology of 8 or more amino acids between MAP1B and MAP1A.

Figure 9 shows the amino acid sequence (SEQ ID NO:2) of a human microtubule associated protein 1A (MAP1A). Underlined and highlighted residues represent overlap between fragments. Highlighted residues represent regions of homology of 8 or more amino acids between MAP1B and MAP1A.

Figure 10 is a table showing clinical information for 95 patients.

DETAILED DESCRIPTION

A specific IgG autoantibody marker (PCA-2) is found in serum of individuals presenting with paraneoplastic neurological disorders and/or cancers associated with PCA-2-specific autoantibodies (e.g., neuroendocrine tumors). The target of PCA-2 was identified herein as MAP1B, a microtubule-associated protein that is found throughout the central and peripheral nervous and is highly expressed in both developing neurons and in neuroendocrine tumors. PCA-2-specific autoantibodies may also be referred to as MAP1B-specific autoantibodies.

This document provides materials and methods for using MAP1B polypeptides or fragments thereof to detect PCA-2-specific autoantibodies in an individual that presents

with a paraneoplastic neurological disorder and/or cancer associated with PCA-2-specific autoantibodies. The presence of PCA-2-specific autoantibodies can be used to diagnose the individual as having a paraneoplastic neurological disorder and/or cancer associate with PCA-2-specific autoantibodies. Also provided herein are materials and methods for treating an individual that presents with a paraneoplastic neurological disorder and/or cancer associated with PCA-2-specific autoantibodies. Any appropriate individual can be diagnosed or treated as described herein. Examples of individuals that can be subjected to the methods described herein include, without limitation, humans, non-human primates, monkeys, bovine species, pigs, horses, dogs, and cats.

Any appropriate paraneoplastic neurological disorders and/or cancer associated with PCA-2-specific autoantibodies can be diagnosed and/or treated using the methods and materials described herein. Paraneoplastic neurological disorders relate to autoimmune or inflammatory conditions that damage nervous system at any level from central nervous system to peripheral nervous system. In some cases, a paraneoplastic neurological disorder associated with PCA-2-specific autoantibodies can be a neurological disorder associated with a neuroendocrine tumor. Paraneoplastic neurological disorders associated with neuroendocrine tumors include, without limitation, encephalitis/encephalopathy, seizures, sleep disorders, cerebellar dysfunction/cerebellar degeneration/cerebellar ataxia, optic neuropathy, retinopathy, movement disorders/non voluntary movements, eye movement abnormalities, peripheral neuropathy, autonomic dysfunction, neuromuscular junction syndromes, Lambert-Eaton myasthenic syndrome (LEMS), Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), paraneoplastic cerebellar degeneration, encephalomyelitis, limbic encephalitis, brainstem encephalitis, opsoclonus myoclonus ataxia syndrome, and polymyositis. For example, an individual having LEMS can be diagnosed and/or treated using the methods and materials described herein. In some cases, a cancer associated with PCA-2-specific autoantibodies can be a neuroendocrine tumor. Neuroendocrine tumors can arise in many different areas of the body (e.g., lungs, intestine, pancreas, gastrointestinal tract, thymus, and thyroid). Examples of neuroendocrine tumors include, without limitation, SCLC, renal carcinoma, squamous cell skin carcinoma, extrapulmonary small-cell carcinoma (EPSCC), prostate adenocarcinoma, primary intrahepatic cholangiocarcinoma, Ewing sarcoma, nasopharyngeal carcinoma, lymphoma, large cell neuroendocrine carcinoma of

the lung (LCNEC), gastroenteropancreatic neuroendocrine tumors (GEP-NET), pituitary tumors, thyroid tumors, and medullary carcinoma. For example, an individual having SCLC can be treated using the methods and materials described herein.

MAP1B Polypeptides and Anti- PCA-2 Antibodies

5 MAP1B polypeptides (and fragments thereof) can be used to detect PCA-2-specific autoantibodies. Examples of MAP1B polypeptide sequences (and the nucleic acids encoding such polypeptides) can be found in the National Center for Biotechnology Information (NCBI) GenBank. Examples of human of MAP1B polypeptide sequences include, without limitation, GenBank Accession Nos. AAA18904 (Version AAA18904.1;
10 GI:473431), CAM06633 (Version CAM06633.1; GI:122703742), CAM12311 (Version CAM12311.1; GI:122703744), and P46821 (Version P46821.2; GI:317373388). Additional MAP1B sequences can be found, for example, in public databases. A representative human MAP1B sequence is shown in Figure 8 (SEQ ID NO:1). In some cases, a fragment of MAP1B polypeptide can be used as described herein to detect PCA-2-
15 specific autoantibodies. Examples of MAP1B fragments that can be used to detect a PCA-2-specific autoantibody can include, without limitation, fragments of SEQ ID NO:1 (e.g., amino acids 1-666 of SEQ ID NO:1, amino acids 576-1990 of SEQ ID NO:1, amino acids 1111-1690 of SEQ ID NO:1, amino acids 1611-2120 of SEQ ID NO:1, or amino acids 2040-2168 of SEQ ID NO:1).

20 A MAP1B polypeptide or fragment thereof can be provided in any appropriate context. In some cases, a MAP1B polypeptide or fragment thereof can be in a solution (e.g., a cell lysate). In some cases, a MAP1B polypeptide or fragment thereof can be in a solid substrate (e.g., a tissue such as brain (e.g., cerebellum, midbrain, cerebral cortex, or hippocampus), kidney, gut, stomach, or other tissues containing peripheral nerve
25 elements).

In some cases, MAP1A polypeptides (and fragments thereof) can be used to detect PCA-2-specific autoantibodies. A representative human MAP1A sequence is shown in Figure 9 (SEQ ID NO:2). Examples of MAP1A fragments that can be used to detect a PCA-2-specific autoantibody can include, without limitation, fragments of SEQ ID NO:2
30 (e.g., amino acids 1-670 of SEQ ID NO:2, amino acids 606-1204 of SEQ ID NO:2, amino

acids 1181-1720 of SEQ ID NO:2, amino acids 1661-2200 of SEQ ID NO:2, or amino acids 2141-2803 of SEQ ID NO:2).

This document also provides nucleic acids and constructs encoding an MAP1B polypeptide (or fragment thereof) described herein. As used herein, nucleic acid (e.g., MAP1B nucleic acid) refers to RNA or DNA. As used herein with respect to nucleic acids, "isolated" refers to (i) a nucleic acid sequence encoding part or all of MAP1B polypeptide, but free of coding sequences that normally flank one or both sides of the nucleic acid sequences encoding MAP1B in the genome; or (ii) a nucleic acid incorporated into a vector or into the genomic DNA of an organism such that the resulting molecule is not identical to any naturally-occurring vector or genomic DNA.

A MAP1B polypeptide can have a sequence that deviates from a wild type MAP1B polypeptide sequence (e.g., SEQ ID NO:1), sometimes referred to as a variant sequence. For example, a MAP1B polypeptide sequence can have at least 80% sequence identity to SEQ ID NO:1. In some embodiments, an MAP1B polypeptide sequence can have at least 85% sequence identity, 90% sequence identity, 95% sequence identity, or at least 99% sequence identity to SEQ ID NO:1. Percent sequence identity is calculated by determining the number of matched positions in aligned nucleic acid or polypeptide sequences, dividing the number of matched positions by the total number of aligned nucleotides or amino acids, respectively, and multiplying by 100. A matched position refers to a position in which identical nucleotides or amino acids occur at the same position in aligned sequences. The total number of aligned nucleotides or amino acids refers to the minimum number of MAP1B nucleotides or amino acids that are necessary to align the second sequence, and does not include alignment (e.g., forced alignment) with non-MAP1B sequences, such as those fused to MAP1B. The total number of aligned nucleotides or amino acids may correspond to the entire MAP1B sequence or may correspond to fragments of the full-length MAP1B sequence as defined herein.

Sequences can be aligned using the algorithm described by Altschul *et al.* (*Nucleic Acids Res.*, 25:3389-3402 (1997)) as incorporated into BLAST (basic local alignment search tool) programs, available at ncbi.nlm.nih.gov on the World Wide Web. BLAST searches or alignments can be performed to determine percent sequence identity between a MAP1B nucleic acid molecule and any other sequence or portion thereof using the Altschul *et al.* algorithm. BLASTN is the program used to align and compare the identity

between nucleic acid sequences, while BLASTP is the program used to align and compare the identity between amino acid sequences. When utilizing BLAST programs to calculate the percent identity between a MAP1B sequence and another sequence, the default parameters of the respective programs are used.

5 MAP1B polypeptides may be obtained from human, mouse or other mammalian neuronal tissue, neuronal cell lines, or transfected cells (e.g., mammalian, *E. coli* or yeast) expressing a recombinant MAP1B nucleic acid, or the MAP1B polypeptide may be synthetic. Polypeptides can be purified. A "purified" polypeptide refers to a polypeptide that constitutes the major component in a mixture of components, e.g., 30% or more, 40%
10 or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more, 95% or more, or 99% or more by weight. Polypeptides may be purified by methods including affinity chromatography or immunosorbent affinity column.

Given a MAP1B polypeptide sequence (see, for example, SEQ ID NO:1), virtually any polypeptide fragment can be generated by, for example, proteolytic cleavage of a
15 polypeptide or chemical synthesis. Fragments of a MAP1B polypeptide can contain one or more epitopic sites (e.g., B cell epitopes). Epitopic sites within MAP1B polypeptides that are pertinent to T-cell activation and suppression (e.g., MHC-I and MHC-II binding epitopes) can be determined by direct investigation, or by using computer algorithms. See, for example, Parker *et al.* (*J. Immunol.*, 152:163 (1994)) and Southwood *et al.* (*J.*
20 *Immunol.*, 160:3363 (1998)).

This document also provides for an antibody, including a monoclonal antibody, with specific binding affinity for MAP1B polypeptides or antigenic fragments thereof. MAP1B polypeptides as described herein can be used to produce monoclonal or polyclonal anti-MAP1B antibodies having specific binding affinity for the MAP1B
25 polypeptide. Such antibodies can be produced using techniques such as hybridoma technology and display technology. As used herein, anti-MAP1B antibodies having "specific binding affinity" for MAP1B polypeptides or fragments thereof are defined as those antibodies that preferentially bind MAP1B polypeptides or fragments thereof, but that do not bind or have very little affinity for non-MAP1B polypeptides. While the
30 MAP1B-specific autoantibodies described herein are IgG antibodies, a recombinant "anti-MAP1B antibody" can be whole antibodies of any class (e.g., IgG, IgA, IgM), portions or fragments of whole antibodies (e.g., Fab or $(Fab)_2$ fragments) having the desired specific

binding affinity, an engineered single chain Fv molecule, or a chimeric molecule, e.g., an antibody that contains the binding specificity of one antibody (e.g., of murine origin) and the remaining portions of another antibody (e.g., of human origin).

This document also provides articles of manufacture (e.g., kits) containing one or more MAP1B polypeptides or fragments thereof. MAP1B polypeptides or fragments thereof that are included in an article of manufacture as described herein can be provided within a cell, in a solution in which they are soluble, or the MAP1B polypeptides or fragments thereof can be provided in a lyophilized form. The kit may further include a second substance that, for example, provides for a detectable signal. In addition, a kit can include directions for using the MAP1B polypeptides and/or directions for practicing a method described herein (i.e., detecting PCA-2-specific autoantibodies in a biological sample).

In some cases, a kit can be designed to include anti-MAP1B antibodies having binding affinity for MAP1B polypeptides or fragments thereof. The kit may also include MAP1B polypeptides or fragments thereof to be used as binding controls or to generate a standardized quantitative curve. The kit may further include a second substance that provides for detectable label. A kit typically includes directions for using an anti-MAP1B antibody (e.g., for detecting or purifying MAP1B polypeptides).

Methods of Detecting

This document also provides for methods of detecting PCA-2-specific autoantibodies. The presence of PCA-2-specific autoantibodies can be used to diagnose a paraneoplastic neurological disorder and/or a cancer associated with PCA-2-specific autoantibodies. In some cases, the detection of PCA-2 specific autoantibodies in patients with LEMS can predict the presence of SCLC. MAP1B polypeptides or fragments thereof can be used in various immunological techniques to detect a PCA-2-specific autoantibody. For example, MAP1B polypeptides can be used in an immunoassay to detect PCA-2-specific autoantibodies in a biological sample. MAP1B polypeptides used in an immunoassay can be in a cell lysate (e.g., a whole cell lysate or a cell fraction), or purified MAP1B polypeptides or fragments thereof can be used provided at least one antigenic site recognized by PCA-2-specific autoantibodies remains available for binding. Depending on the nature of the sample, either or both immunoassays and immunocytochemical

staining techniques may be used. Enzyme-linked immunosorbent assays (ELISA), Western blot, and radioimmunoassays can be used as described herein to detect the presence of PCA-2-specific autoantibodies in a biological sample.

MAP1B polypeptides or fragments thereof may be used with or without modification for the detection of PCA-2-specific autoantibodies. Polypeptides can be labeled by either covalently or non-covalently combining the polypeptide with a second substance that provides for detectable signal. A wide variety of labels and conjugation techniques can be used. Some examples of labels that can be used include radioisotopes, enzymes, substrates, cofactors, inhibitors, fluorescers, chemiluminescers, magnetic particles, and the like.

A “biological sample,” as used herein, is generally a sample from an individual. Non-limiting examples of biological samples include blood, serum, plasma, or cerebrospinal fluid. Additionally, solid tissues, for example, spinal cord or brain biopsies may be used.

Anti-MAP1B antibodies as described herein can be used in various immunological techniques for detecting MAP1B polypeptides. Depending on the nature of the sample, immunoassays (e.g., radioimmunoassays) and/or immunohistochemical / immunocytochemical staining techniques may be used. Liquid phase immunoassays (e.g., competitive inhibition radioimmunoassays) or solid phase immunoassays (e.g., antigen-capture or Western blot analysis) can also be used to detect MAP1B polypeptides. Additionally, enzyme-linked immunosorbent assays (ELISA) can be used for detecting the presence of MAP1B polypeptides.

Anti-MAP1B antibodies may be used with or without modification for the detection of MAP1B polypeptides. Anti-MAP1B antibodies can be labeled either directly or indirectly, and a wide variety of labels, including radioisotopes, enzymes, substrates, cofactors, inhibitors, fluorescers, chemiluminescers and magnetic particles. In some cases, an anti-MAP1B antibody having specific binding affinity for MAP1B polypeptides can be conjugated to an imaging agent. Suitable imaging agents include, but are not limited to, radioisotopes, such as ^{32}P, ^{99}Tc, ^{111}In and ^{131}I.

Methods of detecting MAP1B polypeptides and/or PCA-2-specific autoantibodies can include enumerating or isolating PCA-2-specific autoantibodies from an individual.

This method may be used, for example, to monitor and/or evaluate an individual's immune response, disease state, and/or treatment response.

Methods of Treatment

This document also provides methods for treating an individual (e.g., a human) whose immune system is producing PCA-2-specific autoantibodies.

In some cases, MAP1B polypeptides can be used as described herein to diagnose a paraneoplastic neurological disorder and/or a cancer associated with PCA-2-specific autoantibodies in an individual, and an immunotherapy can be administered to the individual to treat the paraneoplastic neurological disorder and/or a cancer associated with PCA-2-specific autoantibodies. Examples of immunotherapies include, without limitation, immunomodulation (e.g., activation immunotherapies or suppression immunotherapies), antigen specific tolerance induction strategy (e.g., MAP1B specific tolerance induction strategy), and immunotherapy targeting MAP1B specific T cells and/or B cells. Examples of immunomodulatory agents that can be used to suppress the immune response include, without limitation, immunosuppressants (e.g., corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, cyclophosphamide, rituximab, and/or mTOR inhibitors). For example, a corticosteroid can be used to treat paraneoplastic neurological disorder and/or a cancer associated with PCA-2-specific autoantibodies. Examples of immunomodulatory agents that can be used to target T cells include, without limitation, cyclophosphamide and/or tacrolimus. For example, cyclophosphamide and/or tacrolimus can be used to treat paraneoplastic neurological disorder and/or a cancer associated with PCA-2-specific autoantibodies.

In some cases, MAP1B polypeptides described herein can be used in an apheresis method to treat a paraneoplastic neurological disorders and/or cancer associated with PCA-2-specific autoantibodies. For example, apheresis for the treatment of a paraneoplastic neurological disorders and/or cancer associated with PCA-2-specific autoantibodies can be used to remove PCA-2-specific autoantibodies from an individual. Methods and extracorporeal systems for apheresis (i.e., the process of withdrawing blood from an individual, removing components from the blood, and returning the blood, or blood depleted of one or more components, to the individual) can be used as described elsewhere (see, for example, U.S. Patent Nos. 4,708,713; 5,258,503; 5,386,734; and

6,409,696). In some cases, an apheresis method can be used to remove PCA-2-specific autoantibodies from a body fluid of an individual. The method can include withdrawing a body fluid from an individual; removing a substantial portion of PCA-2-specific autoantibodies from the fluid; and returning the fluid to the individual. Antibodies removed can be of any class, e.g., IgG (such as IgG1, IgG2, IgG3, IgG4), IgM, IgD, IgA, or IgE antibodies.

As used herein, a "substantial portion" means removing at least 20% (e.g., at least: 20%; 30%; 40%; 50%; 60%; 65%; 70%; 75%; 80%; 85%; 90%; 93%; 95%; 96%; 97%; 98%; 99%; 99.5%; 99.8%; or even 100%) of the PCA-2-specific autoantibodies that were present in the body fluid prior to removal. The body fluid can be blood plasma or any other body fluid, e.g., lymph or cerebrospinal fluid. According to the methods described herein, depleting PCA-2-specific autoantibodies from individuals with a PCA-2-associated autoimmune disease may result in a reduction or a decrease in one or more of the symptoms.

Removal of PCA-2-specific autoantibodies is generally performed by contacting a body fluid with a MAP1B polypeptide or fragment thereof. The MAP1B polypeptide or fragment thereof can be bound to a solid support. Such solid supports can be, without limitation, membranes, fibers, spherical beads, or granules and can be made with a water-insoluble, preferably porous, biocompatible material, e.g., organic polymers such as agarose, dextran, and polyacrylamide, or inorganic porous materials such as porous glass or porous silica gel. Such materials are suitable or can be adapted (e.g., derivatized with appropriate chemical groups) for attachment of a MAP1B polypeptide.

When the body fluid is blood, the plasma and/or white blood cells can be separated from red blood cells (e.g., erythrocytes) and the red blood cells can be returned to the individual with or without white blood cells. Usually, the blood cells are returned to the individual with artificial rather than their original blood plasma. The "replacement fluid" (e.g., physiological saline) can be administered to the individual after removal of the fluid. Alternatively, the PCA-2-specific autoantibodies can be selectively removed from the blood plasma in the course of apheresis and the blood cells can be mixed with the PCA-2-specific autoantibody-depleted plasma and then re-infused as a mixture into the individual.

The system can be a continuous one in which, for example, blood is pumped out of a blood vessel (e.g., an artery or a vein) passed over a solid support derivatized with

MAP1B polypeptides and pumped directly back into a blood vessel of the individual. As in non-continuous systems, blood cells can be separated from plasma prior to passing of the plasma over the solid support.

This document also provides methods of imaging MAP1B polypeptide-expressing cells in an individual. The method can include administering to the individual an effective amount of an anti-MAP1B antibody having specific binding affinity for a MAP1B polypeptide labeled with an imaging agent, for example, ^{32}P, ^{99}Tc, ^{111}In or ^{131}I, to bind to a MAP1B polypeptide released from, or accessible in, cells, and detecting any complex so formed. A suitable amount of an anti-MAP1B antibody is any amount that is effective to image cells, for example, labelled anti-MAP1B antibodies having about 0.1 mCi to about 50.0 mCi. In addition, an effective amount of an anti-MAP1B antibody may be an amount from about 0.01 mg to about 100 mg.

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

EXAMPLES

Example 1: Target and antigen of PCA-2 in paraneoplastic neurological disorders associated with small cell lung cancer.

Purkinje cell antibody-type 2 (PCA-2) was described in 2000 as an IgG biomarker of paraneoplastic neurologic autoimmunity initiated by small-cell lung carcinoma (SCLC), with an ~ 280-kDa onconeural cytoplasmic antigen expressed in central and peripheral neural tissues and SCLC cells. PCA-2 screening was incorporated into Mayo Clinic's comprehensive serological evaluation for paraneoplastic neural autoantibodies. This example identified the autoantigen as a member of the microtubule-associated protein family (MAP1B), and further defined clinical, oncologic and immunohistochemical characteristics of PCA-2.

Patients

The Mayo Clinic Institutional Review Board approved tissue acquisition and review of patients' histories. Between January 1993 and May 30, 2016 the Mayo Clinic Neuroimmunology Laboratory tested approximately half a million serum or cerebrospinal fluid (CSF) specimens submitted for paraneoplastic neural autoantibody evaluation on a

service basis. Of 118 patients with PCA-2 IgG documented immunohistochemically and by western blot, at least one archival frozen specimen was available for 96 (92 serum and 4 CSF) and clinical information was available for 95 patients, 22 through the Mayo Clinic medical record and 73 through communication with referring physicians. Control sera (98) included: 33 healthy subjects (Mayo Clinic Biobank), 17 patients with miscellaneous immunopathies (6 systemic lupus erythematosus [SLE], 6 Sjogren syndrome, 5 hypergammaglobulinemia), 15 patients with multiple sclerosis, and 32 patients with neurologic autoimmunity associated with an IgG autoantibody prominently reactive with cytoplasm of cerebellar purkinje cells (17 PCA-1 positive) (Greenlee et al., *Ann Neurol* 1983; 14:609-13), and both cytoplasm of cerebellar purkinje cells and their dendrites (16 Inositol Triphosphate Receptor (ITPR)-1 positive; Jarius et al., *J Neuroinflammation* 2014; 11:206).

Immunohistochemical staining

Indirect immunofluorescence assay (IFA): Screening with patient serum and CSF and commercial monoclonal and polyclonal antibodies was performed on a cryosectioned composite of adult mouse tissues (4 μm): cerebellum, midbrain, cerebral cortex, hippocampus, kidney and gut. Sections were fixed using 4% paraformaldehyde, 1 min, permeabilized with 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS) 0.5% in phosphate bufferd saline(PBS), 1 min, blocked 1 hour with normal goat serum (10% in PBS). After PBS-rinse, patient specimen was applied (serum pre-absorbed with bovine liver powder, 1:240 dilution; CSF non-absorbed, 1:2 dilution), or commercial IgG of the following specificities: MAP1A,rabbit polyclonal, Santa Cruz Biotechnology Inc. (Dallas, TX ,USA, MAP1B mouse monoclonal, BD Transduction Laboratories, San Jose, CA, USA , MAP1B Rabbit polyclonal, (Protein Tech (Rosemont, IL, USA). After 40 minutes and PBS wash, species-specific anti-IgG (conjugated with FITC or TRITC; Southern Biotechnology Associates, Inc, (Birmingham, AL,USA) was applied and mounted cover slips using ProLong Gold anti-fade medium (containing DAPI; Molecular Probes ThermoFisher Scientific, USA). Fluorescent images were captured using Olympus BX51 Polarizing microscope with Olympus DP73 high-performance Peltier cooled, 17.28 megapixel camera. Patient specimens yielding positive results were titrated in doubling dilutions to determine the endpoint of autoantibody detection.

Dual staining by confocal microscopy: Colocalization studies utilized patient serum and commercial IgGs specific for MAP1A or MAP1B. Goat IgG secondary antibodies were TRITC or FITC conjugated and specific for rabbit or mouse IgG (Southern Biotechnology Associates, Inc, (Birmingham, AL, USA), goat anti-human IgG was alexa fluor 594 conjugated (Molecular Probes ThermoFisher Scientific, USA). Confocal images were captured using Zeiss LSM780 microscope (63X or 40X water immersion lens).

Protein Purification and Sequencing

Antigen preparation: All steps were at 4°C. Adult mouse cerebellum and SCLC tumor xenografts (Lennon et al., *The Journal of clinical investigation* 2003; 111:907-13; Yu et al., *Ann Neurol* 2001; 49:146-54) were homogenized using a tissue homogeniser with buffer, 3 mL/g (10mM Hepes pH 7.4, 1mM $MgCl_2$, 1 mM EDTA and complete protease inhibitor cocktail [Rochea Indianapolis, IN, USA]). Homogenate was clarified by centrifugation (150,000g, 30 minutes), and supernate was stored at -80C.

Antibody purification: Cerebellar proteins separated electrophoretically in 5% polyacrylamide gel (PAGE), then transferred electrophoretically to nitrocellulose membrane, and blocked in buffer (20 mM Tris, pH 7.6, 137 mM sodium chloride, 0.1% Tween-20) containing 10% powdered milk. Longitudinal edge strips were cut (0.5cm) from the nitrocellulose and probed with patient IgG to locate the immunoreactive band (~280 kDa). The remaining non-exposed central region of the nitrocellulose, containing reactive band (9.5 X 0.8 cm), at approximately 280kDa was cut horizontally (and also a control strip from a non-reactive region). Patient serum (diluted 1:500) was applied to the cut nitrocellulose strips, 1 hour and, after extensive washing, bound human IgG was eluted in 100 mM acetic acid, neutralized, dialyzed against PBS and concentrated. To confirm PCA-2 specificity, the eluted IgG was tested by IFA on mouse tissue sections.

Protein Purification and Sequencing: Patient's affinity purified IgG was complexed to Protein G magnetic beads (Dynabeads, Invitrogen ThermoFisher Scientific, USA). After washing, cerebellar protein extract was added (1 hour), washing was repeated, and beads were boiled 5 minutes in 2x sample buffer. Eluted sample was electrophoresed in 5% (PAGE) and proteins were located by Coomassie G-250 (Bio-Rad, Hercules, California, USA) staining and by western blot. The immunoreactive band was

cut from the stained gel, reduced, alkylated with iodoacetamide, and digested with trypsin. Peptides in the digested sample were analyzed using nano high-pressure liquid chromatography electrospray tandem mass spectrometry (nano-LC-ESI-MS/MS).

Constructs: cDNA encoding full length MAP1A and MAP1B proteins (Genecopoeia Clone # HOC23132 and HOC23292) were used as template for amplification reactions using either Pfx (Invitrogen) or AmpliTaq (Applied Biosytems) DNA polymerase. The coding regions of both genes were amplified as five individual fragments (Table 1) and cloned into pET102D bacterial expression vector (Invitrogen). Clones were selected and sequence integrity was verified by Sanger sequencing. BL-21 cells (Invitrogen) were transformed with plasmid DNA, grown under antibiotic selection and, at optical density of 0.5 – 0.8, were induced with IPTG (400 mM). After 2.5 additional hours at 37°C, cells were pelleted and protein expression was verified by extraction (50 mM $NaPO_4$, 400 mM NaCl, 100 mM KCl, 10% glycerol, 0.5% Triton X-100, 10 mM Imidizole), and western blot (horse radish peroxidase conjugated V5 epitope tag-specific IgG [Invitrogen]).

Absorption of patients' serum with MAP1B

Following incubation with bovine liver powder, 50 µL of serum from 2 MAP1B (PCA-2) IgG-positive patients (patient 74, 82, table 2) and 1 positive ANNA-1(anti-Hu) patient, were incubated with 10 µL of recombinant MAP1B protein, fragment 1, overnight. Postincubation serum was tested by IFA on mouse tissue sections.

RESULTS

Characterization of the autoantibody

Immunohistochemical distribution of the neural antigen: The initial report of the PCA-2 antigen's immunohistochemical distribution noted striking cytoplasmic staining of cerebellar purkinje neuronal perikaryon and dendrites (figure 1a), dentate neurons (figure 1b), myenteric ganglia and enteric nerves extending into gastric mucosa (figure 1c) and sympathetic nerves innervating kidney (Figure 1d). Examination of additional CNS regions represented in the extended mouse tissue substrate revealed a diffuse glow over synapse-rich regions of cerebral cortex and hippocampus (Figure 1e,f) and staining of

dendrites of hippocampal pyramidal neurons (mostly CA-1) and cerebral cortex (Figure 1e, 1f).

Immunochemical characterization of the autoantigen

5 *PCA-2 IgG binds to a ~280 kDa native neural protein:* Western blot probing of mouse brain proteins with patient IgGs confirmed a common immunoreactive band, ~ 280 kDa; control human IgGs were non-reactive (figure 2A). IgG eluted from the immunoreactive region of nitrocellulose, but not from a control region, replicated the original patient serum IgG immunostaining pattern when applied to mouse tissue sections
10 (Figure 2B; compare Figure 1). Mass spectrometry analysis of proteins captured by the eluted IgG when immobilized on magnetic beads identified three candidate proteins of ~280 kDa mass: MAP 1B (270 kDa), MAP1A (326 kDa), and MAP2 (199 kDa) (Sato-Yoshitake et al., *Neuron* 1989; 3:229-38; Lim et al., *J Biol Chem* 2000; 275(27): 20578-87).

15 *Confocal microscopy supports MAP1B as primary antigenic target.* Commercial IgG specific for MAP1B yielded a staining pattern on mouse tissues identical to that of patient IgG (Figure 3A). MAP1A-specific IgG yielded a similar pattern in some but not all nervous system regions (Figure 3B). The staining pattern yielded by MAP2 IgG did not resemble that of patient IgG (not shown).

20 *Western blot characterization of the antigen:* Western blot analysis revealed that recombinant MAP1B had the same electrophoretic mobility as the native protein identified by patient IgG (figure 4); MAP1A and MAP 2 both differed, as predicted from their known properties (Sato-Yoshitake et al., *Neuron* 1989; 3:229-38).

Fragment 1 of MAP1B (encompassing residues 1-666) contains the principal
25 *antigenic region(s) recognized by PCA-2:* Coding regions of both MAP1B and MAP1A genes were amplified as five individual fragments (Table 1) that overlapped by approximately 60-70 residues (figure 8). Serum (diluted 1:500) or CSF (diluted 1:50) from 40 PCA-2 IgG-positive patients were tested by western blot for polypeptide-reactive IgG on all 10 fragments (MAP1A # 1-5, MAP1B # 1-5). IgG in 40 of 40 specimens bound to
30 MAP1B #1 (Figure 5); additional IgGs in a minority of patients bound to other MAP fragments (Figure 5). IgG in 55 of the remaining 57 PCA-2 IgG positive sera bound to MAP1B fragment 1 by western blot.

Table 1. cDNAs encoding full length MAP1A and MAP1B proteins served as template for PCR amplification reactions. The coding regions for each gene were amplified as five individual fragments and cloned into bacterial expression vectors.

	Fragment number	Amino acids encompassed	Number of amino acids in fragment	number of residues overlapping the previous fragment
MAP1A	1	1-670	670	N/A
	2	606-1240	635	65
	3	1181-1720	540	60
	4	1661-2200	540	60
	5	2141-2803	663	60
MAP1B	1	1-666	666	N/A
	2	576-1190	615	91
	3	1111-1690	580	80
	4	1611-2120	510	80
	5	2040-2468	428	80

5 Microtubule-associated protein 1A and 1B [Homo sapiens]

Recombinant MAP1B protein abrogates tissue binding by patient IgG: Preincubation of serum of two PCA-2 positive patients with MAP1B fragment 1, abolished the PCA-2 IgG staining pattern (figure 6A-C). This preincubation did not
10 diminish the immunostaining intensity of ANNA-1 (anti-Hu) IgG in serum of a control patient with SCLC-related paraneoplastic neurologic autoimmunity (figure 6D).

Diverse neurologic accompaniments of MAP1B autoimmunity

Clinical information was available for 95 patients (table 3, Figure 10). The median
15 age at neurologic symptom onset was 68 years (22-89); 55 patients (47%) were women and 82% (55/67) had history of tobacco use. Neurologic presentations varied and in the majority of cases symptoms and signs were subacute in onset (61%).

Table 2. Predominant Neurological Manifestations, MRI Findings and Coexisting Neural
20 Antibodies in MAP1B-IgG (PCA-2) positive patients.

Level involved	Number of patients (%) (data available in 95 patients)	Neurological Manifestations
Cerebral cortex	30 (30%)	Encephalopathy/cognitive decline (26), Limbic encephalitis (7), Scondary generalized seizures (3), complex partial seizures (7),

		lethargy (5), hallucinations (3), personality changes(3), paranoia(2),
Diencephalon	6 (6%)	Sleep disturbance: Insomnia (5), hypersomnia (1)
Cerebellum	36 (38%))	Ataxia only (30)
Optic nerve/retina	8 (8%)	optic neuropathy (4, 2 with ON enhancement on MRI) – 3 with CRMP5-IgG, retinal involvement (5) – 2 with CRMP5-IgG involvement
Brainstem/Basal ganglia		5 Parkinsonism/dystonia/chorea (all 3 patients with chorea had CRMP-5 IgG, 1 of 2 patients with dystonia had amphiphysin IgG), 7 diplopia and eye movement abnormality (7, 3 with CRMP-5 and 1 with ANNA-1), nausea and vomiting (1)
Peripheral Nerve Somatic Autonomic	50 (53%) 43(45%) 14 (15%)	 Paresthesia (22), pain/burning/dysesthesia(9), muscle weakness (13) Orthostatis (2), GI motility disorder (8),
Neuromuscular Junction	5 (5%)	Lambert Eaton syndrome
Multifocal presentations	45 (47%)	

Frequency of Co-existing Neural Autoantibodies (specimen available in 118 patients)

Antibody specificity	Number (%) of patients	Ab	N (%) of patients
CRMP5	30(25%)	ANNA-1	15 (13%)
VGCC P/Q type	24(20%)	GAD 65	18(15%)
VGKC complex*	8(7%)	Alpha 3	7 (6%)
ARBi	4 (3%)	GABA-B	3 (3%)
Amphphysin	2 (2%)	VGCC N type	2 (2%)
AMPA	2 (2%)	AGNA-1 (Sox-1)	2 (2%)
>1 coexisting	10(8%)		

MRI findings (MRI scans available in 44 patients)

Finding	Number of patients (%)	Coexisting neural autoantibody	Neurologic manifestation
Normal Mri	15 (35)		

Nonspecific changes	8 (18)		
Spinal involvement	5 (11)	ANNA-1 (1)	Sensory neuropathy (2), cerebellar (2), limbic encephalitis (1), myelopathy (2)
Brain atrophy	4 (9)	CRMP-5 (2), ANNA-1 (1)	Cerebellar (4), neuropathy (1), limbic encephalitis (1)
Cerebellar atrophy	3 (7)	ANNA-1 (1), CRMP-5 (1)	Cerebellar (3)
Diffuse white matter leisions	3 (7)		Myelopathy (1),Cerebellar (1)
Optic nerve involvement	2 (5)	CRMP-5 (1)	Optic neuropathy/neuritis
Meningial enhancement	2 (5)		Encephalopathy (1),Cerebellar (1), Neuropathy (1)
Temporal lobe involvement	2 (5)	ANNA-1 (2), CRMP-5 (1)	Limbic encephalitis (2)
Caudate nucleus atrophy	1 (2)		Involuntary movements
Brachial plexus	1 (2)		Brachial plexities (bilateral)

* None of the 96 available sera were positive for anti-Leucine-Rich, Glioma Inactivated 1 (LGI1) or contactin-associated protein-like 2 (CASPR2) antibodies.

Peripheral neuropathy, the most common presentation, was reported in 50 patients (53%); 44 had sensory-motor neuropathy (confirmed by EMG in 16), 14 had dysautonomia and other levels of the nervous system were affected in 34 patients. Cerebellar dysfunction was reported in 36 patients (38%). Cortical/subcortical involvement also was commonly encountered; encephalopathy /cognitive decline was reported in 26 patients (27%) of whom 5 had seizures.

Ten patients had symptoms referable to the anterior visual system: The following findings were documented in the medical/laboratory record: disc edema in 3, optic nerve involvement in 4 (3 with CRMP-5 IgG), enhancement of optic nerves on MRI in 2 (1 with CRMP-5 IgG), retinopathy in 5 (3 with CRMP-5 IgG).

Coexisting neural antibodies were detected in 79 of 118 (67%) patients (table 2). The two most common were CRMP5-IgG (25%) and voltage gated calcium channel antibodies (22%).

Reports of MRI brain were available for review in 44 patients: 15 (35%) were normal, 8 (18%) had nonspecific white matter changes in the brain and 20 patients (45%) had substantial changes on MRI (table 2). The most common disease relevant findings were spinal cord involvement (5 with T2 hyper-intensities, 3 with enhancement), cerebral atrophy (4), optic nerve involvement (2, 1 with enhancement) and temporal lobe involvement (2).

MAP1B-IgG alone was detected in 4/5 patients with spinal cord involvement, 2/2 patients with meningeal enhancement and 1/2 patients with optic nerve involvement (the other patient had co-existing CRMP-5 IgG). More than half of the patients with cerebellar or cerebral atrophy and temporal involvement had additional antibodies including CRMP5-IgG and ANNA-1.

Results of CSF examination were available for 29 patients: 15 (52%) had pleomorphic leukocytosis (median white cell count, 20, range 6-162, normal reference range ≤5 per high power field); 21 (74%) had elevated protein (median 60 mg/dL, range 37-203, normal ≤35 mg/dL).

Oncologic associations of MAP1B-IgG (PCA-2)

Among 84 patients with adequate oncologic evaluation information, cancer was found in 66 (79%; table 3). The detection frequency was higher in 44 patients who were singularly seropositive (89%). Lung cancer was most common (80% of all cancers). Small-cell carcinoma was 3 times more common than non-small-cell lung carcinoma (46% and 17%, P<0.01). Cancer diagnosis followed the neurologic presentation in 55% of cases. The median survival for 14 of 39 patients who had SCLC and adequate follow up information was 54 months (range 3-164).

Table 3. Numbers (% frequency) and types of cancer detected in PCA-2 IgG-positive patients with adequate oncologic evaluation.

Cancer type (n/%)	PCA-2 IgG with or without other neural autoantibody) n = 85	PCA-2 IgG only n = 45	Cancer diagnosis followed neurologic presentation n (%)	Survival, number of patients† months; median (range)	
				Alive at last follow-up	Deceased at last follow-up
All malignancies	67 (79%)**	40 (88.8%)	36 (53.7%)	6; 43 (2.5-86)	16; 20.5 (3-164)

Lung	SCLC	39 (46%)	18 (40%)	26 (38.8%)	3; 84 (60-86)	11; 22 (3-164)
	NSCLC	14 (16%)	11 (24.4%)	6 (9%)	1; 4	4; 15 (3-42)
Breast		5 (6%)***	3 (6.7%)	0	NA	NA
Other malignancy*		9 (11%)	8 (17.8%)	3 (4.5%)	N=2, 14.25 (2.5-26)	n=1, 23

* renal carcinoma (1), squamous cell skin carcinoma (1), extrapulmonary small-cell carcinoma – pancreas (1), prostate adenocarcinoma (2), primary intrahepatic cholangiocarcinoma (1), Ewing sarcoma (1), nasopharyngeal carcinoma (1), lymphoma (1).
** 65 proven histologically, 2 PET/imaging based
5 *** all women
† Long term follow-up data regarding survival available for only 22 patients
NA = no data available

Western blot analysis of proteins extracted from 10 SCLC tumor cell lines with
10 commercial MAP1B-specific IgG confirmed MAP1B protein expression in 6 (figure 7).

Data regarding response to immunotherapy were available for only 26 patients: 14 had physician reported benefit from immunosuppression (neurologic symptoms stabilized or improved); 8/16 had a beneficial response to corticosteroids, 3/4 to plasmapheresis, 2/2 to cyclophosphamide and 0/2 to high dose IV immune globulin. Some neurologic benefit
15 was reported in 11 of 15 patients after chemotherapy for cancer.

These results demonstrated that MAP1B, the PCA-2 autoantigen, represents a novel target in paraneoplastic neurologic disorders with a high predictive value for SCLC. Its relatively high prevalence, compared with other recognized paraneoplastic neural autoantibodies, justifies its testing in comprehensive paraneoplastic neural autoantibody
20 evaluation.

OTHER EMBODIMENTS

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

WHAT IS CLAIMED IS:

1. A method of detecting the presence or absence of a PCA-2-specific autoantibody in a biological sample from an individual, comprising the steps of:

contacting said biological sample with a MAP1B polypeptide or fragment thereof to form a MAP1B-PCA-2-specific autoantibody complex if said biological sample contains said PCA-2-specific autoantibody; and

detecting the presence or absence of said complex.

2. The method of claim 1, wherein the presence of said PCA-2-specific autoantibody in said biological sample is associated with a paraneoplastic neurological disorder or a cancer associated with PCA-2-specific autoantibodies in said individual.

3. The method of claim 2, wherein said paraneoplastic neurological disorder is selected from the group consisting of encephalitis/encephalopathy, seizures, sleep disorders, cerebellar dysfunction/cerebellar degeneration/cerebellar ataxia, optic neuropathy, retinopathy, movement disorders/non voluntary movements, eye movement abnormalities, peripheral neuropathy, autonomic dysfunction, neuromuscular junction syndromes, Lambert-Eaton myasthenic syndrome (LEMS), Cushing syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), paraneoplastic cerebellar degeneration, encephalomyelitis, limbic encephalitis, brainstem encephalitis, opsoclonus myoclonus ataxia syndrome, and polymyositis.

4. The method of claim 3, wherein said paraneoplastic neurological disorder is LEMS.

5. The method of claim 2, wherein said cancer is selected from the group consisting of small-cell lung cancer (SCLC), renal carcinoma, squamous cell skin carcinoma, extrapulmonary small-cell carcinoma (EPSCC), prostate adenocarcinoma, primary intrahepatic cholangiocarcinoma, Ewing sarcoma, nasopharyngeal carcinoma, lymphoma, large cell neuroendocrine carcinoma of the lung (LCNEC), gastroenteropancreatic

neuroendocrine tumors (GEP-NET), pituitary tumors, thyroid tumors, and medullary carcinoma.

6. The method of claim 5, wherein said cancer is SCLC.

7. The method of claim 1, wherein said method comprises performing a Western blot to detect said complex.

8. The method of claim 1, wherein said method comprises detecting the presence of said complex.

9. The method of claim 1, wherein said method comprises detecting the absence of said complex.

10. The method of claim 1, wherein said biological sample is selected from the group consisting of serum, plasma, cerebrospinal fluid, and blood.

11. A kit comprising a MAP1B polypeptide or fragment thereof and instructions for using said MAP1B polypeptide to detect a PCA-2-specific autoantibody in an individual.

12. The kit of claim 11, wherein said kit is used to diagnose the presence or absence of a paraneoplastic neurological disorder or a cancer associated with PCA-2-specific autoantibodies in said individual.

13. The kit of claim 11, further comprising a monoclonal antibody having specific binding affinity for a MAP1B polypeptide or fragment thereof.

14. The kit of claim 11, further comprising a PCA-2-specific autoantibody.

15. A method of treating an individual having a paraneoplastic neurological disorder associated with PCA-2-specific autoantibodies, said method comprising:

identifying an individual as having a paraneoplastic neurological disorder associate with PCA-2-specific autoantibodies; and

administering an immunomodulatory agent to said individual.

16. The method of claim 15, wherein said identifying an individual as having a paraneoplastic neurological disorder associate with PCA-2-specific autoantibodies comprises the steps of:

contacting a biological sample from said individual with a MAP1B polypeptide or fragment thereof to form a MAP1B-PCA-2-specific autoantibody complex if said biological sample contains said PCA-2-specific autoantibody; and

detecting the presence of said complex.

17. The method of claim 15, wherein said immunomodulatory agent comprises a corticosteroid.

18. The method of claim 15, wherein said immunomodulatory agent comprises cyclophosphamide.

19. The method of claim 15, wherein said immunomodulatory agent comprises tacrolimus.

FIG. 1

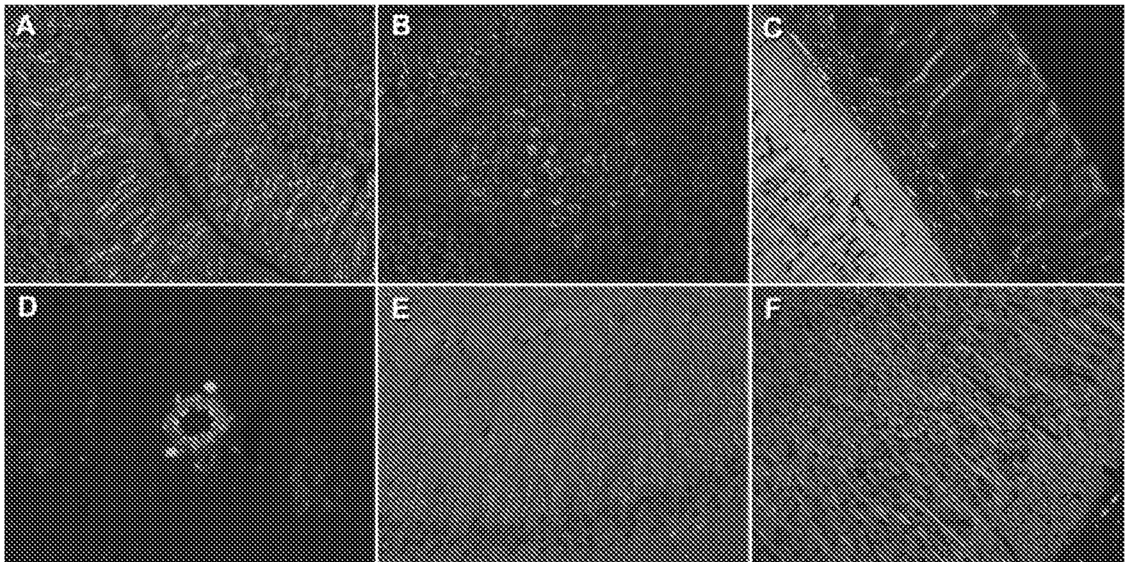


FIG. 2A

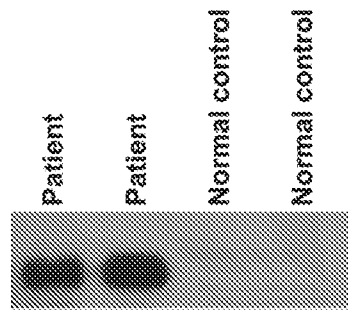


FIG. 2B

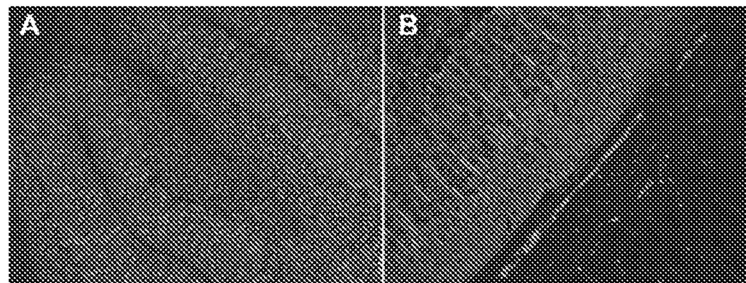


FIG. 3A

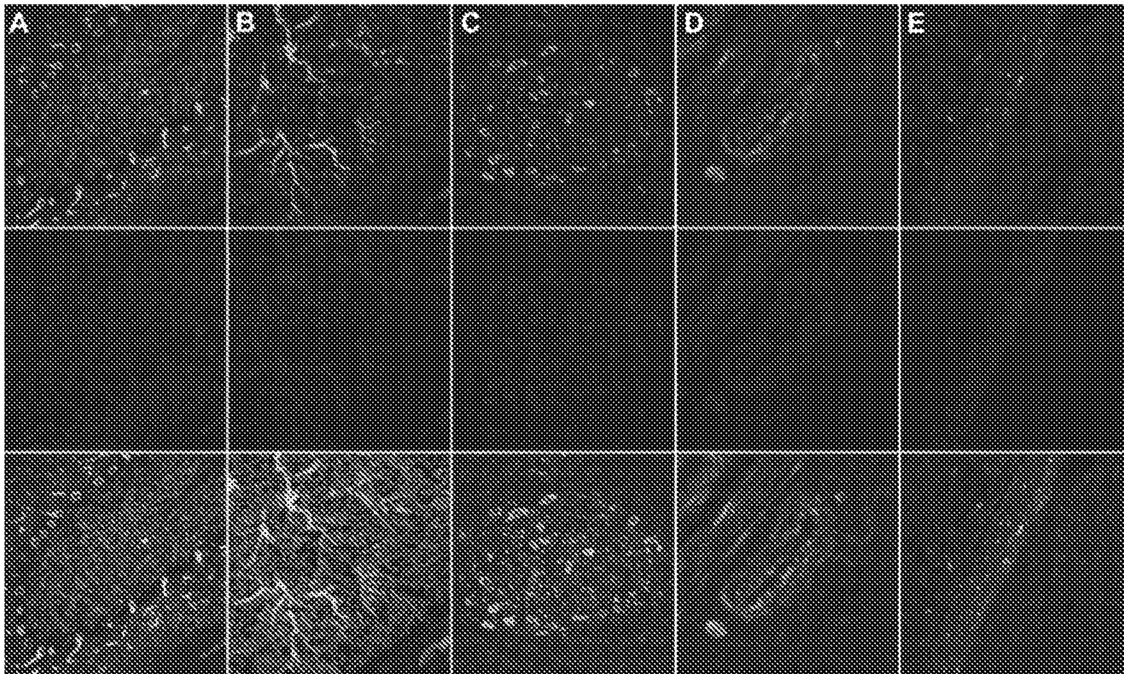


FIG. 3B

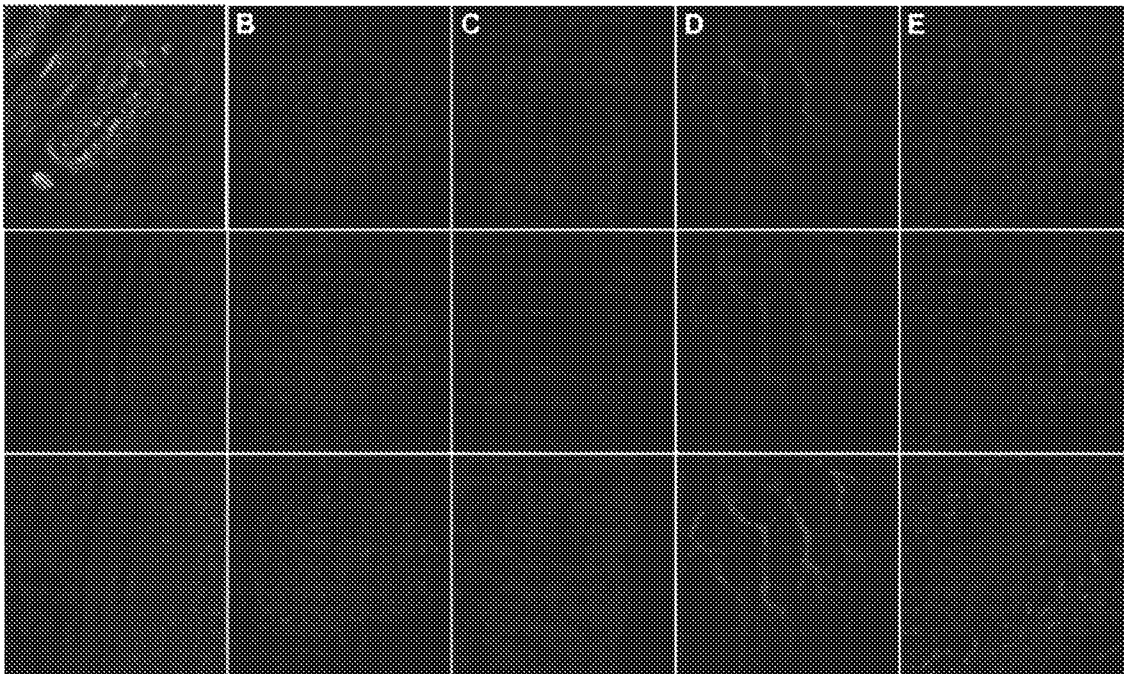
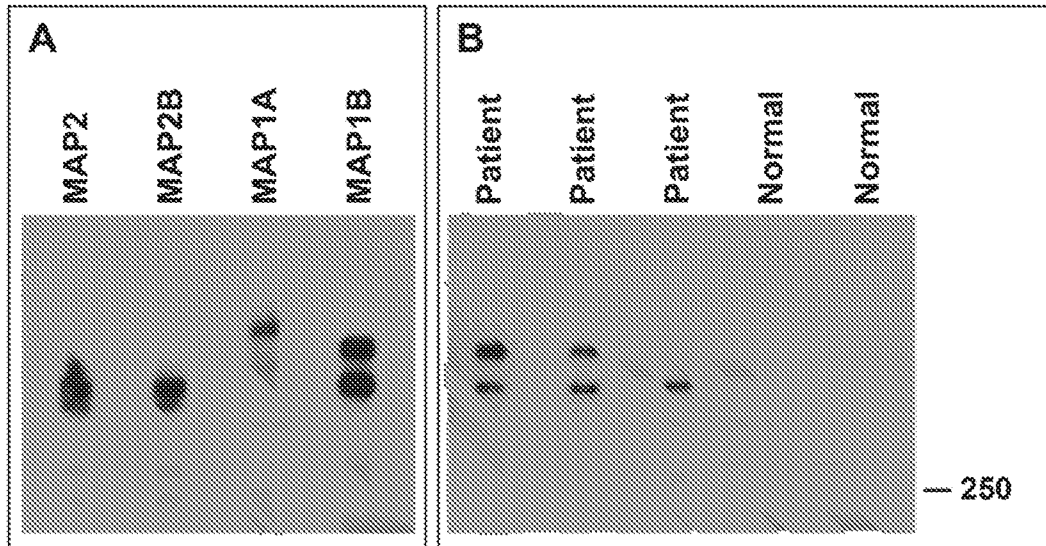


FIG. 4



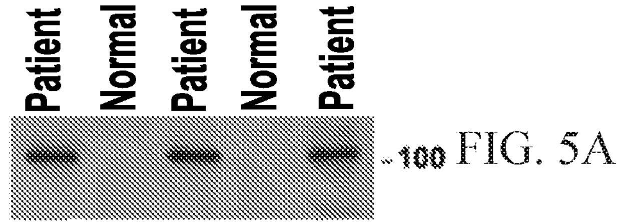


FIG. 5A

patient	map 1b-1	map 1b-2	peptide 540-693	map 1b-3	map 1b-4	map 1b-5	map 1a-1	map 1a-2	map 1a-3	map 1a-4	map 1a-5
1	pos	pos	pos	neg	pos	pos	pos	neg	neg	neg	neg
2	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
3	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
4	pos	pos	neg	neg	neg	*+/-	neg	neg	neg	neg	neg
5	pos	neg	pos	neg	neg	neg	neg	neg	neg	neg	neg
6	pos	pos	pos	pos	neg	*+/-	neg	neg	neg	neg	pos
7	pos	pos	pos	neg	neg	neg	neg	neg	neg	neg	neg
8	pos	pos	pos	neg	pos	neg	*+/-	neg	neg	neg	neg
9	pos	pos	pos	neg	*+/-	*+/-/+	neg	neg	neg	neg	neg
10	pos	neg	pos	neg	neg	pos	neg	neg	neg	neg	neg
11	pos	neg	pos	neg	neg	neg	neg	neg	neg	neg	neg
12	pos	pos	pos	neg	pos	neg	neg	neg	nrg	neg	neg
13	pos	pos	pos	neg	neg	pos	*+/-	neg	neg	neg	neg
14	pos	neg	pos	neg	*+/-	neg	*+/-	neg	neg	neg	neg
15	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
16	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
17	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
18	pos	*+/-	pos	neg	neg	neg	neg	neg	neg	neg	neg
19	pos	*+/-	pos	neg	neg	neg	neg	neg	neg	neg	neg
20	pos	*+/-	pos	neg	neg	neg	neg	neg	neg	neg	neg
21	pos	pos	pos	pos	pos	pos	pos	neg	neg	neg	pos
22	pos	neg	pos	neg	neg	neg	neg	pos	neg	neg	neg
23	pos	pos	pos	neg	neg	*+/-	*+/-	neg	neg	neg	neg
24	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
25	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
26	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
27	pos	pos	pos	neg	pos	*+/-	neg	neg	neg	neg	neg
28	pos	pos	pos	neg	neg	neg	*+/-	neg	neg	neg	neg
29	pos	pos	pos	neg	neg	neg	neg	neg	*+/-	*+/-	neg
30	pos	pos	pos	neg	neg	neg	neg	neg	neg	neg	neg
31	pos	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg
32	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
33	pos	pos	pos	neg	neg	neg	*+/-	neg	*+/-/+	neg	neg
34	pos	pos	pos	neg	neg	neg	neg	*+/-	pos	pos	neg
35	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg
36	pos	pos	pos	neg	neg	neg	neg	neg	neg	neg	neg
37	pos	neg	pos	neg	neg	neg	neg	neg	neg	neg	neg
38	pos	pos	pos	neg	neg	neg	neg	neg	neg	neg	neg
39	pos	neg	pos	neg	neg	neg	neg	neg	neg	neg	neg
40	pos	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg

FIG. 5B

FIG. 6

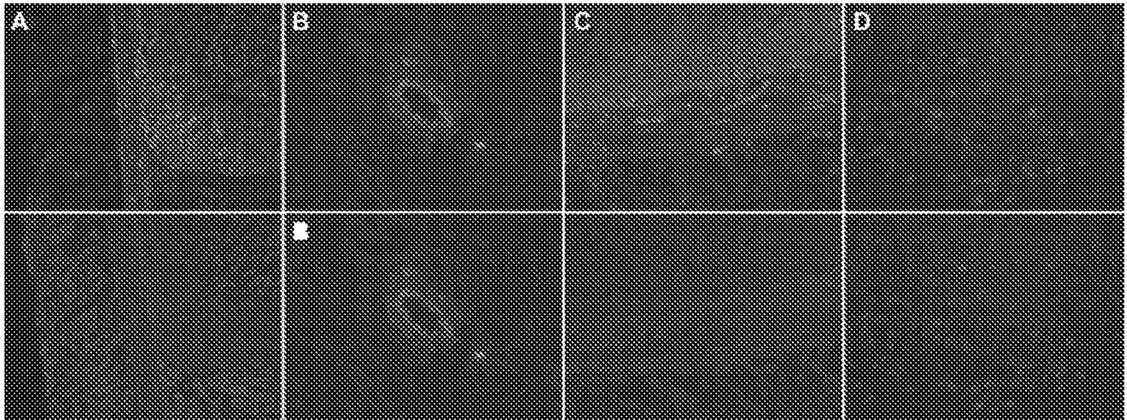


FIG. 7

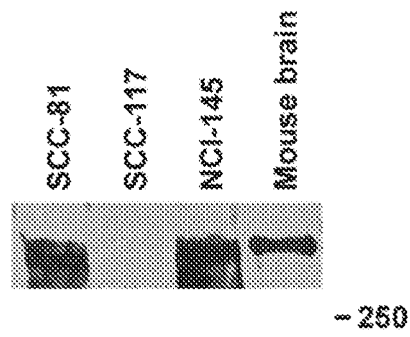


FIG. 8

Microtubule-associated protein 1B [Homo sapiens]

MATVVVEATEPEPSGSIANPAASTSPSLSHRFLDSKFYLLVVVGEIVTEEHLRRAIGNIELGIRSWDTN
LIECNLDQELKLFVSRHSARFSPEVPGQKILHHRSDVLETVVLINPSDEAVSTEVRLMITDAARHKLLV
LTGQCFENTGELILQSGSFSFQNFIEIFTDQEIGELLSTTHPANKASLTLFCPEEGDWKNSNLDRHNLQ
DFINIKLNSASILPEMEGLSEFTEYLSESVEVPSPFDILEPPTSGGFLKLSKPCCYIFPGGRGDSALFA
VNGFNMLINGGSERKSCFWKLIRHLDRVDSILLTHIGDDNLPGINSMLQRKIAELEEEQSQGSTTNSDW
MKNLISPDLGVVFLNVPENLKNPEPNIKMKRSIEEACFTLQYLNKLSMKPEPLFRSVGNTIDPVILFQK
MGVGKLEMYVLNPVKSSKEMQYFMQQWTGTNKDKAEFILPNGQEVDLPISYLTSVSSLIVWHPANPAEK
IIRVLFPGNSTQYNILEGLEKLKHLDFLKQPLATQKDLTGQVPTPVVKQTKLKQRADSRESLKPAAKPL
PSKSVRKESKEETPEVTKVNHVEKPPKVESKEKVMVKKDKPIKTETKPSVTEKEVPSKEEPSPVKAEVA
EKQATDVKPKAAKEKTVKKETKVKPEDKKEEKEKPKKEVAKKEDKTPIKKEEKPKKEEVKKEVKKEIKK
EEKKEPKKEVKKETPPKEVKKEVKKEEKKEVKKEEKEPKKEIKKLPKDAKKSSTPLSEAKKPAALKPKV
PKKEESVKKDSVAAGKPKEKGKIKVIKKEGKAAEAVAAAVGTGATTAAVMAAAGIAAIGPAKELEAERS
LMSSPEDLTKDFEELKAEEVDVTKDIKPQLELIEDEEKLKETEPVEAYVIQKEREVTKGPAESPDEGIT
TTEGEGECEQTPEELEPVEKQGVDDIEKFEDEGAGFEESSETGDYEEKAETEEAEEPEEDGEEHVCVSA
SKHSPTEDEESAKAEADAYIREKRESVASGDDRAEEDMDEAIEKGEAEQSEEEADEEDKAEDAREEEYE
PEKMEAEDYVMAVVDKAAEAGGAEEQYGFLTTPTKQLGAQSPGREPASSIHDETLPGGSESEATASDEE
NREDQPEEETATSGYTQSTIEISSEPTPMDEMSTPRDVMSDETNNEETESPSQEFVNITKYESSLYSQE
YSKPADVTPLNGFSEGSKTDATDGKDYNASASTISPPSSMEEDKFSRSALRDAYCSEVKASTTLDIKDS
ISAVSSEKVSPSKSPSLSPSPPSPLEKTPLGERSVNFSLTPNEIKVSAEAEVAPVSPEVTQEVVEEHCA
SPEDKTLEVVSPSQSVTGSAGHTPYYQSPTDEKSSHLPTEVIEKPPAVPVSFEFSDAKDENERASVSPM
DEPVPDSESPIEKVLSPLRSPPLIGSESAYESFLSADDKASGRGAESPFEEKSGKQGSPDQVSPVSEMT
STSLYQDKQEGKSTDFAPIKEDFGQEKKTDDVEAMSSQPALALDERKLGDVSPTQIDVSQFGSFKEDTK
MSISEGTVSDKSATPVDEGVAEDTYSHMEGVASVSTASVATSSFPEPTTDDVSPSLHAEVGSPHSTEVD
DSLSVSVVQTPTTFQETEMSPSKKKCPRPMSISPPDFSPKTAKSRTPVQDHRSEQSSMSIEFGQESPEQ
SLAMDFSRQSPDHPTVGAGVLHITENGPTEVDYSPSDMQDSSLSHKIPPMEEPSYTQDNDLSELISVSQ
VEASPSTSSAHTPSQIASPLQEDTLSDVAPPRDMSLYASLTSEKVQSLEGEKLSPKSDISPLTPRESSP
LYSPTFSDSTSAVKEKTATCHSSSSPPIDAASAEPYGFRASVLFDTMQHHLALNRDLSTPGLEKDSGGK
TPGDFSYAYQKPEETTRSPDEEDYDYESYEKTTRTSDVGGYYYEKIERTTKSPSDSGYSYETIGKTTKT
PEDGDYSYEIIEKTTRTPEEGGYSYDISEKTTSPPEVSGYSYEKTERSRRLLDDISNGYDDSEDGGHTL
GDPSYSYETTEKITSFPESEGYSYETSTKTTRTPDTSTYCYETAEKITRTPQASTYSYETSDLCYTAEK
KSPSEARQDVDLCLVSSCEYKHPKTELSPSFINPNPLEWFASEEPTEESEKPLTQSGGAPPPPGGKQQG
RQCDETPPTSVSESAPSQTISIVPFEIESCPSITADANIDSEDESETIPTDKTVTYKHMDPPPAPVQDR
SPSPRHPDVSMVDPEALAIEQNLGKALKKDLKEKTKTKKPGTKTKSSSPVKKSDGKSKPLAASPKPAGL
KESSDKVSRVASPKKKESVEKAAKPTTTPEVKAARGEEKDKETKNAANASASKSAKTATAGPGTTKTTK
SSAVPPGLPVYLDLCYIPNHSNSKNVDVEFFKRVRSSYYVVSGNDPAAEEPSRAVLDALLEGKAQNGSN
MQVTIIPTHDSEVMREWYQETHEKQQDLNIMVLASSSTVVMQDESFPACKIEL

FIG. 9

Microtubule-associated protein 1A [Homo sapiens]

MDGVAEFSEYVSETVDVPSPFDLLKPPTSGGFLKLSKPCCYIFPGGRGDSALFAVNGFNILVDGGSDRK
SCFWKLVRHLDRIDSVLLTHIGADNLPGINGLLQRKVAELEESQFQGSSSYSDWVKNLISPELGVVFFN
VPEKLRLPDASRKAKRSIEEACLTLQHLNRLGIQAEPLYRVVSNTIEPLTLFHKMGVGRLDMYVLNPVK
DSKEMQFLMQKWAGNSKAKTGIVLPNGKEAEISVPYLTSITALVVWLPANPTEKIVRVLFPGNAPQNKI
LEGLEKLRHLDFLRYPVATQKDLASGAVPTNLKPSKIKQRADSKESLKATTKTAVSKLAKREEVVEEGA
KEARSELAKELAKTEKKAKESSEKPPEKPAKPERVKTESSEALKAEKRKLIKDKVGKKHLKEKISKLEE
KKDKEKKEIKKERKELKKDEGRKEEKKDAKKEEKRKDTKPELKKISKPDLKPFTPEVRKTLYKAKVPGR
VKIDRSRAIRGEKELSSEPQTPPAQKGTVPLPTISGHRELVLSSPEDLTQDFEEMKREERALLAEQRDT
GLGDKPFPLDTAEEGPPSTAIQGTPPSVPGLGQEEHVMKEKELVPEVPEEQGSKDRGLDSGAETEEEKD
TWEEKKQREAERLPDRTEARREESEPEVKEDVIEKAELEEMEEVHPSDEEEEDATKAEGFYQKHMQEPLK
VTPRSREAFGGRELGLQGKAPEKETSLFLSSLTTPAGATEHVSYIQDETIPGYSETEQTISDEEIHDEP
EERPAPPRFHTSTYDLPGPEGAGPFEASQPADSAVPATSGKVYGTPETELTYPTNIVAAPLAEEEHVSS
ATSITECDKLSSFATSVAEDQSVASLTAPQTEETGKSSLLLDTVTSIPSSRTEATQGLDYVPSAGTISP
TSSLEEDKGFKSPPCEDFSVTGESEKRGEIIGKGLSGERAVEEEEEETANVEMSEKLCSQYGTPVFSAP
GHALHPGEPALGEAEERCLSPDDSTVKMASPPPSGPPSATHTPFHQSPVEEKSEPQDFQEADSWGDTKR
TPGVGKEDAAEETVKPGPEEGTLEKEEKVPPPRSPQAQEAPVNIDEGLTGCTIQLLPAQDKAIVFEIME
AGEPTGPILGAEALPGGLRTLPQEPGKPQKDEVLRYPDRSLSPEDAESLSVLSVPSPDTANQEPTPKSP
CGLTEQYLHKDRWPEVSPEDTQSLSLSEESPSKETSLDVSSKQLSPESLGTLQFGELNLGKEEMGHLMQ
AEDTSHHTAPMSVPEPHAATASPPTDGTTRYSAQTDITDDSLDRKSPASSFSHSTPSGNGKYLPGAITS
PDEHILTPDSSFSKSPESLPGPALEDIAIKWEDKVPGLKDRTSEQKKEPEPKDEVLQQKDKTLEHKEVV
EPKDTAIYQKDEALHVKNEAVKQQDKALEQKGRDLEQKDTALEQKDKALEPKDKDLEEKDKALEQKDKI
PEEKDKALEQKDTALEQKDKALEPKDKDLEQKDRVLEQKEKIPEEKDKALDQKVRSVEHKAPEDTVAEM
KDRDLEQTDKAPEQKHQAQEQKDKVSEKKDQALEQKYWALGQKDEALEQNIQALEENHQTQEQESLVQE
DKTRKPKMLEEKSPEKVKAMEEKLEALLEKTKALGLEESLVQEGRAREQEEKYWRGQDVVQEWQETSPT
REEPAGEQKELAPAWEDTSPEQDNRYWRGREDVALEQDTYWRELSCERKVWFPHELDGQGARPHYTEER
ESTFLDEGPDDEQEVPLREHATRSPWASDFKDFQESSPQKGLEVERWLAESPVGLPPEEEDKLTRSPFE
IISPPASPPEMVGQRVPSAPGQESPIPDPKLMPHMKNEPTTPSWLADIPPWVPKDRPLPPAPLSPAPGP
PTPAPESHTPAPFSWGTAEYDSVVAAVQEGAAELEGGPYSPLGKDYRKAEGEREEEGRAEAPDKSSHSS
KVPEASKSHATTEPEQTEPEQREPTPYPDERSFQYADIYEQMMLTGLGPACPTREPPLGAAGDWPPCLS
TKEAAAGRNTSAEKELSSPISPKSLQSDTPTFSYAALAGPTVPPRPEPGPSMEPSLTPPAVPPRAPILS
KGPSPPLNGNILSCSPDRRSPSPKESGRSHWDDSTSDSELEKGAREQPEKEAQSPSPPHPIPMGSPTLW
PETEAHVSPPLDSHLGPARPSLDFPASAFGFSSLQPAPPQLPSPAEPRSAPCGSLAFSGDRALALAPGP
PTRTRHDEYLEVTKAPSLDSSLPQLPSPSSPGAPLLSNLPRPASPALSEGSSSEATTPVISSVAERFSP
SLEAAEQESGELDPGMEPAAHSLWDLTPLSPAPPASLDLALAPAPSLPGDMGDGILPCHLECSEAATEK
PSPFQVPSEDCAANGPTETSPNPPGPAPAKAENEEAAACPAWERGAWPEGAERSSRPDTLLSPEQPVCP
AGGSGGPPSSASPEVEAGPQGCATEPRPHRGELSPSFLNPPLPPSIDDRDLSTEEVRLVGRGGRRRVGG
PGTTGGPCPVTDETPPTSASDSGSSQSDSDVPPETEECPSITAEAALDSDEDGDFLPVDKAGGVSGTHH
PRPGHDPPPLPQPDPRPSPPRPDVCMADPEGLSSESGRVERLREKEKVQGRVGRRAPGKAKPASPARRL
DLRGKRSPTPGKGPADRASRAPPRPRSTTSQVTPAEEKDGHSPMSKGLVNGLKAGPMALSSKGSSGAPV
YVDLAYIPNHCSGKTADLDFFRRVRASYYVVSGNDPANGSPSRAVLDALLKGSAQWGENLQVTLIEKEK
TEVTREWYQQTHEQQQQLNVLSRASYSVVMQIESFPASSLF

FIG. 10

Pt No/Sex/ Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
1/f/69	LES, Brain stem encephalitis, nausea, vomiting, dysautonomia	CCN,CCPQ	Yes	No	SCLC/prior	NA	NA	NA	NA
2/f/82	Sensory motor neuropathy and ataxia	ARBi, GAD-65	NA	NA	NA	NA	NA	NA	NA
3/f/72	Sensory motor neuropathy, ataxia and LES	CCPQ	Yes	No	SCLC/follow	NA	NA	NA	Steroids/NA
4/f/60	Limbic encephalitis, seizures and myelitis	CCPQ, Alpha3, GAD 65	Yes	No	SCLC/follow	HC lesion	NA	NA	NA
5/f/62	ataxia	GAD 65, CCN, CCPQ	Yes	No	NSCLC/follow	NL	NA	NA	NA
6/m/66	Sensory neuropathy, ataxia and hand dystonia	Amphiphysin	NA	NA	Renal */prior	NA	NA	NL	Chemo/NA
7/f/68	Cerebellar		NA	NA	SCLC/follow	NA	NA	Lymphocytosis **	Chemo/Yes
8/f/73	Ataxia and sensory neuropathy		Yes	No	Breast */follow	SVD	NL	1/37/1/12	CTX/Yes
9/f/68	Painful neuropathy		NA	NA	Skin SQ/prior	NA	NA	NA	NA
10/f/74	Diffuse pain	Alpha-3	NA	NA	SCLC/prior	NA	NL	NL*	Chemo/NA
11/f/49	Painful peripheral neuropathy	CRMP-5, GAD-65, CCN	NA	NA	Pancreas SCC/follow	NA	NA	NA	Res/NA
12/f/76	NA	NA	NA	NA	NA	NA	NA	NA	NA
13/m/44	Ataxia and autonomic dysfunction	CRMP-5, alpha-3	NA	NA	SCLC/follow	NA	NA	NA	NA
14/f/74	Peripheral neuropathy, LEMS and encephalopathy	CCPQ, GAD-65	Yes	No	SCLC/follow	NA	NA	NA	NA

FIG. 10 (cont.)

Pt No/Sex/Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
15/m/77	Sensory motor peripheral neuropathy and dysarthria	CRMP-5, GAD-65, CCPQ, CCN	Yes	NA	SCLC/follow	NA	NA	18/97/NA/I**	Chemo/yes
16/f/39	myelopathy	GAD-65	NA	NA	Breast */prior	Demyelination	NA	0/NL/3/I**	Chemo+res/NA
17/m/77	Encephalopathy, cerebellar and autonomic	GAD-65	Yes	NA	Prostate */prior	Meningeal enhancement	NL	75/203/2/1.29	Steroids/Yes
18/m/80	Limbic encephalitis, motor weakness	CRMP-5, STR, GAD-65, VGKC	Yes	NA	NA	NA	NA	I**/I**/NA/NA	NA
19/m/88	LEMS and encephalopathy	CCPQ, CCN	Yes	MAP1B-2	SCLC/at	NA	NA	NA	NA
20/f/61	NA	CCPQ, GAD-65	Yes	NA	NA	NA	NA	NA	NA
21/m/73	Limbic encephalitis		Yes	No	SCLC/prior	NA	NA	NA	NA
22/m/70	Left extremities weakness and paresthesia		Yes	NA	NSCLC/at	NA	NA	NA	Radiation/N.A
23/f/72	Bilateral optic neuropathy and peripheral neuropathy	CRMP-5	Yes	NA	SCLC/prior	Enhancement of optic nerves	NA	162/84/NA/NA	Steroids/Yes
24/m/72	Suspected LEMS	CCPQ, GAD-65	Yes	NA	SCLC/follow	NA	NA	NA	NA
25/f/64	Painful sensory neuropathy	VGKC, Amphi	Yes	NA	SCLC/follow	NA	NA	NA	NA
26/m/59	Cerebellar ataxia dysarthria and blurred vision	CCPQ	Yes	NA	NA	NA	NA	NA	NA

FIG. 10 (cont.)

Pt No/Sex/ Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
27/m/72	Diplopia and peripheral neuropathy with weakness		Yes	No	SCLC/at	NL	NA	NA	Chemo/NA
28/m/62	Peripheral neuropathy	CCN, CCPQ	Yes	NA	SCLC/follow	NA	NA	NA	NA
29/f/64	Pan cerebellar	CRMP-5	Yes	NA	SCLC/prior	Cerebellar atrophy	NA	NA	Chemo+rad/No
30/m/75	Limbic encephalitis	ANNA-1, CRMP-5	Yes	NA	NSCLC/follow	Temporal and parietal lobes signal abnormalities	NA	1/58/1/I	NA
31/m/77	Ataxia	GAD-65, VGKC	Yes	NA	Lung SQ/at	NA	NA	NA	Chemo+rad/NA
32/f/81	Lethargy and generalized weakness		No		SCLC/follow	NA	NA	NA	NA
33/m/62	NA	ANNA-1, CCPQ, VGKC	Yes	NA	NA	NA	NA	NA	NA
34/m/66	NA	CRMP-5, CCPQ	Yes	MAP1B-2	NA	NA	NA	NA	NA
35/f/66	Limbic encephalitis, ataxia, sensory neuropathy, chorea, decreased vision	CRMP-5, Amphi	Yes	NA	SCLC/follow	T2 hyperintencities in the basal ganglia	NA	6/39/NA/NA	Chemo+steroids /stable†
36/f/66	Sensory neuropathy and spasms	ANNA-1	Yes	NA	No	NL	NA	NA	Steroids/No
37/m/69	Ataxia and diplopia, abnormal eye movements	ANNA-1, GAD-65	Yes	NA	SCLC/follow	SVD	NA	NA	No/NA

FIG. 10 (cont.)

Pt No/Sex/ Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
38/f/65	Sensory motor polyneuropathy	CRMP-5	Yes	NA	NA	NA	NA	NA	NA
39/m/71	Ataxia + sensory motor peripheral neuropathy	CRMP-5	Yes	NA	SCLC/follow	NA	NA	10/NA/NA/NA	NA
40/f/61	Seizures and transverse myelitis		Yes	NA	No	NL	NA	I*/NA/I*/NA	NA
41/f/64	Ataxia	STR, ANNA-1, CRMP-5	Yes	NA	SCLC/prior	NA	NA	NA	Chemo+rad/NA
42/m/75	Ataxia and bilateral optic neuritis	CRMP-5, ANNA-1, CCN	Yes	NA	SCLC/at	SVD	NA	4/83/1/NA	Chemo, steroids, CTX/Yes
43/m/70	Widespread pain		NA	NA	SCLC/follow	NA	NA	NA	Chemo/Yes
44/f/79	Limbic encephalitis	ANNA-1	Yes	NA	No	Temporal hyperintencities and hippocampal atrophy	NA	1/54/NA/NA	No
45/m/73	Ataxia + blurred vision	GAD-65	Yes	NA	SCLC/NA	NL	NA	No	NA
46/f/73	Ptosis and eye deviation		NA	NA	NA	NA	NA	NA	Steroids, IVIG, PLX/No
47/m/75	Gastrointestinal dysmotility		NA	NA	NCSLC	NA	NA	NA	NA
48/f/57	Seizures and aphasia	CCPQ, AGNA-1	NA	NA	NA	NA	NA	NA	NA
49/f/65	Ataxia, dysarthria and diplopia	CRMP-5	Yes	NA	SCLC/follow	Atrophy	NA	2/60/3/0.6	Chemo, steroids/stable†
50/f/59	Ataxia	ANNA-1	Yes	NA	SCLC/at	NA	NA	NA	Chemo, steroids/No
51/m/80	Sensory motor peripheral neuropathy		Yes	MAP1B-2	Lung */follow	NA	NA	NA	NA

FIG. 10 (cont.)

Pt No/Sex/Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
52/m/63	Peripheral motor neuropathy, visual disturbance and sensory level	CRMP-5, CCPQ, CCN	Yes	NA	SCLC/prior	NA	NA	NA	PLX/No
53/m/74	NA	NA	NA	NA	NA	NA	NA	NA	NA
54/f/81	Sensory motor neuropathy/radiculopathy, ataxia, seizures		Yes	MAP1B-2, 4, 5, MAP1A-1	No	NOS/SVD	NA	6/66/7/0.65	CTX/steroids/Yes
55/f/57	NA	VGKC	Yes	No	NA	NA	NA	NA	NA
56/f/68	Confusion and paranoia	ANNA-1	Yes	NA	SCLC/NA	diffuse white matter abnormalities	NA	NL/NL/NA/NA	Chemo/Yes
57/m/53	Cerebellar	CRMP-5	Yes	NA	NA	NA	NA	NA	NA
58/m/52	Ataxia and sensory neuropathy	CRMP-5	Yes	NA	No	mild atrophy	hyperintence lesions with enhancement	4/54/I/NA	Steroids/Yes
59/m/73	Limbic encephalitis, gait unsteadiness	ANNA-1	Yes	NA	SCLC/follow	atrophy and scattered T2 white matter hyperintensities	mild contrast prominence in the inferior thoracic spine	8/112/NA/NA	Chemo, steroids/Yes
60/m/69	Ataxia, transverse myelitis		Yes	MAP1B-2, 4, 5, MAP1A-3, 5	SCLC/NA	NA	subtle changes on cord	NA	NA
61/f/84	Subacute cognitive decline	ANNA-1, Amphi, VGKC	NA	NA	No	NA	NA	NA	NA

FIG. 10 (cont.)

Pt No/Sex/Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
62/f/51	NA	NA	NA	NA	NA	NA	NA	NA	NA
63/m/74	NA	CCN, CCPQ,	Yes	MAP1B-2, 4	NA	NA	NA	NA	NA
64/f/53	Cerebellar ataxia and encephalopathy	GAD-65	Yes	MAP1A-2	SCLC/follow	NA	NA	NA	Chemotherapy/stable†
65/m/41	Sensory ataxia with cerebellar involvement	GABA-B, CCN	Yes	NA	No	NA	NA	NA	NA
66/f/63	NA	Alpha-3	Yes	MAP1B-2	NA	NA	NA	NA	NA
67/f/82	Peripheral neuropathy		Yes	No	No	NA	NA	NA	NA
68/f/67	Motor axonal neuropathy	CRMP-5	Yes	NA	SCLC/follow	NA	NL	NA	NA
69/f/32	NA		NA	NA	No	multiple lesion	NA	NA	NA
70/m/61	Sensory motor peripheral neuropathy, clumsiness of hands and ataxia	CCPQ, VGKC	NA	NA	SCLC/follow	NOS	patchy areas of increased T2 signal with enhancement, meningeal enhancement.	22/102/3/1.45	Chemo+rad/Yes
71/m/67	LEMS	CCPQ, ARBi	NA	NA	NA	NA	NA	NA	NA
72/m/74	Weakness of lower extremities and general weakness		Yes	MAP1B-2, 5	Lung SQ/at	NA	NA	NA	Chemo+rad/NA
73/m/65	Demyelinating sensory motor peripheral neuropathy	CCPQ	Yes	No	SCLC/prior	NA	NA	NA	NA
74/m/68	NA	CRMP-5, ANNA-1	Yes	NA	NA	NA	NA	NA	NA
75/m/74	Vision loss - retinopathy		Yes	No	Liver adenocarcinoma/follow	NA	NA	NA	Chemo/No

FIG. 10 (cont.)

Pt No/Sex/Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
76/m/57	NA	CCPQ, CCN	Yes	MAP1B-2, 4	NA	NA	NA	NA	NA
77/m/75	NA		NA	NA	NA	NA	NA	NA	NA
78/m/66	Gait ataxia and leg weakness	CRMP-5, GAD-65	Yes	NA	SCLC/follow	NA	NA	NA	NA
79/m/73	NA	CCPQ, CCN	Yes	NA	NA	NA	NA	NA	NA
80/m/64	NA	ANNA-1	Yes	NA	NA	NA	NA	NA	NA
81/m/69	NA		Yes	MAP1B-5	NA	NA	NA	NA	NA
82/m/62	Sensory motor peripheral neuropathy, cognitive decline, hallucinations,		Yes	NA	Lung */follow	SVD	NA	NL/NL/I/NA	PLX,CPT/Yes
83/f/67	Dysautonomia	CRMP-5	Yes	NA	Breast *, ovary */prior	NA	NA	NA	NA
84/m/71	NA		Yes	MAP1B-2	NA	NA	NA	NA	NA
85/m/57	Paresthesia, small fiber neuropathy, chorea	CRMP-5, alpha-3	Yes	NA	SCLC/follow	NL	NA	NL/NL/NL/NA	Chemo, steroids/Yes
86/m/83	Confusion and delirium		Yes	MAP1B-2, MAP1A-3	Prostate */follow	Atrophy	NA	149/I/NA/NA	Res/minimal ‡
87/f/74	NA	CRMP-5, CCN	Yes	NA	NA	NA	NA	NA	NA
88/f/71	NA		Yes	MAP1B-2	NA	NA	NA	NA	NA
89/m/82	Sensory motor peripheral neuropathy	GAD-65	Yes	MAP1B-2	Lung */NA	NA	NA	NA	Chemo, PLX/stable†
90/m/27	Vision loss - retinopathy	GAD-65, alpha-3, CCN, VGKC	Yes	NA	Ewing sarcoma/follow	NA	NA	NA	RTX+steroids
91/m/49	Ataxia and hand clumsiness	VGKC, alpha-3, CCN	NA	NA	NSCLC/follow	NA	NA	NA	NA
92/m/89	Sub-acute myelopathy, gait disturbance	STR	Yes	MAP1B-2, MAP1A-3	Nasopharyngeal adenocarcinoma/at	non enhancing lesion	NA	NA	Steroids/Yes

FIG. 10 (cont.)

Pt No/Sex/ Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
93/m/72	Progressive weakness		Yes	MAP1B-2, MAP1A-3, 4	No	NA	NA	NA	NA
94/f/72	Peripheral neuropathy and ataxia	ANNA-1, CRMP-5, CCPQ	Yes	NA	SCLC/NA	cerebellar atrophy	NA	NA	NA
95/f/50	Stiffness and generalized pain		Yes	No	Lung adenocarcinoma/prior	NL	metastasis	NA	Chemo, steroids/No
96/f/24	Pseudo-obstruction	ANNA-1, CRMP-5, STR	Yes	MAP1B-2	No	NA	NA	NA	NA
97/m/58	Inflammatory myopathy	STR, ARBi	Yes	No	No	NA	Thoracic spine lesion-T10-11 bad disc bulge.	NA	Steroids/Yes
98/m/70	Limbic encephalitis		NA	NA	SCLC/follow	NA	NA	NA	NA
99/m/76	Ataxia and Oscillopsia	CRMP-5, STR, ARBi	Yes	NA	SCLC/follow	NA	NA	74/86/NA/NA	NA
100/m/68	Sensory motor peripheral neuropathy		Yes	No	No	SVD	NL	2/50/NA/NA	NA
101/f/67	Limbic encephalitis, seizures	GABA-B, AMPA, CCN	Yes	NA	Lung */NA	NA	NA	NA	Chemo/NA
102/f/60	NA	CCN, CCPQ, GABA-B	Yes	NA	NA	NA	NA	NA	NA
103/f/79	Memory decline and headache		Yes	MAP1B-2	No	NL	NA	NA	NA
104/f/75	NA	GAD-65	Yes	NA	NA	NA	NA	NA	NA
105/f/81	Diplopia and ptosis		Yes	MAP1B-2, 4	SCLC/follow €	NA	NA	NA	NA
106/f/57	Bilateral optic neuritis and uveitis, limb numbness		Yes	MAP1B-2, 5	SCLC/follow	Swelling of the optic nerves	NA	NA	Chemo/Yes

FIG. 10 (cont.)

Pt No/Sex/Age	Clinical syndrome	Additional antibodies	MAP1B pos	Additional MAPs pos	Cancer/time of diagnosis	MRI brain	MRI spine	CSF WCC*/Pro/OCBs/ IgG I	Treatment /response
107/f/63	Memory decline	AGNA-1, CCPQ	Yes	NA	Thymoma	NL	NA	NA	NA
108/f/70	NA		No		NA	NA	NA	NA	NA
109/m/32	NA		Yes	NA	NA	NA	NA	NA	NA
110/m/74	NA		Yes	MAP1B-2, 5	NA	NA	NA	NA	NA
111/f/62	Hemi Chorea	CRMP-5, STR, ARBi, AMPA	NA	NA	Thymoma	NL	NA	NA	NA
112/f/22	Paresthesia in arms		NA	NA	Large cell anaplastic lymphoma/prior	NL	NL * (brachial plexitis)	NA	NA
113/m/69	Ataxia and involuntary movements in all limbs and mouth	CCN	Yes	No	Lung */follow ф	Caudate atrophy	NA	NA	Steroids, PLX/Yes
114/f/63	Myelopathy, sensory neuropathy and visual disturbance	CRMP-5	Yes	NA	Lung* /NA ф	Mild volume loss	NL	NL/I/NA/NA	Steroids, PLX, IVIG/No
115/m/74	Flaccid weakness, diplopia and depression	CRMP-5	Yes	NA	No ¥	NL	NL	33/43/NA/NA	PLX, IVIG/No
116/m/65	Confusion, altered mental status and diplopia	ANNA-1, CRMP-5, GAD-65	Yes	NA	No ¥ £	Some T2 changes around the aqueduct.	NL	10/47//NA/NL	IVIG/No
117/m/71	Ataxia, numbness in all limbs		Yes	NA	No ¥	NOS	NA	NA	NA
118/m/70	Altered mental status		Yes	NA	NSCLC/at	NL	NA	NA	Chemo/NA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/51152

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C12Q 1/68; G01N 33/68, 33/53, 33/574 (2017.01)
CPC - G01N 33/6896, 33/5308, 33/564; C07K16/18; C12Q 1/6883

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	(GUPTA, HV et al.) Purkinje Cell Cytoplasmic Antibody (PCA-2)-related Chorea-Dystonia Syndrome. Tremor and other hyperkinetic movements. 24 September 2016, Vol. 6, No. 420; page 1, 1st column, 1st and 2nd paragraphs; page 3, 1st column, 1st paragraph; DOI: 10.7916/D8SX6DFJ	15, 17-18 ------------ 19
Y	(ROSENFELD, MR et al.) Diagnosis and Management of Paraneoplastic Neurologic Disorders. Current Treatment Options in Oncology. December 2013, Vol. 14, No. 4; pages 528-538; page 4, 1st paragraph; DOI: 10.1007/s11864-013-0249-1	19
A	(JARIUS, S et al.) 'Medusa head ataxia': the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 3: Anti-Yo/CDR2, anti-Nb/AP3B2, PCA-2, anti-Tr/DNER, other antibodies, diagnostic pitfalls, summary and outlook. Journal of Neuroinflammation. 17 September 2015, Vol. 12, No. 168; page 8, 2nd column, 5th paragraph; page 9, 1st column, 4th and 5th paragraph; DOI: 10.1186/s12974-015-0358-9	1-14, 16
A	WO 2011/160096 A2 (BANYAN BIOMARKERS, INC). 22 December 2011; paragraph [0032], Table 1	1-14, 16
A	(JONES, AL et al.) Responses to and Outcomes of Treatment of Autoimmune Cerebellar Ataxia in Adults. JAMA Neurology. November 2015, EPUB 28 September 2015, Vol. 72, No. 11; pages 1304-1312; page 1305, 1st column, 4th and 5th paragraphs; page 1306, 2nd column, 5th paragraph; DOI: 10.1001/jamaneurol.2015.2378	1-14, 16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search
7 November 2017 (07.11.2017)

Date of mailing of the international search report
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Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer
Shane Thomas
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/51152

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/268252 A1 (BANYAN BIOMARKERS, INC). 24 September 2015; paragraph [0095], Table 4.	1-10
A	CN 1339494 A (YUMIN, M et al.) 13 March 2002; abstract	11-14, 16
P, X	(GADOTH, A et al.) Microtubule-Associated Protein 1B: Novel Paraneoplastic Biomarker. Annals of Neurology. February 2017, Vol. 81, No. 2; pages 266-277; DOI: 10.1002/ana.24872	1-19
P, X	(GADOTH, A et al.) Microtubule Associated Protein (MAP) 1B: Antigen of PCA-2 IgG, Biomarker of Small-Cell Lung Carcinoma-related Paraneoplastic Neurological Autoimmunity. Neurology. 18 April 2017, Vol. 88, No. 16; Supplement S41.007	1-19

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专利名称(译)	评估和治疗癌症的材料和方法		
公开(公告)号	[EP3519592A4]()	公开(公告)日	2020-05-13
申请号	EP2017857186	申请日	2017-09-12
[标]申请(专利权)人(译)	梅约医学教育与研究基金会		
申请(专利权)人(译)	梅奥基金会的医学教育和研究		
当前申请(专利权)人(译)	梅奥基金会的医学教育和研究		
[标]发明人	PITTOCK SEAN J KRYZER THOMAS J GADOTH AVI MCKEON ANDREW LENNON VANDA A FRYER JAMES P		
发明人	PITTOCK, SEAN J. KRYZER, THOMAS J. GADOTH, AVI MCKEON, ANDREW LENNON, VANDA A. FRYER, JAMES P.		
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优先权	62/400420 2016-09-27 US		
其他公开文献	EP3519592A1		
外部链接	[Espacenet]()		

摘要(译)

该文献提供了用于检测PCA-2特异性自身抗体的方法和材料，其可能与副肿瘤神经疾病和与PCA-2特异性自身抗体有关的癌症有关。