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Literature-related discovery (LRD): Potential treatments for Multiple Sclerosis[☆]

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Abstract

Literature-related discovery (LRD) is the linking of two or more literature concepts that have heretofore not been linked (i.e., disjoint), in order to produce novel, interesting, plausible, and intelligible knowledge (i.e., potential discovery). The open discovery systems (ODS) component of LRD starts with a problem to be solved, and generates solutions to that problem through potential discovery. We have been using ODS LRD to identify potential treatments or preventative actions for challenging medical problems, among myriad other applications. The previous three papers in this Special Issue describe the application of ODS LRD to Raynaud's Phenomenon (RP), cataracts, and Parkinson's Disease (PD).

Multiple Sclerosis (MS) is a progressive neurodegenerative disorder (typically preceded by periods of remission and relapse), affecting mainly people in their early-mid life. MS is characterized by changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, or difficulty to move; difficulties with coordination and balance (ataxia); problems in speech (Dysarthria) or swallowing (Dysphagia), visual problems (Nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, bladder and bowel difficulties, cognitive impairment, or emotional symptomatology (mainly depression).

We selected the subject of MS because of its global prevalence, and its apparent intractability to all treatments except for palliative remediation mainly through drugs or surgery. Our first goal was to identify non-drug non-surgical treatments that would 1) prevent the occurrence, or 2) reduce the progression rate, or 3) stop the progression, or 4) maybe even reverse the progression, of MS. Our second goal was to demonstrate that we could again solve an ODS problem (using LRD) with no prior knowledge of any results or prior work (unlike the case of

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the RP problem). As in the ‘cataract’ and PD examples, we used the MeSH taxonomy of MEDLINE to restrict potential discoveries to selected semantic classes, and to identify potential discoveries efficiently. Our third goal was to generate large amounts of potential discovery in more than an order of magnitude less time than required for the RP study. The discovery generation methodology has been developed to the point where ODS LRD problems can be solved with no results or knowledge of any prior work.

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1. Introduction

1.1. Overview

The previous three papers in this Special Issue describe the application of ODS LRD to Raynaud’s Phenomenon (RP) [1], cataracts [2], and Parkinson’s Disease (PD) [3]. The present paper presents a comprehensive approach for systematic acceleration of potential discovery, and demonstrates the generation of large amounts of potential discovery for treatment of MS. The definitions of discovery and innovation and the approach background were shown in the first paper of this Special Issue [4], and the approach methodology was shown in the second paper [5]. The present paper provides an overview of the etiology and treatment of MS, then proceeds to retrieve and analyze the core MS literature, and literatures related directly and indirectly to the core MS literature. These related literatures contain the seeds of potential discovery for MS, and some examples of potential discovery are presented for both classes of related literatures. Also, examples of interesting but non-discovery concepts from the core MS literature are presented, since they have practical value in their own right.

1.2. Purpose of study

MS is a progressive neurodegenerative disorder (typically preceded by periods of remission and relapse), affecting mainly people in their early-mid life. It is characterized by changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, or difficulty to move; difficulties with coordination and balance (ataxia); problems in speech (Dysarthria) or swallowing (Dysphagia), visual problems (Nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, bladder and bowel difficulties, cognitive impairment, or emotional symptomatology (mainly depression). We selected the subject of MS because of its global prevalence, and its apparent intractability to all treatments except for palliative remediation mainly through drugs or surgery. Our main goal was to identify non-drug non-surgical treatments that would 1) prevent or delay the onset, or 2) reduce the progression rate, or 3) stop the progression, or 4) maybe even reverse the progression of MS. A second goal was to demonstrate that we could solve an ODS LRD problem with no prior knowledge of any results or prior work, and that we could use more elements of our flow chart process without decrementing our streamlined process [5] significantly. We used the MeSH taxonomy of MEDLINE to restrict potential discoveries to selected

semantic classes. Before proceeding to describe our specific approach and results, we summarize the medical issues and mainline treatments for MS.

2. Multiple Sclerosis background

2.1. Overview

MS (also known as disseminated sclerosis or encephalomyelitis disseminata) is a chronic, inflammatory, demyelinating disease that affects the central nervous system (CNS) [6]. MS can cause a variety of symptoms, including changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, cognitive impairment, problems with balance, overheating, and pain. MS will cause impaired mobility and disability in more severe cases [7].

MS may take several different forms, with new symptoms occurring either in discrete attacks or slowly accruing over time. Clinically, most patients present with a relapsing–remitting course, which correlates initially with an inflammatory phase of the disease. Later, it becomes more of a neurodegenerative phase, called secondary progressive. Between attacks, symptoms may resolve completely, but permanent neurologic problems often persist, especially as the disease advances [8]. MS currently does not have a cure. Several treatments are available that may slow the appearance of new symptoms, although these treatments have their own side-effects.

MS affects an estimated 300,000 people in the United States and probably more than 1 million people around the world — including twice as many women as men [9]. Most people experience their first signs or symptoms between ages 20 and 40. A significantly higher incidence of the disease is found in the northernmost latitudes of the northern and the southern hemispheres compared to southernmost latitudes. This observation is based on the incidence of the disease in Scandinavia, northern United States and Canada, as well as Australia and New Zealand [10].

2.2. Pathology

MS affects neurons, the cells of the brain and spinal cord that carry information, create thought and perception, and allow the brain to control the body. Surrounding and protecting some of these neurons is a fatty layer known as the myelin sheath, which helps neurons carry electrical signals. MS causes gradual destruction of myelin (demyelination) and transection of neuron axons in patches throughout the brain and spinal cord. The name MS refers to the multiple scars (or scleroses) on the myelin sheaths. This scarring causes symptoms that vary widely, depending upon which signals are interrupted.

Pathologically, MS is characterized by the presence of areas of demyelination and T-cell predominant perivascular inflammation in the brain white matter. Some axons may be spared from these pathological processes.

The severity of demyelination may be assessed by relative preservation or destruction of oligodendroglia. It is demonstrated that early in the course of the disease more oligodendroglia are preserved in the plaque; thus, some degree of remyelination remains possible. In other patients, there is a complete loss of oligodendroglia. In this group of patients, possibility of remyelination is dramatically decreased [11].

Whatever route the pathological process takes from inflammation to demyelination, the effects of myelin loss by the nerve fibers are quite dramatic. Saltatory conduction is much more energy efficient

than nerve impulses transmitted along the entire length of the nerve fiber. Loss of myelin results in one or all of the following:

- conduction block at the site of lesion
- slower conduction time along the affected nerve
- increased subjective feeling of fatigue secondary to compensation for neurologic deficits.

The primary triggers of inflammation result in auto-reactive cells being made. Then, the disease can go into a quiescent phase until secondary triggers come about. Blood–brain barrier permeability increases after secondary triggers have acted [12]. Then, there is amplification of the immune response, which goes into the inflammatory phase of the disease. If the inflammatory phase of the disease has not halted after several relapses and phases, it goes into a degenerative phase. With demyelination, there is also axonal loss with scarring, probably the most significant factor in disability.

There is evidence of blood–brain barrier disruption in the inflammatory stage of the disease. With peripheral initiation of disease and the secondary triggers coming in, activation and disruption of blood–brain barrier occur. The immune cells upregulate cell adhesion molecules of the blood–brain barrier, expediting cell entry and ingress of activated lymphocyte trafficking.

The blood–brain barrier consists of specialized endothelial cells with tight junctions. It is under the control of several adhesion cell molecules that allow trafficking of certain cells and controls, even solute trafficking of most substances. The process of lymphocyte trafficking through the blood–brain barrier involves lymphocytes first rolling around the endothelial membrane. They get arrested, usually with upregulation of the alpha-4, beta-1 integrin molecule or VCAM interactions with its ligand, and then firm adhesion involves other adhesion molecules. The transmigration follows from that. If this process is upregulated, it results in the increased trafficking of lymphocytes [12].

Microglial cell activation and demyelination is probably the key event that takes place in the final destruction of myelin. Proinflammatory cytokines activate the microglial cells, these release free oxygen, free radicals, and proteases that actually eat up the myelin, and cause the actual myelin loss. If unchecked, it almost always leads to axonal loss, and that's what ultimately causes irreversible damage in MS [13].

2.3. Causes

The predominant theory today is that MS results from attacks by an individual's immune system on the nervous system and it is therefore usually categorized as an autoimmune disease [14]. There is a minority view that MS is not an autoimmune disease, but rather a metabolically dependent neurodegenerative disease. Although much is known about how MS causes damage, its exact cause remains unknown [15].

In MS, immune dysfunction can be detected locally in the central nervous system (CNS) and cerebral spinal fluid, as well as systemically in peripheral circulation. Autoimmune nature of MS has long been suspected. It is known that patients with MS have inflammation and demyelination in their CNS and oligoclonal bands in their cerebrospinal fluid. These abnormal immunoglobulins are identified in a high percentage of patients with clinically definite MS during exacerbations of relapsing–remitting disease, or persistently in significant proportion of chronic–progressive patients. A dysregulated immune system no longer prevents memory T-cells from becoming activated against myelin, entering the CNS, and mediating damage associated with the disease.

2.4. Treatments

There is no curative treatment available for MS [16]. However, a number of medications can be used to treat the disease symptomatically [17]. Corticosteroids are medications of choice for treating exacerbations. Interferon β -1B (Betaseron) as well as Interferon β -1a (Avonex) are successfully used to reduce the frequency and severity of relapses [18]. Interferon beta-1b (Betaseron) and interferon beta-1a (Avonex, Rebif) are genetically engineered copies of proteins that occur naturally in the body. They help fight viral infection and regulate the immune system [19].

Glatiramer (Copaxone) is an alternative to beta interferons for relapsing–remitting MS. Doctors believe that glatiramer works by blocking the immune system’s attack on myelin.

Natalizumab (Tysabri) is administered intravenously once a month. It works by blocking the attachment of immune cells to brain blood vessels – a necessary step for immune cells to cross into the brain – thus reducing the immune cells’ inflammatory action on brain nerve cells [20]. Copolymer 1 is now being investigated in clinical trials and also appears to decrease the disease activity. Specific medications are also available to treat fatigue, pain, spasticity, bladder control problems, etc.

All of the above approaches address MS symptoms only (not causes), have side-effects ranging from moderate to severe [21], and eventually lose their impact. They are ‘magic bullet’ types of approaches, and, at a minimum, need to be supplemented by the anti-MS lifestyle that will be implied by our findings.

3. Approach

Fig. 2 in the second paper of this Special Issue (Methodology) [5] is a flow chart that outlines the steps used in the present study. For the MS study, more steps from the flow chart were used than in the previous medical ODS LRD studies. This resulted in a very minor decrement in the streamlining of the process, and allowed for the retrieval of more potential discovery. The specific steps employed were as follows.

3.1. Core MS literature

The MEDLINE database was used, since we wanted to take advantage of the time-saving capabilities afforded by its MeSH taxonomy. The first step involved retrieving the core MS literature. We used the phrase “Multiple Sclerosis” (both as a MeSH term and a text phrase) as a query to retrieve the core MS literature (Steps 1 and 2 in Fig. 2 of the Methodology paper). Over the time period 1980–2007, we retrieved 28,637 records total, of which 22,864 records had Abstracts and could be used for clustering (June 2007).

3.2. Directly related literature

In our three previous medical studies (RP, cataracts, PD), we used document clustering only to identify the main medical thrusts for query development. In the present MS study, we decided to supplement this document clustering step with other grouping approaches to ascertain what advantages, if any, the additional grouping approaches offer. We added auto-correlation mapping of phrases, and factor matrix analysis of phrases, using our TechOasis software package [22].

3.2.1. Document clustering

With use of our CLUTO document clustering software [23], which groups only those records that contain Abstracts, we grouped the 22,864 retrieved records (MS core literature) into the main medical categories that characterize the MS core literature. These main medical thrusts (emphasizing biomedical phenomena) included: demyelination and remyelination; indirect autoimmune contributors to inflammation/blood–brain barrier; direct autoimmune contributors to inflammation; myelin basic protein, and viruses, as well as a number of diagnostic, treatment, symptom, genetic, and risk factor clusters (not included in query development).

3.3. Auto-correlation maps and factor matrix analysis

The phrase auto-correlation maps display phrases by their degree of correlation with each other, essentially based on their co-occurrence in Abstracts. Typically, a number of thematic phrase groups can be discerned from the map. The number of groups is used to estimate the number of factors required by the algorithm for factor matrix generation.

The factor matrix is a graphical representation of a factor analysis. The columns are the factors, and represent important technical themes in the database. The rows are important technical phrases (selected by the analyst from all available phrases), and the numerical cell entries represent the quantitative contribution of a specific phrase to the theme of a specific factor.

Perhaps five-six groups could be distinguished from the auto-correlation map. The factor matrix analysis was then performed parametrically, with number of factors ranging from two to six. For the six factor matrix, the factor themes, and key (high value) phrases, were as follows:

Factor 1: Myelin sheath proteins and maintenance cells (myelin basic protein; myelin oligodendrocyte glycoprotein*; proteolipid protein*; experimental autoimmune encephalomyelitis; oligodendrocyte*; encephalitogenic; epitope*; immunization; immunodominant)

Factor 2: Indirect contribution of lymphocytes to inflammation by secretion of cytokines, chemokines, and lymphokines (cytokine*; tumor necrosis factor-alpha; peripheral blood mononuclear cells; interferon-gamma; proinflammatory; interleukin*)

Factor 3: Viral contributions to inflammation (murine encephalomyelitis virus; virus; viral; demyelinating)

Factor 4: Autoimmunity (cerebrospinal fluid; oligoclonal IgG bands; isoelectric focusing; glial fibrillary acidic protein; Intrathecal IgG; IgG index; immunofixation; electrophoresis)

Factor 5: Demyelination and remyelination (oligodendrocyte*; demyelinat*; glial fibrillary acidic protein; astrocyte*; axon*; myelin oligodendrocyte glycoprotein*; remyelinat*)

Factor 6: Blood–brain barrier (vascular cell adhesion molecule-1; intercellular adhesion; ICAM-1; endothelial; endothelial cell*; cell adhesion molecule; endothelium).

There is essentially a mapping between the clusters (from the document clustering analysis) and the six factors, with the exception that one of the clusters combines the indirect contribution of the lymphocytes to inflammation (secretion of cytokines, etc.) with blood–brain barrier disruption phenomena (endothelial cells/vascular cell adhesion molecules), whereas the factor matrix treats these as two separate factors.

3.3.1. Directly related literature query development

The factors and clusters identified could be classified into two generic types. One type covers observable symptoms/characteristics of MS (demyelination, blood–brain barrier disruption, to some

extent), while the other type covers underlying causes (autoimmunity, viruses, inflammation). Test literature retrievals showed that the underlying phenomena retrievals (because of their generality, and applicability to many diseases) were an order of magnitude greater than the symptom-oriented retrievals (because of their relative specificity). In our previous ODS LRD medical studies, the directly related literature queries tended to focus on the more specific characteristics of the disease, and the indirectly related literature queries tended to focus on the more generic underlying characteristics of the disease. We decided to follow the same strategy for the MS directly related literature query and indirectly related literature query. Thus, ‘directly related’ should be interpreted as the literature characteristic of the more specific/unique disease biomedical characteristics, and ‘indirectly related’ should be interpreted as the literature characteristic of the more generic disease biomedical characteristics.

In MS, the more specific/unique disease biomedical characteristics are the stripping of the myelin sheath from the axons, the loss of axons, and the death of the oligodendrocytes primarily, and the disruption and breakdown of the blood–brain barrier secondarily. These are not independent phenomena. We used the key phrases from the two clusters that addressed these directly related phenomena. We did not use combinatorials of these phrases in the directly related literature query, since the phrases are relatively specific, and combination of specific phrases would have been overly restrictive. We have found from the cataracts [2] and PD [3] studies that combinations of the more generic terms are extremely valuable for semantic filtering purposes, but combinations of specific terms may be excessively restrictive.

For analytical purposes (not discovery), we also wanted to retrieve core literature records in semantic classes of interest, those classes from which potential discovery could be drawn in the related literatures. Following our assumptions for potential solution classes made in our previous medical ODS LRD studies, we restricted potential discoveries from the related literatures to non-drug and lifestyle modification approaches. We then retrieved core MS records restricted to those classes where the non-drug class filter was approximated by (plants, medicinal or plants, edible or “plant extracts” or “plant preparations” or “plant oils” or phytotherapy or fruit or vegetables or “fish oils” or algae or nuts or “dairy products” or fats or diet or flavonoids or “dietary supplements”).

There were two classes of records in this ‘filtered’ retrieved core literature. One class of records, had they been in one of the related literatures, would have been potential discovery candidates. The other class, had they been in one of the related literatures, would not have been potential discovery candidates. We observed that the records in the first class, those most relevant to potential discovery, tended to have more than one of the key query mechanism terms (identified from the clusters) in the MeSH and text fields. We examined a sample of these records, and identified additional text and MeSH phrases from specific text and MeSH phrase patterns.

The key text terms identified through the CLUTO clustering process were: oligodendrocyte*; remyelinat*; axon*; demyelinat*; myelin basic protein*; normal white matter; axonal damage; oligodendrocyte progenitor cells; microglia; myelin oligodendrocyte glycoprotein; optic neuritis; white matter lesions.

The key text terms identified through examination of the interesting non-discovery records were: inflammatory and (cytokine* or mediator*); oxidative phosphorylation; mitochondrial dysfunction; ataxia; demyelinat* or demyelination; neurodegenerat*; oxidative stress; antioxidant; corpus callosum; remyelinat*; myelin regeneration; neurologic disability; oligodendrocyte* and (apoptosis or death or degeneration or damage or dystrophy); neuroinflammat*; neuroprotection; microglia*; mitochondrial insufficiency; reactive oxygen species; axonal and (demyelination or destruction); radical

scavenging; muscle spasticity; myelin* and (formation or damage or regeneration or phagocytosis); inhibit* and (complement or cytokine*); oligodendroglial apoptosis; optic neuritis; autoreactive t-cells; phosphate depletion; oxidative reactions.

The key MeSH terms identified through the CLUTO clustering process were: muscle spasticity; ataxia; nerve degeneration; TNF-related apoptosis; cognitive disorders; neurogenic inflammation; antioxidants; neurodegenerative diseases; oxidative stress; nervous system diseases; demyelinating disease; corpus callosum; cognition disorders; myelin sheath; regeneration; oligodendroglia.

The key MeSH terms identified through examination of the interesting non-discovery records were: myelin basic proteins; nerve regeneration; axons; myelin associated glycoproteins; cell death; nerve growth factor; mitochondrial diseases; tremor; reactive oxygen species; apoptosis regulatory proteins; neuroprotective agents; demyelinating autoimmune diseases; anti-inflammatory agents, non-steroidal; complement inactivator proteins; optic neuritis; anti-inflammatory agents; microglia; hypophosphatemia.

Using all the text and MeSH phrases obtained from the clustering, factor matrix analysis, phrase auto-correlation map, and identification of text patterns in interesting core non-discovery records (restricted to the two primary medical thrusts mentioned above), we generated a query for retrieving the directly related literature unrestricted to semantic classes. This query was as follows: ((demyelinat* OR remyelinat* OR “myelin sheath pathology” OR (“myelin sheath” AND (damage OR degenerat*)) OR “axonal loss” OR “axonal destruction” OR (oligodendrocyte* AND (apoptosis OR death OR degenerat* OR damage OR dystrophy)) OR (oligodendroglia* AND (apoptosis OR destruct* OR loss))) OR (“blood–brain barrier”AND (disruption OR “cell adhesion”OR “activated lymphocyte*”OR “adhesion molecule*”OR (lymphocyte* AND trafficking) OR breakdown OR transmigration OR dissolution)))) NOT “multiple sclerosis”.

The first group of terms represents the biomedical phenomena that comprise the main thrusts of the MS core literature (essentially degradation of the myelin sheath and disruption/breakdown of the blood–brain barrier), and the final negation term ‘(Multiple Sclerosis)’insures that the records retrieved will be disjoint from the core MS literature. The terms were used to search the text fields and the MeSH field, and 25,504 semantically-unrestricted records were retrieved.

The query was then intersected with the same semantic classes identified for core literature analysis, the resultant terms were used to search the text fields and the MeSH field, and 427 semantically-restricted records were retrieved.

Some examples of potential discovery from these 427 directly related literature retrievals are listed in the Results section.

3.4. Indirectly related literature

To obtain potential discovery from the indirectly related literature, the following steps were taken. The directly related literature (the fraction of the 25,504 records mentioned above with Abstracts) was clustered using CLUTO, and the main medical thrusts were identified from the text phrases in each cluster’s Abstracts and the MeSH terms. Additionally, phrase auto-correlation maps and factor matrices were generated.

In parallel, as in the development of the directly related literature query, the potential discovery candidate records from the directly related literature were examined for textual patterns both in the Abstract text and in the MeSH terms especially compared to textual patterns from the non-discovery records. We observed that the non-discovery records typically contained one of the key phrases as a

MeSH term (sometimes none) and as a text term as well, whereas the potential discovery candidates typically contained two or more of the key phrases as MeSH terms (and as text terms as well).

All the above input data were integrated, and a query was generated. There were three main components to the query: biomedical, negation, semantic classes. The biomedical component consisted of five sub-components, based on biomedical thrusts. The terms for the five biomedical sub-components (thrusts) are as follows:

Thrust 1 — Myelin dysfunction

- 1=(Oligodendro* AND (Progenitor* OR Precursor* OR Differentiation OR Death))
- 2=(“Schwann Cell Cytoplasm” OR “Schwann Cell Proliferation” OR “Schwann Cell Differentiation”)
- 3=(“Microglial Cell*” OR “microglial Activation” OR “microglial Death”)
- 4=(“Mitochondrial Dysfunction” OR “mitochondrial Swelling”)
- 5=“Mitogen-Activated Protein Kinase Kinases”
- 6=“Mitogen-Activated Protein Kinases”
- 7=“Glial Fibrillary Acidic Protein”
- 8=(Astrocyte* AND Reactiv*)
- 9=“Oxidative Phosphorylation”
- 10=(Caspase-3 AND Activat*)
- 11=“Nerve Degeneration”
- 12=“Enzyme Activation”
- 13=“Enzyme Inhibitors”

Thrust 2 — Oxidation destruction

- 1=“Neurodegenerative Disease*”
- 2=“Reactive Oxygen Species”
- 3=“Oxidation-Reduction”
- 4=“Hydrogen Peroxide”
- 5=“Oxidative Stress”
- 6=“Free Radicals”
- 7=Antioxidants

Thrust 3 — Blood–brain barrier disruption

- 1=“Cell Membrane Permeability”
- 2=“Active Biological Transport”
- 3=“Endothelial Growth Factor*”
- 4=“Cell Surface receptors”
- 5=“Capillary Permeability”
- 6=“Blood–Brain Barrier”
- 7=“Carrier Protein*”
- 8=“Tight Junction*”

Thrust 4 – Myelin inflammation

- 1=“Tumor Necrosis Factor receptor*”
- 2=“recombinant Interferon Gamma”
- 3=“Inflammatory Response”
- 4=“Inflammatory Cytokine*”
- 5=“Activated Macrophage*”

- 6=“Macrophage Infiltration”
- 7=“Interferon Type II”
- Thrust 5 — Autoimmune myelin destruction
- 1= (“Myelin Basic Protein*” AND Immunology)
- 2= (“Peptide Fragment*” AND Immunology)
- 3= “Major Histocompatibility Complex”
- 4= “CD4 Positive T-Lymphocyte*”
- 5= “CD8 Positive T-Lymphocyte*”
- 6= (Antigens AND Immunology)
- 7= “Blood Mononuclear Cell*”
- 8= “Leukocyte Chemotaxis”
- 9= “Immunophenotyping.

Each biomedical sub-component contained a combinatorial grouping of the terms within the sub-component only (intra-thrust combinations). For the first two sub-components listed above, which contained relatively generic terms, all combinations of three terms were used combinatorially in the query. For the last three sub-components listed above, which contained more relatively specific terms, all combinations of two terms were used combinatorially in the query. The full query is contained in [24].

In some sense, the biomedical phenomena combinations component can be viewed as a filter that targets potential discovery candidates more precisely, based on patterns associated with previously-identified potential discoveries. Whether this combination approach also filters out potential discovery remains to be seen. For the present study, this was not an issue, since we obtained large amounts of potential discovery.

The second of the query components was the negation component (the core MS query and the directly related literature query, connected to the biomedical component by the NOT Boolean to insure that the indirectly related literature would be disjoint from the core and directly related literatures). This unrestricted two component indirectly related literature query returned 38,190 records.

The third query component (semantic class restriction) was then added to the query to retrieve the filtered indirectly related literature records. A sampling showed there was a reasonable fraction of potential discovery candidates. Use of additional medical thrust text or MeSH phrases would have returned additional records and additional potential discovery candidates. Some examples of potential discovery from the indirectly related literature retrieved by this query are shown in the Results section. The vetting issues are similar to those from the PD study, and are discussed in Ref. [3].

4. Results

This section contains representative examples of potential discovery from literatures related directly and indirectly to the core MS literature. Before proceeding to analyses, we present a few illustrative examples from the core MS literature restricted to semantic classes. While these are not discovery, they nevertheless reflect the types of impact that the non-drug approaches could potentially have for delaying or preventing the onset of MS. In addition, as we will discuss later, some of these core concepts are prime candidates for innovation.

For example, UCP4-mRNA expression is increased in brain cells of rats maintained on caloric restriction. Neural cells with increased levels of UCP4 exhibit reduced reactive oxygen species (ROS)

production and decreased mitochondrial calcium accumulation. The UCP4-mediated shift in energy metabolism reduces ROS production and increases the resistance of neurons to oxidative and mitochondrial stress, providing antiaging and neuroprotective effects [25]. Side-effects of caloric restriction, as exhibited in rodent and primate studies, are positive on many fronts, and include increased life span [26]. There is an accumulating body of evidence for the positive effects of caloric restriction on UCP4 and other coupling proteins in both the MS core and non-core literatures, yet we have seen no mention of this harmless supplement in any of the mainline reviews.

4.1. *Non-drug concepts in the core MS literature*

1. “Prenatal hypovitaminosis D causes a dramatic dysregulation of several biological pathways including oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity and neurotransmission. A computational analysis of these data suggests that impaired synaptic network may be a consequence of mitochondrial dysfunction. Since disruptions of mitochondrial metabolism have been associated with both multiple sclerosis and schizophrenia, developmental vitamin D deficiency may be a heuristic animal model for the study of these two brain diseases.” [27]
2. “Synthetic metal ion chelators continue to show promise as a new therapeutic approach for neurodegenerative disorders. Dietary chelators, unlike most vitamins, are, however, capable of negating or even reversing the roles of metal ions by: (i) decorporation of metal ions, (ii) redox silencing, (iii) dissolution of deposits, and (iv) generation of an antioxidant enzyme mimetic. This review gives a critical evaluation of recent progress in, and potential for, dietary control of neurodegeneration on the basis of the formation of antioxidant enzyme mimetics.” [28]
3. “...we have experimented with alternate day calorie restriction, one day consuming 20–50% of estimated daily caloric requirement and the next day ad lib eating, and have observed health benefits starting in as little as 2 weeks, in insulin resistance, asthma, seasonal allergies, infectious diseases of viral, bacterial and fungal origin (viral URI, recurrent bacterial tonsillitis, chronic sinusitis, periodontal disease), autoimmune disorder (rheumatoid arthritis), osteoarthritis, symptoms due to CNS inflammatory lesions (Tourette’s, Meniere’s) cardiac arrhythmias (PVCs, atrial fibrillation), menopause related hot flashes. We hypothesize that other many conditions would be delayed, prevented or improved, including Alzheimer’s, Parkinson’s, multiple sclerosis, brain injury due to thrombotic stroke atherosclerosis, NIDDM, congestive heart failure.” [29]
4. “The positive preclinical outcomes in treating CNS disorders by complement regulatory molecules, such as vaccinia virus complement control protein, suggest the possibility of using complement-inhibitory molecules as neuroprotective agents. Several active ingredients of herbal origin are found to have complement-inhibitory activity. These herbal ingredients along with other anti-inflammatory roles might be useful in treating neuroinflammation associated with CNS disorders. Active ingredients of herbal origin with complement-inhibitory ingredients are summarized and classified according to their chemical nature and specificity towards the major pathways activating the complement system. The structure activity relationship of some specific examples is also discussed in this report. This information might be helpful in formulating a natural panacea against complement-mediated neuroinflammation”. [30]
5. “*N. sativa* may protect brain and medulla spinalis tissues against oxidative stress-induced by EAE. In addition, *N. sativa* display its antioxidant and regulatory effects via inflammatory cells rather than the host tissue (brain and medulla spinalis) for EAE in rats”. [31]

6. “Recent studies in multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE), point to the fact that even in the early phase of inflammation, neuronal pathology plays a pivotal role in the sustained disability of affected individuals. We show that the major green tea constituent, (-)-epigallocatechin-3-gallate (EGCG), dramatically suppresses EAE induced by proteolipid protein 139-151. EGCG reduced clinical severity when given at initiation or after the onset of EAE by both limiting brain inflammation and reducing neuronal damage”. [32]
7. “We show that in vivo treatment of SJL/J mice with quercetin (i.p. 50 or 100 µg every other day) ameliorates EAE in association with the inhibition of IL-12 production and neural antigen-specific Th1 differentiation... suggest its use in the treatment of MS and other Th1 cell-mediated autoimmune diseases.” [33]

4.1.1. Observations on non-drug core MS literature concepts

When reviewing the large number of interesting core MS literature concepts, it became clear that a number were in common with those from the PD literature (including concepts from both literatures not reported in this paper or the PD paper). The question arose whether this commonality extended to other neurodegenerative diseases as well (we did not address commonality beyond neurodegenerative diseases, although, as was shown by the sulforaphane example in the PD study [3], there may well be commonality of interesting concepts (potential treatments) among neurodegenerative and non-neurodegenerative ailments). A brief study was undertaken comparing potential treatments in the core literatures of MS, PD, AD (Alzheimer’s Disease), and HD (Huntington Disease), and searching for those that are common.

For each of these diseases, the core literature was retrieved, and intersected with the non-drug semantic classes (as was done in the MS study reported here). Initially, the MeSH terms from each literature were extracted, tagged, and combined. Later, the same process was applied to the Abstract text phrases. Those common to four diseases, common to three diseases, two diseases, and those applied to one disease only, were identified.

The MeSH terms common to four and three diseases were inspected visually, and those reflecting potential treatments were extracted. Only a handful existed for MeSH terms common to four diseases. One reason was that the core HD literature was much smaller than the other three core literatures (almost by an order of magnitude), and limited the number of concepts available. Many more potential treatments were common among three diseases, mainly (not exclusively) those with the larger core literatures.

For the MeSH terms, potential core treatments common among four diseases included: caloric restriction, tea (green tea), smoking elimination, Omega-3 fatty acids, exercise. Potential core treatments common among three diseases included: *Ginko biloba*, curcumin, blueberry, quercetin, mercury elimination.

For the Abstract phrases, potential core treatments common among four diseases included: zinc and smoking habits, and biomedical phenomena common among four diseases included mitochondrial dysfunction, oxidative stress, and tardive dyskinesia. Potential core treatments common among three diseases included: alcohol consumption (reduce), ascorbic acid, beta-carotene, cannabinoids, curcumin, dairy products (reduce), green tea, fruit, *Ginko biloba*, etc.).

The universality of some of these potential treatments must be treated with caution. Clinical medicine is replete with treatment strategies that are effective in one organ system or for one class of disease that (by our understanding of pathophysiology) should also be useful in other organs and/or disease classes, yet when tested, they are ineffective.

Finally, for those readers interested in a more comprehensive overview of the contents of the non-drug core neurodegenerative disease literature in MEDLINE, see [24], Appendices 7–11. We used a

moderately more comprehensive list of semantic classes than we had used for the PD or MS studies, and presented the citations for the retrieval listed in [24], Appendices 7–11. Specifically, these appendices contain retrievals for AD, PD, MS, ALS, HD, respectively, arranged in order of number of articles with Abstracts. No analyses were performed on these records in Appendices 7–11; because of their modest numbers, they can be perused visually quite rapidly. In [24], Appendix 6, we performed a clustering analysis of a PD non-drug core retrieval with an even more expanded list of semantic classes, and presented results for each cluster in the hierarchical taxonomy.

4.2. *Non-drug potential discovery concepts in the directly related literature*

“On the basis of these results, PA [petasignolide A] is suggested to be a major neuroprotective agent primarily responsible for the protective action of the butanol fraction of *P. japonicus* extract against kainic acid-induced neurotoxicity in the brains of mice.” [34].

“These results suggest that orally administered QF808 [*Mangifera indica* L. extract] is absorbed across the blood–brain barrier and attenuates neuronal death of the hippocampal CA1 area after ischaemia-reperfusion. These protective effects are most likely due to the antioxidant activity of QF808.” [35].

“...tiliroside and gnapthaliin are antioxidants against in vitro Cu(2+)-induced LDL oxidation in the same order of magnitude compared to that of the reference drug, probucol.” [36].

“Tissue damage was slowed by decreased levels of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) and an associated rise in lipid peroxidation (LPO) in mitochondria, which were reversed by CQE [*Cissus quadrangularis* extract]. In addition, CQE prevents oxidative damage of DNA by reducing DNA fragmentation indicating its block on cell death. Ulcer protection in CQE treated rats was confirmed by histoarchitecture, which was comprised of reduced size of ulcer crater and restoration of mucosal epithelium. Thus, reduced neutrophil infiltration, antiapoptotic and antioxidant action have a pivotal role in the gastroprotective effect of CQE.” [37].

“AIAE [*Artemisia iwayomogi*] attenuated the phorbol 12-myristate 13-acetate plus calcium ionophore A23187-stimulated tumor necrosis factor- α and interleukin-6 secretion in human mast cells.” [38].

4.3. *Non-drug potential discovery concepts in the indirectly related literature*

Kalpaamruthaa (KA) showed an enhanced antioxidant potential in the management of a rheumatoid arthritis model in rats. “Kalpaamruthaa (KA), a modified indigenous Siddha preparation constituting *Semecarpus anacardium* nut milk extract (SA), *Embllica officinalis* (EO) and honey was evaluated for its synergistic antioxidant potential in adjuvant induced arthritic rats than sole SA treatment...The profound antioxidant efficacy of KA than SA alone might be due to the synergistic action of the polyphenols such as flavonoids, tannins and other compounds such as vitamin C and hydroxycinnamates present in KA.” [39] (*another example of the benefits of synergistic combinations*).

Salvia miltiorrhiza Bunge (a Chinese herbal medicine) attenuates increased endothelial permeability induced by TNF- α . “*Salvia miltiorrhiza* Bunge, a traditional Chinese herbal medicine, is often used for prevention and treatment of cardiovascular disorders such as atherosclerosis... Data from this study suggest that one of the mechanisms *S. miltiorrhiza* exerts its pharmacological effect is through its modulation of endothelial cell permeability.” [40].

Inchinko TJ-135 (a Japanese herbal medicine) inhibits inflammatory cytokines and enhances production of anti-inflammatory cytokines. “These results suggest that con A-induced hepatitis was

ameliorated by pretreatment with TJ-135. With regard to the mechanism of these effects of TJ-135, we speculate that TJ-135 inhibits the production of inflammatory cytokine and enhances the production of anti-inflammatory cytokines. Therefore administration of TJ-135 may be useful in patients with severe acute hepatitis accompanying cholestasis or in those with autoimmune hepatitis.” [41].

“These results suggest that SM [Silymarin] may to protect the SNC [substantia nigra pars compacta] by oxidative damage for its ability to prevent lipid peroxidation and replenishing the GSH levels.” [42].

“Potent free radical scavenger, edaravone, suppresses oxidative stress-induced endothelial damage” [43].

“Sopoongsan inhibits mast cell-mediated anaphylactic reactions and inflammatory cytokine secretion.” [44].

“Rhapontigenin, isolated from the Korean medicinal plant *Rheum undulatum*, was found to scavenge intracellular reactive oxygen species and hydrogen peroxide. Rhapontigenin protected against oxidative stress-induced cellular damage such as H₂O₂-induced membrane lipid peroxidation and cellular DNA damage. Rhapontigenin protected cells against oxidative damage by enhancing cellular antioxidant activity and modulating cellular signal pathways” [45].

Butea monosperma Lam., a methanol extract of *Butea monosperma* flowers, was found by the Pharmacy Department of the University of Baroda in India to be an antioxidant. Free radical scavenging activities was demonstrated against 2,2 diphenyl-1-picrylhydrazyl (DPPH) radical, nitric oxide radical, superoxide anion radical, hydroxyl radical, and 2, 2' azo-bis (amidinopropane) dihydrochloride (AAPH) [46].

Because the purpose of the MS study was to demonstrate an approach, and not necessarily to be comprehensive, a number of shortcuts were taken. Not all possible semantic categories for potential discoveries were identified, only the most obvious. Relatively few terms were selected for both the direct and indirect queries; many more were available. Not all retrieved records were examined; only enough to demonstrate the quality of results. The potential expansion to indirectly related literatures using citation linking described previously was not done. Thus, the results obtained should be viewed as the tip of a very large iceberg.

5. Discussion

The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study) is a synergy of lifestyle/dietary practices that could be interpreted as anti-MS. Along with non-discovery items such as Vitamin D, dietary chelators, caloric restriction, complement-inhibitory herbs, *Nigella sativa* oil, green tea, and quercetin are potential discovery items such as Shogaol, Ethanol, Iron, Petasignolide A, *Mangifera indica* L, Tiliroside, Gnaphaliin, *Cissus quadrangularis* extract, Kalpaamruthaa, *Salvia miltiorrhiza* Bunge, Inchinko TJ-135, Silymarin, Edaravone, Sopoongsan, and *Artemesia iwayomogi*. As stated above, more laboratory tests and field trials would have to be done on all these items to insure that they are anti-MS and safe, but these preliminary literature-based results offer some promise of what is possible.

We are finding a major disconnection between the therapies presently or potentially available presented on all the major medical websites (and in MS mainstream journal review papers), and the therapies suggested by what has already been demonstrated in the core MS literature, much less what we have generated from the related literatures. The major medical websites (and journal reviews) present about a half-dozen drug

treatment options for MS. We have seen very few medical websites that even mention any of the non-drug approaches shown in the MS core Results section. We believe the core literature and related literature potential discoveries and innovations have the potential to supplement the mainline medical treatments.

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