Appendix e-1

Original documents provided by the working groups

Work group 1: Pathogenesis

Committee Members: Janice Holton (Chair), Thomas Gasser (pre-meeting), Matt Huentelman, Poul Henning Jensen, Ronald Melki, Shoji Tsuji

Recommendation 1: To understand the relationship between oligodendroglial pathology and neuronal death and determine methods to influence these interactions.

Need

- The relationship between oligodendroglial pathology and neurodegeneration is poorly understood. Whether these represent independent pathological pathways or relate to each other is unknown and how other pathological changes influence these processes remains to be clarified. Understanding these fundamental questions is essential to highlight pathways that may be amenable to therapeutic intervention and the development of translational studies. There is a requirement for access to human tissue to address these issues. Animal and cell models will also be essential.

Pathway

1. Establish biobanking including brain banking as in Recommendation 1. Such collections should employ standardized protocols for collection, sampling and storage.
2. Establish investigations to determine the degree of neuronal degeneration in areas being variously affected by oligodendroglial pathology and correlate with markers for pathological processes such as microglial and astroglial activation, immune and vascular involvement.
3. Test hypotheses derived from these studies in animal and cell models of MSA
4. Conduct '-omics' analyses on the investigated areas to search for early disease markers and disease promoting signals with the aim of developing new hypotheses and identifying signals amenable to modulation.

✓ Requires collaborative interaction, resources for experimental work and access to human tissues, animal and cell models. Bioinformatics support will be required to handle data derived from '-omics' studies.

Feasibility

- Initiation: Steps1-2 – 1-3 years; steps 3 - 4 > 3 years
- Completion: Step1 ongoing; step 2 – 1-3 years; step 3 -4 – 4-7 years

Recommendation 2: To understand the role of α-syn in MSA by investigating protein structure, assembly into filaments and propagation of abnormal structure.

Need

- Implementing new technological approaches such as in vitro amplification reactions of α-syn should allow: i- a better understanding of MSA etiology and pathogenesis, ii- determining whether α-syn assembly propagation contributes to disease evolution, iii- developing highly specific diagnostic tools and iv- designing tailored and innovative therapeutic approaches.

Pathway:

1. Investigate the concept of α-syn strains using *in vivo* and *in vitro* experimental systems.
2. *In vivo* properties and effect of *in vitro* amplified MSA-associated α-syn assemblies.
3. Thorough characterization at the molecular level of MSA-associated α-syn assemblies to better understand MSA specificities
4. Identification of α-syn epitopes specific to MSA to design highly specific monoclonal antibodies for diagnostic purposes
5. Identification of highly specific monoclonal antibody paratopes through proteomic approaches to design novel and tailored therapeutic tools.

✓ Requires resources for experimental work. Proteomics will require access to biobank samples and bioinformatics support will be required to handle large data sets.

Feasibility

- Initiation: Steps1- 5 – 1-3 years
- Completion: Steps1- 5 – 4-7 years

Recommendation 3: Investigations are required to understand regional vulnerability to pathology, **initiating factors, early cellular and pathological changes that precede** α-syn accumulation, aggregation, post-translational modifications, cell-to-**cell transmission of** α-syn and their role in driving disease.

Need

- The early cellular and pathological changes preceding α-syn accumulation in oligodendrocytes and other brain cells require exploration as these may provide targets for therapeutic intervention. The neuronal and glial responses to MSA-associated α-syn accumulation and assemblies and how these are related to cytotoxicity and myelin loss are currently poorly understood. Identification and quantitative assessment of altered gene and protein expression using genomic and proteomic tools following: i) pre-α-syn GCI formation, ii) development of or exposure to pathological α-syn assemblies would enhance understanding of this important question. To investigate the hypothesis of α-syn propagation from one neuron/glial cell to another and the specificities of this process in MSA as compared to PD, there is a need to compare the propagation of MSA- and PD-associated α-syn assemblies. The mechanism of cell-cell transmission of α-syn may favour the formation of inclusions in oligodendrocytes in preference to neurons. Excretion of α-syn by neurons and/or oligodendrocytes resulting in extracellular α-syn may play an active role in the neurodegenerative process and contribute to pathological disease progression. Altered α-syn structure due to post-translational modification or incorporation into macromolecular assemblies may be important. Impaired degradation of α-syn by neurons and oligodendrocytes may play a role in disease. Understanding the intercellular factors, other than α-syn species, causing neurodegeneration and those responsible for the regional susceptibility to the disease process also requires investigation.

Pathway

6. International collaboration to set up a comprehensive programme of investigation of the pathogenesis of MSA using the biobank and brain banking resources established in Recommendation 1 to provide required material
7. Utilize existing animal models of oligodendroglial dysfunction to test for characteristics of MSA
8. Utilize the proteomic expertise and bioinformatics established in Recommendation 2 to support the studies including investigation of regional vulnerability and biochemical alterations preceding α-syn aggregation.
9. Basic science studies will feed into drug development

Feasibility

- Initiation: Steps1- 3 – 1-3 years; step 4 >3 years
- Completion: Steps1- 3 – 4-7 years; step 4 >8 years

Work group #2: Preclinical modeling

Committee Members: Gregor K. Wenning (Chair), Patrik Brundin, Un Kang, Vikram Khurana, Woojin Scott Kim, Eliezer Masliah, Wassilios Meissner

Recommendation 1: To develop novel in vivo models of MSA for interventional target discovery

Need

- Current in vivo MSA models incompletely replicate the disease process partly accounting for their failure to predict therapeutic benefit. The discovery of more promising interventional targets requires accelerated development of novel rodent MSA models based on non-vertebrate and in vitro models and human brain tissue studies. To this end, emerging findings in human genetic studies (incl. CoQ2) should be incorporated into existing and novel in vivo models for MSA. There is a strong need to understand the propagation properties of glial and neuronal α-syn species in MSA models.

Pathway

10. Screening of cell specific viral vectors expressing α-syn, CoQ2 mutations/variants, emerging mutations/polymorphisms etc in vitro (incl. iPSC and existing cell lines) and invertebrate models (yeast, worms or flies).
11. Novel rodent MSA models will be developed on the basis of this work. This includes AAV mediated oligodendroglial α-syn overexpression in rats as well as the generation of transgenic mice expressing pathogenic CoQ2 mutations.
12. Rodents will receive intracerebral injections of oligomeric, fibrillar, or phosphorylated α-syn species derived from human MSA brain tissue to test the hypothesis whether α-syn pathology can propagate and induce neurodegeneration.

Feasibility

- Initiation: steps 1-3: 1-3 years
- Completion: steps 1-3: 4-7 years

Recommendation 2: To characterize existing tg MSA models using non-motor endpoints, wet biomarkers and multimodal neuroimaging

Need

- Behavioural studies in MSA animal models mainly focus on motor deficits whereas non-motor endpoints have not been studied systematically. However, both outcomes are equally relevant for drug discovery in MSA since patients are affected by motor impairment and generalized autonomic failure. Further, wet biomarkers and multimodal neuroimaging need to be established in transgenic MSA models to interrogate the impact of candidate interventions.

Pathway

13. Extend non-motor phenotyping in tg MSA mice including cardiovascular, gastrointestinal, respiratory and sleep
14. Characterize wet biomarkers such as CSF oligomeric and phospho-α-syn in tg MSA mice
15. Establish small animal MRI markers (volumetry, diffusion-weighted imaging) in tg MSA mice
16. Establish PET imaging targeting □α-syn, dopamine-transporter function, D2 receptor status, microglial activation and glucose metabolism. The rate-limiting factor is the development and validation of □α-syn PET ligands. This can be resolved by systematic screening for candidate ligands specifically binding to pathogenic □α-syn species.
17. Longitudinal assessment of multimodal neuroimaging and wet biomarkers in animal models of MSA

Feasibility

- Initiation: steps 1-4: 1-3 years; step 5: 4-7 years
- Completion: steps 1-5: 4-7 years

Recommendation 3: To develop iPSC models of MSA for interventional target discovery and screening of candidate neuroprotective agents

Need

- Induced pluripotent stem (iPS) cells offer a potentially transformational method to capture MSA "in a dish". iPS cells are disease-relevant because they derived directly from patients with a disease. They may be particularly helpful in generating hypothesis-blind models of a disease like MSA in which the genetics and disease pathogenesis are as yet poorly understood (making the development of rodent and other cellular models problematic).

Pathway

18. Incorporate fibroblast banking into existing biomarker programs. It will be particularly advantageous to have fibroblasts from patients who are clinically well-characterized and from whom other biomarker data are available. These fibroblasts can be reprogrammed into iPS cells, and phenotypic characterization of iPS cells can be cross-compared to clinical and biomarker data from individual patients.
19. Generate protocols that reliably yield specific cell types such as oligodendrocytes and neurons from human iPS cells. One of the critical problems facing the iPS cell disease models is the reproducible differentiation of specific cell-types. These protocols need to be optimized and standardized in the MSA research community.
20. Examine the properties of these cells using co-cultures and grafting paradigms. Theoretically, increasingly sophisticated models of the disease could be generated with iPSc technology, from co-cultures in vitro to grafted cells in rodents to generate human-rodent chimeric models.
21. Utilize genome editing to test emerging genetic findings in this cellular model system. Considerable work is being done in MSA genetics. One of the difficulties in interpreting MSA genetic data is that the patient numbers are relatively small. Thus, functional genomics platforms – in which variants are introduced to test for a causal relationship to the disease process- are sorely needed. If reliable phenotypes can be identified in iPSc-derived neurons or glia, emerging genome-editing technologies (like CrispR-Cas9 for example) could be used to introduce putative disease variants into the iPSc system for functional validation.

Feasibility

- Initiation: steps 1-4: 1-3 years
- Completion: steps 1-4: 4-7 years

Work group #3: Preclinical MSA – Target Development

Committee Members: Glenda Halliday (Chair), Gal Bitan, Dale Schenk, Nadia Stefanova, Patricia Walicke

Recommendation 1: Develop biomarkers for and treatments of the increased α-syn in animal models overexpressing α-syn in oligodendroglia

Need

- MSA pathomechanisms are poorly understood. Further research is required to determine the most critical event/s, and possibly identify new targets for intervention. Currently, the most obvious target is α-syn because of the abundant oligodendroglial α-syn inclusions in MSA and the observation of the same oligodendroglial α-syn inclusions in a small number of presymptomatic cases without the neuronal loss. Many studies show an order of magnitude increase in α-syn concentration levels in MSA brain tissue. Animal models overexpressing α-syn in oligodendroglia have been developed. Therefore, current target development should focus on: 1) measuring and reducing α-syn pathology in these models for translation into human trials; and 2) identification/validation of biomarkers through bi-directional/iterative feedback with human studies.

Pathway

22. Use animal models overexpressing α-syn in oligodendroglia for target development.

23. Develop biomarkers for measuring α-syn levels in the brain using imaging agents, and in CSF, saliva, and blood products using Western blotting, LC-MS and ELISAs in these animal models.
24. Develop treatments to reduce α-syn levels in these animal models using a variety of methods
25. α-syn immunotherapy or similar specific approach for increased α-syn clearance. Develop an understanding of how peripheral antibodies or antibody-like products affect brain α-syn concentrations.
    - increasing α-syn clearance from the brain via other methods.
    - increasing general protein turnover.
    - decreasing α-syn protein production via RNA mechanisms.
    - increasing α-syn catabolism through enhancement of degradation by the proteasome, autophagy, and/or specific proteases.
    - increasing α-syn solubility, e.g., with small-molecule chaperones, is expected to increase its catabolism and/or clearance by the mechanisms listed above.

Feasibility

- Animal models and many techniques are available.
    - Transgenic mice – advantages: easier and less expensive to produce and maintain. Disadvantage: less translatable to human studies than higher-order animals.
    - Transgenic rats – advantages: brain imaging and CSF analysis more straightforward and can be done in more research centers than in mice. Disadvantages: higher costs of producing and maintaining. Higher cost of therapeutic interventions.
- Many aspects of this pathway could be immediately initiated and depending on the animal model/s used, be completed in 3-5 years

Worg Group #4: MSA Phenotype

Committee Members: Niall Quinn (Chair), Peter Lewitt, Jeremy Schmahmann, David Robertson, Florian Krismer

Recommendation 1: Develop a patient-completed clinical questionnaire and physician-confirmed check-list to aid early clinical diagnosis of MSA-P and MSA-C

Need 1

- As with other neurodegenerative disorders, it is essential for any effective treatment to be started as early as possible in MSA, especially a disease-modifying treatment. Currently, however, the disease is typically diagnosed midway or later through its aggressive clinical course that averages about 8 years from start to finish.

✓ *Background:* In the Queen Square Brain Bank series from 1989-2013 (for which the *clinical* criteria are somewhat variable and not specified), 77% of subjects with pathologically proven MSA had been diagnosed correctly in life (sensitivity). Conversely, 75% of those clinically diagnosed with MSA in life had autopsy-proven MSA (PPV)-(unpublished observations). When previously tested against part of this series, the 2008 second Consensus Criteria for possible MSA had only 41% diagnostic sensitivity at first visit, rising to 92% at last visit. For probable MSA, these figures were 18% and 63%, respectively, emphasizing the current difficulty in diagnosing early cases.
The available clinical data in pathological series are variable in quality and completeness, and have usually not been gathered in a systematic manner, hampering optimal diagnosis and clinicopathological correlations.
In order to diagnose MSA earlier in its clinical course, a systematic, relevant and manageable patient-completed clinical questionnaire and physician-confirmed check-list is needed.

Pathway & Feasibility

- Immediate action:

    - Draw up a first draft proforma, drawing on additional ad hoc expertise in different areas, e.g urogenital function. To be of maximum use, this will need to be administered at first and at subsequent visits to all subjects presenting with parkinsonism or with a suspected Idiopathic Late-Onset degenerative Cerebellar Ataxia ("ILOCA") in order to detect the less common MSA cases, so liaison with PD, PSP and cerebellar groups is also needed
- 1-3 year plan:
    - An agreed final English language version will be submitted for publication (online open access), for use in the above patient groups.
    - Translations and publication in other languages will be solicited.
    - These will serve as aide-memoires to patient and physician to elicit all relevant clinical items, ensuring that clinical diagnostic clues are not missed
- Long-term vision:
    - Systematic clinical data collection will aid diagnosis of MSA, and improve the quality of clinicopathological studies. This will enable existing, and any future, clinical diagnostic criteria to be better validated against autopsy diagnosis.

Recommendation 2: Diagnostic criteria operations manual

✓ To write an "operations manual" on how to diagnose MSA

✓ To develop a global *clinical* score-based aid to diagnose MSA that can be used in all healthcare settings, and does not necessarily require, but can be supplemented by, special investigations

Need 2

- Many health systems in the world lack adequate facilities for complex and expensive specialised investigations. However, in everyday clinical practice it is possible to diagnose MSA in most cases purely on clinical grounds, providing one asks the right questions and does a relevant clinical examination.

Pathway & Feasibility

- Immediate action:
    - Start work on an "Operations manual" on diagnosis of MSA
    - Start work on a numerical clinical scoring system (i.e., a ranking score of diagnostic certainty) for MSA diagnosis
- 1-3 year plan:
    - Submit and publish manual with open online access
    - Draw up a first version of a numerical clinical scoring system to assist in everyday *clinical* diagnosis of MSA, and pilot its use and utility
    - Develop an App to make this scoring system easier to apply in clinic
- Long-term vision:
    - The elements of this scoring system, with and without additional incorporation of selected biomarkers and imaging recommended by other workgroups, and also the current Consensus criteria, will be validated/revalidated in more recent cohorts of pathologically proven MSA cases, with more standardised and complete clinical information resulting from recommendation 1.
    - This scoring system will *not* supplant the 2008 Consensus Criteria, but will provide useful material to incorporate when the next Criteria are developed
    - We propose that new Criteria, when they are finally developed, will still enable a purely clinical diagnosis of MSA to be made if other tests are unavailable, but will incorporate investigations in parallel. We also propose that the sensitivity and PPV of any new Criteria are validated before they are published, so that necessary adjustments can be made before they are set in stone.

Work group #5: Clinical Outcome Measures (including global registry)

Committee Members: Olivier Rascol (Chair), Art Hewitt, William Holt, Horacio Kaufmann, Thomas Klockgether, Glenn Stebbins

Recommendation 1: Development of a valid international rating scale based on the revision and improvement of the existing UMSARS

Need

- Revision and improvement of the existing Unified MSA Rating Scale (UMSARS) in order to provide clinicians and researchers with an optimal international rating scale for MSA. The already available UMSARS has been developed and validated 10 years ago, following a spontaneous initiative convened by European investigators. The UMSARS has been used successfully during the last decade in several surveys and trials. However, there is a general agreement that this scale has a number of limitations and deserves a careful revision leading to useful improvements. This can be achieved on the model of what has been conducted successfully by the International Parkinson and Movement Disorders Society (MDS) for the UPDRS in Parkinson disease.

Pathway

26. Create a UMSARS Working Group to revise the UMSARS, in collaboration with groups interested in the field (for example the MDS MSA International Taskforce and patients associations)
27. Develop a financial strategy to secure sufficient funding to support the activities of such a Working Group (target for example at patients associations, charities, international societies like MDS, pharmaceutical industries)
28. Critique by the Working Group of the existing UMSARS and analyze its strengths and weaknesses
29. Develop a revised version of the UMSARS, including a dimension measuring MSA patients' functional condition, on the model what has been achieved for the MDS-UPDRS
30. Validate internationally this revised version, including its translation in different languages, on the model what has been achieved for the MDS-UPDRS
31. If possible, a revision of other scales allowing to measure more specifically important symptoms of MSA (autonomic dysfunction, ataxia) is also desirable

Feasibility

- Immediately:
    - Create a UMSARS Working Group to revise the UMSARS, in collaboration with groups and experts interested in the field (for example the MDS MSA International Taskforce and patients associations)
    - Develop a financial strategy to secure sufficient funding to support the activities of such a Working Group (patients associations, charities, international societies like MDS, pharmaceutical industries)
- 1-3 years:
    - Critique by the Working Group of the existing UMSARS and analyze its strengths and weaknesses
    - Develop a revised version of the UMSARS, including a dimension measuring MSA patients' functional condition, on the model what has been achieved for the MDS-UPDRS
    - Validate internationally this revised version, including its translation in different languages, on the model what has been achieved for the MDS-UPDRS
- > 3years:
    - If possible, a revision of other scales allowing to measure more specifically important symptoms of MSA (autonomic dysfunction, ataxia) is also desirable

Recommendation 2: Creation of a unified dataset for MSA and implementation of an international global registry in order to allow access to well phenotyped subjects for clinical research, including (among other goals) the development of reliable biomarkers and the screening of patients for international clinical trials

Need

- Creating a large global international registry/dataset in MSA. This should be a realistic goal, as reliable international diagnostic criteria for the diagnosis of MSA exist, and an international rating scale for MSA (UMSARS to be revised, as described above) will be available. Previous MSA cohorts have been initiated in the past, but included limited numbers of

patients recruited in a limited number of centers in Europe or in the US (MDS MSA Study Group, GLOMSAR Contact Registry, NIH initiative). Similar international cohorts have already been successfully implemented in other neurodegenerative disorders, like Huntington disease for example (with the support of CHDI and University of Ulm). There is consensus that an international registry will be particularly valuable if it provides a certain degree of phenotype data and if it is linked to local biobanks/biomaterial collections as well as to imaging data.

Pathway

32. Create a specific Working Group including the already existing North-American, European and Japanese cohorts/registries
33. Develop a financial strategy to secure enough funding to initiate and keep motivation for such a long-term enterprise and cover expenses to guarantee completion of the forms by the centers and monitoring of the data (Public funding opportunities for rare disorders?)
34. Identify existing datasets and compare their advantages/disadvantages
35. Create an inventory of existing biomaterial collections and imaging datasets
36. Elaborate a unified eCRF compatible/acceptable by the different partners of the project (potential need to start working with paper forms, define a clear strategy for handling of missing data)
37. Implement an international network using such an eCRF for a global dataset (not underestimating important practical issues such as differences in regulatory and legal aspects from one country to another, centers certification, funding)

Feasibility

- Immediately:
    - Create a specific Working Group including the already existing North-American, European and Japanese cohorts/registries
    - Develop a financial strategy to secure enough funding to initiate and keep motivation for such a long-term enterprise and cover expenses to guarantee completion of the forms by the centers and monitoring of the data (Public funding opportunities for rare disorders)
- 1-3 years
    - Identify existing datasets and compare their advantages/disadvantages
    - Create an inventory of existing biomaterial collections and imaging datasets
    - Elaborate a unified eCRF compatible/acceptable by the different partners of the project (potential need to start working with paper forms, define a clear strategy for handling of missing data)
    - Implement an international network using such a eCRF for a global dataset (not underestimating important practical issues such as differences in regulatory aspects from one country to another, centers certification, funding)

Work group #6a: Clinical MSA-Biomarkers (Imaging)

Committee Members: David Eidelberg (Chair), David Brooks, Klaus Seppi, Andrew Siderowf, Ryan Walsh

Recommendation 1: Develop standardized protocols for MRI-based diagnostics at conventional field strengths and explore sensitivity of multimodal approach (e.g PET/MRI) to disease progression and preclinical diagnosis.

Need

- "MSA-typical" MR-based changes assess regional cerebral atrophy quantitatively with correlation to clinical disease characteristics of MSA. Furthermore, rates of disease progression are derived for serial volumetric MRI and DWI/DTI. There is a rich "MRI repertoire" with potential to be used in diagnosis, natural history, and treatment studies. There is, however, lack of evidence for MR-based changes of MSA at magnetic fields of 3.0T or higher, scarce evidence for early

MR-based changes in MSA, and limited comparability between studies given heterogeneous MRI protocols and different segmentation techniques.

Pathway & Feasibility

- Immediate action:
  - Create a multicenter MRI task force to identify the most replicable MR-based technique(s) and a framework for their development
  - Assess MR-based changes in MSA at magnetic fields of 3.0T or higher including newer MRI techniques
- 1- 3 year plan:
  - Develop application of multimodal (e.g. PET/MRI) imaging
  - Develop and standardize assessment of early MR-based changes
- Long-term vision:
  - Develop and validate MR-based MSA diagnostic criteria
  - Formally explore MR-based diagnostic, disease-tracking, and therapeutic response potential via multicenter network

Recommendation 2: Develop multicenter task force to explore, assess, and implement functional imaging protocols with currently available tracers to evaluate MSA-related brain networks and dopaminergic integrity using existing PET and SPECT tracers.

Need

- Promising but currently underdeveloped methods exist to evaluate MSA at the network level. FDG PET shows a replicable MSA-related metabolic network that discriminates MSA from PD at the single case level (including correlation with disease severity). Moreover, imaging of putamen dopamine D2-binding is reduced in MSA and tracks disease progression. Despite availability of these imaging modalities, FDG PET and dopamine receptor binding have not been widely taken-up for MSA diagnosis or monitoring disease status.

Pathway & Feasibility

- Immediate action:
  - Develop a consortium of imaging centers with access to functional imaging tools and expertise in network-based outcome measures in MSA
- 1- 3 year plan:
  - Validate network imaging measures in multicenter analyses
  - High affinity D2 SPECT and/or PET needs to be made available in MSA centres to develop these methodologies for disease tracking
- Long-term vision:
  - Standardize and validate functional imaging biomarkers for MSA diagnosis, disease progression, and response to treatment

Recommendation 3: Develop sensitive and replicable imaging agents to assess molecular aspects of MSA pathology including α-syn aggregation and local CNS inflammatory activity in the brains of MSA patients.

Need 3

- Molecular imaging has the potential to visualize MSA pathology in vivo. Two particularly promising areas for molecular characterization of MSA pathology are ligands that target neuro-inflammation and α-syn aggregates. While markers of neuro-inflammation are available, further refinements in terms of potency and specificity are possible. A-syn imaging

presents greater challenges due to the lack of available tracers, low density of the aggregated a-syn target and need for selectivity over native α-syn and other mis-folded protein species, particularly a-beta and tau.

Pathway & Feasibility

- Immediate action:
    - Develop a molecular imaging consortium for MSA that has access to tissue and other reagents for tracer development as well as qualified PET and SPECT sites for clinical studies
    - Support pre-clinical studies to develop potent and selective a-syn tracers for MSA glial and neuronal inclusions
- 1-3 year plan
    - High affinity fluoro-inflammation markers are now available for PET (e.g. DPA714 or GE180) which could be set up across multicenter network

- Long-term vision,:
    - There is potential for a multi-modal approach combined with structural-MRI and PET/fMRI functional scans, along with other molecular imaging for tau/a-beta and microglia.

Work group 6b: Clinical MSA-Biomarkers (Non-Imaging)

Committee Members: Leslie M Shaw (Chair), Roy Freeman, Andreas Jeromin, Michael Schlossmacher, Jing Zhang

Recommendation 1: To identify and establish infrastructure needs including standardized procedures for biological biomarkers--both collection of fluids and tissues and the biomarker tests that will be recommended for use--in MSA multicenter studies.

Need

- A very important unmet need in support of MSA-focused clinical studies and trials is to identify and then to put in place the infrastructure and standard operating procedures for the participating clinical sites and bioanalytical laboratory to assure that performance of biological biomarker testing is done under highly standardized conditions.
- Since biomarker data for MSA is sparse and knowledge of change of biomarker concentration over time is non-existent, a critical need is to assure that an array of well-vetted rugged performing test methods are put into place for both cross sectional and longitudinal studies. The types of tests anticipated by this WG will require standardized collection of biofluids(CSF, blood, plasma, serum) and tissues(skin biopsy; CNS and ANS at autopsy).

Pathway

38. Assemble a task force of biomarker experts from centers performing neurodegenerative diseases biomarker studies with their charge to define the biological biomarker tests and state of the art methods for fluid and tissue collections to be included in a multicenter longitudinal study. This is likely the most important first step for the non-imaging biomarkers.
39. Candidate tests include total a-SYN and tau as well as modified forms of -SYN and a lipidomics panel.
40. Define SOPs for biological samples and analytical methods already well vetted and in place in large multicenter studies such as the ADNI and PPMI studies and the American and European autonomic rare disease consortium.
41. Assess the biomarker changes in MSA using the most robust and reliable methods in ongoing trials (e.g. PPMI, ADNI and the American and European autonomic rare disease consortium).
42. Rate limiting is the need for appropriate analytical performance and clinical performance formal validation and acquiring administrative and financial support for infrastructure building.

Feasibility

- Given the current state of the field,
    - Assembly of a non-imaging task force should be achievable within a 1 year period provided administrative support for this task force is made available. Once this has been determined, the actual assembly of this task force should be accomplished within the short term period (within 6 months of the time administrative support is committed and a task force chair is appointed).

- Once the task force is assembled, and the charge to this task force communicated, that group then begins deliberations, and the work of defining SOPs as noted in the Pathway above. This process should be doable within a 12 month period of time. An early goal of this task force will be to identify data from ongoing studies that include MSA subjects, and assess biomarkers at BASELINE for MSA and non-MSA controls(particularly α-synucleinopathies, and normals free of neurodegenerative diseases), and to assess biomarker changes in MSA patients from studies that use well defined SOPs longitudinal data for assessments of change over time. Development of an analysis plan for assessment of the predictive performance of biomarkers at baseline for clinical decline is a recommended

Recommendation 2: Determine the "pathologic biomarker profiles" in MSA patients using pathology-based and "unbiased" validated biomarker tests in biofluids and CNS/ANS autopsy tissues in ongoing multicenter studies.

Need

- There is an unmet need for measurement, using validated assays, candidate "pathophysiologic" biomarkers in CSF and tissues in a sufficient number of MSA patients at baseline and longitudinally to permit rigorous statistical assessment of the diagnostic and prognostic utilities of these tests. Achievement of these goals depends directly on Recommendation #1
- Achievement of the goal for Recommendation #2 is dependent upon having available validated methods for biomarker tests for a-SYN, modified forms of -SYN as well as a lipidomics panel for reliable measurements in CSF and in nervous tissues including brain collected at autopsy and peripheral tissues. Running in parallel with Recommendations #1 and #3, this recommendation requires the systematic collection, under standardized collection protocols, of CSF as well as brain and peripheral tissues collected at autopsy. Thus having as many paired CSF and brain/peripheral tissues will permit defining the correlations needed to establish the pathologically based biomarker profiles in CSF.
- In subsequent longitudinal studies in these study subjects the changes in these biomarker levels in CSF as well as relationships to clinical changes, particularly the relationships between the baseline values and subsequent clinical progression of disease, will be characterized.

Pathway

43. Working in concert with the biomarkers taskforce, defined in Recommendation #1 for non-imaging biomarkers, biomarker researchers who are developing validated tests for a-SYN, including total and phospho-a-SYN and post-translationally modified a-SYN (phosphorylation, nitration and oxidation) will provide documentation of and recommendations for validated test methods for these biomarkers.
44. Another significant area of investigation is the role of lipid metabolism perturbations associated with MSA with a special interest in demyelination in the early stages of the disease. Using new mass spectrometry based methods the hypothesis that dysregulation of lipid metabolism involved in myelin synthesis and maintenance by oligodendrocytes plays a substantive role in the unique neuropathology of MSA will be tested

✓ Rate limiting steps

- An essential need is having and applying formally validated methodology for the above described biomarker tests and especially for the lipid profiles given their complexity and challenges to establish stable and reliable assays has to be acknowledged as a challenge. There are well established ongoing efforts to validate all of the described biomarker tests and it will be essential for the Task Force to have regular interaction with these studies.

Feasibility

- The timeline for achieving this recommendation depends upon the degree of success within the next 1-2 years in validation work that is ongoing for validated, standardized method development. An early goal of the Task Force will need to be to conduct regular critical reviews of the ongoing validation and standardization work for both the fluid and tissue collection protocols, and the analytical measurement biomarker methods. It is hoped that this can be accomplished within the next 1-2 years dependent on the success of the method validation work that is going on.

Recommendation 3: To develop a cutaneous biomarker for multiple system atrophy by measuring α-syn deposition in cutaneous autonomic nerves.

Need:

- There is an unmet need for a diagnostic and prognostic biomarker in MSA. Skin biopsy is minimally invasive, can be repeated frequently and has a very low complication rate. -SYN containing oligodendroglia are the pathological hallmark of MSA. Cutaneous α-SYN deposition, can be reliably measured in Parkinson's disease (PD) and is increased in PD patients compared with controls.
- Specifically (1) increased deposition of α-syn is present in cutaneous, sympathetic, adrenergic fibers innervating the piloerector muscles and sympathetic, cholinergic fibers innervating the sweat glands but not in cutaneous sensory fibers; and (2) greater α-syn deposition is associated with worsening Hoehn and Yahr scores and with measures of sympathetic and parasympathetic nervous system function on clinical autonomic testing.
- In preliminary studies similar analyses have been done on a small number of MSA patients. Deposition of α-SYN is detectable in MSA although amounts are substantially less than in patients with Parkinson's disease and pure autonomic failure. These findings are consistent with reports of peripheral nervous system involvement in 10-40% of MSA patients.

Pathway:

45. Working in concert with the biomarkers taskforce, defined in Recommendation #1 for non-imaging biomarkers, develop a validated cutaneous biomarker for MSA by measuring α-SYN in cutaneous autonomic nerves. The following are recommended studies
    - o Cross-sectional and longitudinal studies to determine the association and prognostic predictive value of cutaneous αSN deposition in well worked up MSA patients (history, questionnaire, structured examination, autonomic testing); control groups to include healthy subjects, idiopathic Parkinson's disease, pure autonomic failure).
    - o Comparison studies with other biomarkers, e.g., CSF, imagining
    - o Combination studies with other biomarkers
    - o Studies in animal models

✓ Rate limiting steps

- o An essential need is a formally validated methodology for -SYN measurement in cutaneous nerves for which establishing reliable antibodies for histopathology is key
- o Complexity of multicenter projects, e.g., site training in biopsy techniques, biopsy transport

Feasibility

- The timeline for achieving this recommendation is dependent upon gaining support for the inclusion of the skin biopsy protocol into ongoing trials that include MSA patients, e.g. PPMI and others. It is hoped that this can be accomplished within the next 1-2 years dependent on success in acceptance of this protocol into these studies. Several more years, ~ 2-5 years, will be required for accumulation of a sufficient number of MSA and disease and non-disease controls in order to permit analysis and interpretation of this data.

Working Group 7: Clinical – Treatments and Trials

Committee Members: Phillip Low (Chair), Werner Poewe, Wendy Galpern, Steven Piantadosi, Hubert Fernandez, Victor Abler, Susanne Ostrowitzki

Recommendation 1: Characterize and validate clinical markers of disease activity and progression through natural history studies to inform the design of clinical trials.

Need

- Major inroads have been made into defining diagnostic criteria, clinical subtypes, and natural history of MSA. Yet, as novel therapeutic agents aimed at modifying the course of MSA are developed, there will be a critical need to identify patients earlier in the disease course and to develop markers, including molecular markers of disease progression and response to treatments. Currently there are limited data on rates of disease progression, and changes in outcomes over time are incompletely characterized. Such natural history data will facilitate the design of clinical trials.

Pathway

- Establish prospective cohort studies to define progression rates and sensitivity to change over time of clinical (rates of change of scales, objective motor and non-motor tests), imaging and other (wet) markers.
- Identify features that characterize the prodromal phase of MSA and develop novel diagnostic criteria and algorithms that will be sensitive to very early or prodromal MSA stages. This approach needs to be enhanced by validated biomarkers of disease activity and progression.
- Further characterize phenotypes, prevalence, and natural history of MSA through collaborative consortia employing global registries as well as common diagnostic criteria and clinical assessments incorporating the use of common data elements to facilitate data sharing and meta-analyses.
- Compare phenotypic, natural history and genetic data globally and promote data sharing amongst participatory groups

Feasibility

- 1-3 years: Establish registries and parameters to define progression rates and study biomarkers.
- >3 years: Define progression rates and sensitivity to change of clinical scales and biomarkers in multiple regions.
- >3 years: Multi-center cohort study of clinical, imaging and wet biomarkers of early MSA.

Recommendation 2: Develop sensitive outcomes to evaluate disease modifying therapies including validated biomarkers of disease activity, progression, and response to treatment.

Need

- The diagnosis of MSA relies primarily on clinical features and evidence of disease progression, and primary outcome measures in clinical trials are typically changes on clinical rating scales. We have made significant progress with clinical biomarkers including autonomic (cardiac MIBG; CASS; TST%), imaging, and early efforts on skin, CSF, blood and molecular biomarkers. Future studies need to link such biomarkers to disease activity in early and prodromal phases of MSA to better quantitate activity and progression. Biomarker-based diagnosis and measures of disease progression should supplant current clinical measures.

Pathway

- Identify and validate fluid biomarkers of disease activity and progression, incorporating standardized methodology of sample collection and processing and comparing with controls and other α-synucleinopathies.
- Develop protocols for harmonized sampling methods and establish biomaterial (CSF, serum, DNA, tissue) banks to facilitate studies of biomarkers within multisite consortia and
- Establish imaging biomarkers of disease activity and progression

Feasibility

- 1-3 years: Establish biomaterial banks
- 1-3 years: Identify biomarkers of disease activity/progression and optimize methodology to measure such biomarkers
- 1-3 years: Establish MRI morphometric biomarkers of disease activity and progression.
- >3 years: Application of biomarkers to research studies to enable earlier diagnosis and better indices of disease activity.

Recommendation 3: Identify disease modifying therapies, and initiate exploratory and confirmatory randomized clinical trials (RCT).

Need

RCTs aimed at modifying the course of the disease have been negative to date. To improve likelihood of successful treatment of a fatal rare disease, the necessary conditions include:

- We need to design an "optimistic" pipeline to move exploratory studies forwards efficiently for drugs or approaches with little or no clinical testing, but show promise in experimental models or case reports.
- Establish sound scientific basis. The drug should cross the BBB, show target engagement, and have measurable biologic activity
- Improved outcome measures including biomarkers, patient reported outcomes and composite time to disability milestones.

Pathway

- Establish a panel of experts in MSA from NIH, Industry and Academia to review and prioritize candidate agents defining when a potential agent or approach is ready for RCT
- Once the scientific rationale is established, exploratory studies combine evaluation of safety with efficacy and minimize study duration by use of biomarkers and composite endpoints
- Design robust comparative studies of different drugs or different dosages of the same drug ideally over a shorter study period. A key impediment is the lack of robust biomarkers of response to therapy.
- Partner with industry to collaborate on new therapeutic entities in drug development be doing the following:
    - Find which companies are involved in re-purposing and developing new indications for already approved medications / generics for collaboration
    - Within these companies, work with the clinical pharmacology R&D division to see what drugs are likely to have target engagement, cross the BBB and measurable biological activity for MSA
- For RCTs of disease modifying agents, provide infrastructure and oversight to ensure adequate implementation of confirmatory studies.

Feasibility

- 1-3 years: Establish panel of experts and review potential agents and provide infrastructure for RCT
- 1-3 years: Design and implement exploratory studies.
- >3 years: Design confirmatory studies. Delay is related to definitive of robust biomarkers.

Recommendation 4: Identify promising treatments to improve major symptoms and function in patients with MSA

Need

- Many major symptoms of MSA, such as orthostatic hypotension (OH), neurogenic bladder or ataxia are not managed adequately with available therapies. Improved understanding of pathogenesis of MSA and symptoms pathophysiology could lead to novel therapeutics. In addition, there is a need to determine the magnitude of the placebo response in MSA.

Pathway:

RCTs of major symptoms:

- Orthostatic Hypotension (OH).
    - Explore interventions that improve OH with only minimal worsening of supine hypertension. Candidate approaches might include acetylcholinesterase inhibition (pyridostigmine), pyridostigmine + droxidopa; broadening the action potential (3,4 DAP), blocking norepinephrine reuptake (NET inhibition with atomoxetine).
    - Initiate trials of Non-pharmacologic approaches to improve standing BP
- Motor function Including Ataxia
    - Evaluate treatments including non-pharmacological interventions (exercise & training, specific types of physiotherapy approaches to improve balance and mobility)
- Sleep problems.
    - Studies of novel approaches to control stridor and sleep apnea in MSA.
- Neurogenic bladder. Studies to minimize symptoms and delay progression

Feasibility

- 1-3 years: Evaluate potential therapies for OH pyridostigmine, droxidopa-pyridostigmine, 3,4 DAP, atomoxetine.
- 1-3 years: RCT of non-pharmacologic treatment of OH
- 1-3 years: RCT of intensive rehabilitation in MSA mobility and ataxia
- 1-3 years: RCT on management of neurogenic bladder

Working Group 8: MSA patient advocacy

Committee Members: Pam Bower (Co-chair), Larry Kellerman (Co-chair), Judy Biedenharn, Philip Fortier, Carol Langer, Cyndi Roemer, Lily Shih, Sharon Sutton

Recommendation 1: Increase knowledge about MSA among medical professionals by developing a continuing education program that emphasizes patient-centered care. Develop accredited MSA centers of excellence to serve as models.

Need

MSA is too frequently mis-diagnosed by clinicians because of lack of experience and/or lack of knowledge of the diagnostic criteria. The needs of MSA patients are not fully recognized by a wide variety of medical specialists and allied health professionals, leaving patients underserved in comparison to those with more well known diseases.

Pathway

- Develop the "gold standard of care" for MSA through the survey of knowledgeable medical specialists.
- Work with MSA organizations around the world, drawing from the expertise of their medical and scientific advisors to implement a “gold standard of care” program and move toward accreditation of centers of excellence for MSA clinical care.
- Provide financial support to research/medical conferences that include agenda topics on MSA.
- Develop a comprehensive MSA medical education program drawing on a variety of modalities including CME workshops, conferences, rounds, fellowships, media, etc.
- Promote the use of a medical text book detailing Multiple System Atrophy.

Recommendation 2: Initiate a funded liaison who works with stakeholders to access funds, cultivate the development of innovative technologies, and nurture collaborative research programs.

Need:

As centers continue to advance in research pathways and innovative technologies, there is a demand for more sophisticated global collaboration. This liaison position will identify, coordinate and maintain collaborative efforts between government programs and foundation activities.

Pathway:

- Identify partnering organizations, government agencies or funding programs and MSA-related foundations that will work together to meet the WGs' recommendations
- Create a funded liaison position with appropriate oversight and ethical guidelines funded through a mix of dollars.
- Liaison will report to an oversight board, providing semi-annual reports that will be placed on the web for public access.

Recommendation 3: Institute a public information structure to develop and disseminate information tailored for advocacy and awareness.

Need:

Current quality advocacy materials are needed for medical professionals to encourage earlier and more effective treatment, and for the general public as advocacy is very important for funding, support and awareness.

Pathway:

- Identify medical researchers/practitioners who will guide development of advocacy materials.
- Establish a clearinghouse of information funded from a mix of public and private sources.
- Dispense advocacy materials through multiple modalities.
- Facilitate a pathway for greater involvement for those expressing interest.
- Implement a survey program to assess efficacy of materials.

Recommendation 4: Develop a dynamic and collaborative network of partnerships among relevant organizations that will strengthen advocacy and support patient responsive research.

Need:

Presently there are insufficient networking activities in place. Access to potential positive treatment opportunities and clinical trials for patients is limited. Partnering is a powerful tool to support advocacy efforts and patient responsive research.

Pathway:

- Implement a database of possible treatments, results of clinical trials, patient survey results and feedback with a system of exchange between patients and researchers and make advocates aware of this information as appropriate to facilitate outreach.
- Develop global programs to encourage patients to participate in any clinical trial in the world.
- Establish collaborative efforts with other organizations to strengthen advocacy and patient responsive research.
- Ensure a dynamic network through implementation of an annual review program.