Multiple system atrophy (MSA) is an α-synucleinopathy with a very aggressive course and poor prognosis. It is less common as compared to Parkinson’s disease (PD), but due to its fast progression after clinical diagnosis and the limited availability of symptomatic amelioration, MSA represents a serious health and social problem. The disease lacks efficient treatment and poses a great challenge to translational research at present.

1. Diagnostic limitations

MSA presents with a variable set of non-motor and motor symptoms that makes the early diagnosis difficult. Classically, based on the current diagnostic criteria (Gilman et al., 2008), MSA is diagnosed clinically with partial degree of certainty (possible or probable) only when motor symptoms occur (Fanciulli and Wenning, 2015). However, the motor symptoms are usually preceded by a set of non-motor features including urogenital dysfunction, orthostatic hypotension, REM sleep behavior disorder (RBD) that may seem unspecific but indicate a much earlier disease onset. The efforts to identify early body fluid-, tissue-, or imaging biomarkers are yet insufficient to support the early diagnosis of MSA before the onset of parkinsonism or cerebellar symptoms (Jellinger and Wenning, 2016). Therefore, the first bottleneck in the successful identification of translational therapies for MSA remains the difficulty to provide early diagnostic markers and markers of disease progression.

2. Therapeutic target definition in MSA – unresolved etiology and candidate downstream disease mechanisms

What is the trigger of MSA? A single study to date provides evidence for mutations in the COQ2 gene linked to MSA in Japanese families (The Multiple-System Atrophy Research Collaboration, 2013). However, these mutations were not found to play a role in other cohorts of MSA patients (Sharma et al., 2014; Ogaki et al., 2014; Chen et al., 2015) proposing a possible population-specific predisposition. Genome-wide association studies and estimates of heritability fail to confirm a strong role of genetic predisposition as a prominent risk factor for MSA (Sailer et al., 2014; Ogaki et al., 2014; Chen et al., 2015) but indicate a much more unresolved etiology and candidate downstream disease mechanisms.
MSA brain (Papp et al., 1989; Spillantini et al., 1998; Wenning et al., 2008). α-syn has been shown to form aggregates also in the neuronal cytoplasm in affected neuronal circuits, however these neuronal inclusions show different properties as compared to classical Lewy bodies (Cykowski et al., 2015).

The reason for the unique pattern of α-syn accumulation in MSA remains to date greatly speculative. Currently, two major theories exist – one suggesting that a primary oligodendrogliopathy is the reason for the ectopic GCI formation (Wenning et al., 2008), and the second proposing the existence of disease-specific α-syn species and distinct protein assemblies which may explain the specific pathology and phenotypes in α-synucleinopathies (Peelaerts et al., 2015; Melki, 2015).

The idea of possible primary oligodendrogliarial dysfunction is supported by the observation that p25α relocation from myelin to the soma and aggregation in the cytoplasm of MSA oligodendrocytes may precede the aggregation of α-syn and the formation of the classical GCIs (Song et al., 2007). However, it remains unclear how this event is triggered.

Another unresolved mystery of MSA pathogenesis which may be linked to a primary oligodendrogliopathy in this disorder, is the source of α-syn in GCIs. It is considered that α-syn is a neuronal protein that is not expressed in mature oligodendrocytes (Miller et al., 2005; Solano et al., 2000). A recent study which applies laser dissection microscopy to provide a more precise characterization of the SNCA mRNA expression in healthy and MSA oligodendroglia suggests that α-syn expression might be present in these cells and even show a tendency towards increase in MSA brains (Asi et al., 2014). However, these results contradict reports suggesting that the expression level of α-syn mRNA is unchanged in MSA post-mortem samples (Ozawa et al., 2001). Respectively, if the latter is true, the protein degradation rather than the production of α-syn may be disturbed in oligodendrocytes and trigger the GCI pathology. Currently, experimental indirect evidence supports this hypothesis (Schwarz et al., 2012; Puksas et al., 2015; Stefanova et al., 2012b) but the data from post-mortem studies in MSA brains confirming its validity is limited (Tanji et al., 2013; Langerfeld et al., 2007; Miki et al., 2016).

Finally, the hypothesis of α-syn inclusion spreading linked to distinct α-syn strains is currently widely discussed and studied in MSA as well as in other α-synucleinopathies. The principle possibility of α-syn transfer from neurons to oligodendrocytes has been experimentally suggested in an AAV-α-syn overexpressing rat model of PD receiving rat oligodendroglial grafts in the striatum (Reyes et al., 2014). However, α-syn aggregates have not been detected in striatal grafts in MSA transgenic mice overexpressing α-syn in oligodendrocytes (Stefanova et al., 2009). A study by Peelaerts and co-workers suggested that the transfer of α-syn to oligodendrocytes may be dependent on the type of recombinant α-syn strains inoculated in the rodent brain (Peelaerts et al., 2015). The ability of α-syn derived from MSA brains to trigger aggregate spreading was shown in A53T transgenic mouse model of PD (Watts et al., 2013; Prusiner et al., 2015), however this study failed to demonstrate α-syn aggregation in oligodendrocytes. Furthermore, “a prion transmission of neurological disease”, as claimed by Prusiner and co-workers in relation to MSA, has been observed only in genetically modified transgenic mice overexpressing the A53T mutation of α-syn, but not in wild type animals (Watts et al., 2013; Prusiner et al., 2015). These results suggest that only a specific condition of the host brain but not the MSA α-syn species per se may trigger disease transmission.

In summary, the role of α-syn pathology in the pathogenesis of MSA is unequivocal, but its exact origin and genesis as well as the role of preceding oligodendrogliarial dysfunction remain unresolved and warrant further studies. It is possible that both, propagation from neurons to oligodendrocytes as well as oligodendrogliarial expression of α-syn may contribute to the formation of GCIs. However, at present there is insufficient evidence to claim the existence of “MSA prions” and label MSA a prion disease.

3. Animal models of MSA - advantages and limitations

A key problem and major limitation in modelling MSA to date is the limited knowledge on the initiation of the disease process. Over the years, transgenic models overexpressing human α-syn in oligodendrocytes using different promoters have been a valuable tool to identify downstream mechanisms of disease progression in MSA. Each of these models shows different degree of functional deterioration (Table 1) and MSA-like neuropathology (Table 2). The myelin basic protein (MBP)-α-syn mouse presents with prominent demyelination which is α-syn-dose dependent and leads to secondary neuronal loss in neocortex and axonal degeneration in striatum (Shults et al., 2005). The 2,3-Cyclic-nucleotide 3’-phosphodiesterase (CNP)-α-syn transgenic mouse suggested the role of endogenous α-syn accumulation in axons that may lead to secondary axonal degeneration affecting predominantly the cortex and the spinal cord (Yazawa et al., 2005). The proteolipid protein (PLP)-α-syn transgenic mouse suggests a leading role of microglial activation resulting in selective striatonigral degeneration (SND)
Table 2
Neuropathology in experimental MSA models with α-synuclein pathology.

| Model                   | GCl          | Regions with neuronal loss                                                                 | Microglial activation | Astrogliosis | Demyelination | Oligodendroglial loss |
|-------------------------|--------------|--------------------------------------------------------------------------------------------|-----------------------|--------------|---------------|-----------------------|
| MBP-α-syn mice          | YES          | Neocortex, Terminal loss in striatum                                                        | NO                    | YES          | YES           | NO                    |
| CNP-α-syn mice          | YES          | Spinal cord, Hippocampus                                                                     | NO                    | na           | YES           | NO                    |
| PLP-α-syn mice          | YES          | Substantia nigra pars compacta, Striatum, Locus coerules, N. ambiguus, Laterodorsal tegmental nucleus, Pedunculopontine tegmental nucleus, Pontine micturition center, Medullary raphe nuclei, Onu's nucleus, Intermediolateral columns (parasympathetic outflow) | YES                    | NO           | NO            | NO                    |
| AAV-MBP rat             | YES          | Substantia nigra pars compacta, Striatum                                                     | na                    | na           | na            | na                    |
| AAV-Olig001 rat         | YES          | na                                                                                          | YES                   | na           | na            | na                    |

na - not assessed. (Shults et al., 2005; Yazawa et al., 2005; Stefanova et al., 2005; Stefanova et al., 2007; Krismer et al., 2013; Boudes et al., 2013; Kuzdas et al., 2013; Stefanova et al., 2013; Flabbe et al., 2014; Fernagut et al., 2014; Bassil et al., 2017b; Mandel et al., 2017; Hartner et al., 2016; Stefanova et al., 2014).

similar to the human disease (Stefanova et al., 2005; Stefanova et al., 2007; Stefanova and Wenning, 2015). Intriguingly, exposure to the mitochondrial toxin 3-nitropropionic acid (3-NP) or a proteasome inhibitor exacerbates the phenotype leading to olivopontocerebellar atrophy (OPCA) proposing that α-syn together with protein degradation deficits or mitochondrial dysfunction may play synergistic roles in the pathogenesis of MSA (Stefanova et al., 2005; Stefanova et al., 2012b).

Recently, viral overexpression of α-syn in oligodendrocytes has been suggested to model MSA-like pathology in rats and non-human primates (Bassil et al., 2017b; Mandel et al., 2017) and holds promise as an alternative strategy for preclinical target validation for MSA (Tables 1 and 2).

Even though the models of MSA based on overexpression of α-syn in oligodendrocytes mechanistically replicate the GCI pathology typical for the human disease, they: i) prove the causative role of oligodendroglial α-syn accumulation in MSA-like neurodegeneration; and ii) suggest the possible role of downstream mechanisms like microglial activation and demyelination which may prove important therapeutic targets for MSA.

4. Target validation in experimental MSA

Despite the uncertainties in the etiology and pathogenesis of MSA, α-syn emerges as the first-choice therapeutic target in MSA. Second in line, with relevance to the progression of the disease, is microglial activation. Still in experimental phase, research interest is further directed to possible brain insulin resistance, changed epigenetic control, and oligodendroglial dysfunction/demyelination in MSA (see Table 3).

At present targeting α-syn pathology in experimental MSA (eMSA) involves immunization approaches, other anti-α-syn aggregation strategies, small molecules, or repurposed drugs with α-syn lowering activity. There have been several preclinical screening studies proving biological activity and target engagement of several different approaches (Table 3).

First experimental results applying active immunization with AFFITOPE (AFF1) in transgenic MSA mice support the hypothesis that this approach may lead to reduction of the α-syn load through upregulated clearance by activated microglia, thereafter resulting in motor amelioration, reduced demyelination and neurodegeneration (Mandler et al., 2015). Elegant experimental design using fluorescence-labeled AFF1-antibodies confirmed their trafficking in the CNS which is crucial for the feasibility of the immunization approach. According to the current understanding, immunotherapies target extracellular α-syn species that are considered important for the disease progression in α-synucleinopathies (Lee and Lee, 2016) However, intracellular binding of AFF1-antibodies to α-syn has also been observed in MSA mice. These complexes presumably are cleared by the intracellular protein degradation system as suggested by experiments in PD models (Masliah et al., 2011), however further studies are needed to evaluate their faith in diseased oligodendrocytes in MSA. Another unresolved issue remains the interaction of the α-syn-antibodies with the normal function of the protein in long term. Phase I clinical trials seem to support the safety of the approach over a period of 12 months (NCT01568099, NCT02267434, NCT02270489). Therefore, immunotherapy is considered an attractive candidate for disease modification in MSA.

Small molecules represent another very attractive approach for therapies in MSA and other α-synucleinopathies. An advantage of this strategy is that the small molecules usually target the pathology-linked species of α-syn (oligomers and/or fibrils) without interfering with the soluble protein and its physiological function. An interesting small molecule that has been shown to modulate α-syn oligomer formation is Anle138b (Wagner et al., 2013). Anle138b effectively inhibits disease progression in a PD model with mild disease progression (Levin et al., 2014). Primary observations in young PLP-α-syn transgenic mice receiving Anle138b over a period of 5 months support the efficacy of the drug for eMSA (unpublished data). However, the drug induces partial motor amelioration in a model of advanced eMSA with less prominent neuropathological benefit (Fellner et al., 2016) suggesting that the efficacy of α-syn targeting strategies in MSA in a clinical setting may be strongly depend on the stage of the disease. Another potent candidate in the early stages of experimental investigation is the molecular tweezers CLR01. This small molecule is able not only to prevent the formation of α-syn oligomers, but also to enhance clearance of already formed oligomers (Prabhudesai et al., 2012; Acharya et al., 2014; Attar and Bitan, 2014). Preliminary results suggest the efficacy of CLR01 to ameliorate the α-syn pathology in PLP-α-syn transgenic mice when applied intracerebroventricularly (Stefanova et al., 2017) and together with the data collected in PD models (Prabhudesai et al., 2012; Richter et al., 2017) may hold promise for the further development of the approach. More work is needed to provide formulations with better brain permeability that will ensure feasible application in patients.

Alternative ways of fighting α-syn aggregation in eMSA brains include modulation of post-translational modifications, boosting endogenous clearance, and interference with epigenetic mechanisms (Table 3). Experimental evidence in young MSA mice proposes the caspase-1 inhibitor produg VX-765 as an alternative strategy to reduce α-syn aggregation by reducing its C-terminal truncation and provide neuroprotection and motor improvement in very early stage disease
### Table 3
Target validation in experimental MSA models with α-synuclein pathology and first translational efforts.

| Intervention | Target | Stage of intervention development | Preclinical screening in eMSA | Clinical trial in MSA | Translational notes |
|--------------|--------|-----------------------------------|-------------------------------|-----------------------|---------------------|
| Rifampicin   | α-Synuclein | Phase II completed | MBP-α-syn mouse; treatment initiation after motor symptom onset (12 mo of age); treatment duration – 3 mo; GCI reduction, neuroprotection, no functional readout (Ubhi et al., 2008) | No change in rate of progression (Low et al., 2010) | Lack of functional improvement in the preclinical study; Differences between preclinical and clinical outcome measures. |
| AFFITOPE     | α-Synuclein | Phase I completed | MBP-α-syn mouse; treatment initiation before motor symptom onset (4-5 mo of age); treatment duration – 6 mo; GCI reduction, neuroprotection, mild motor improvement (Mandler et al., 2015) | – | Efficacy shown in early stage disease in eMSA models only. |
| Anle138      | α-Synuclein | Towards Phase I | PLP-α-syn mouse; treatment initiation before motor symptom onset (2 mo of age); treatment duration – 5 mo; GCI reduction, neuroprotection, motor improvement in early disease, but less prominent efficacy in advanced eMSA (PLP-α-syn mouse + 3-nitropropionic acid model) (unpublished, (Fülsher et al., 2016)) | – | Efficacy shown only when therapy initiated in early stage disease in eMSA model, but limited in advanced eMSA, suggesting the importance of therapy onset. |
| VX-765       | α-Synuclein | Repurposing | PLP-α-syn mouse; treatment initiation before motor symptom onset (2 mo of age); treatment duration – 2.5 mo; GCI reduction, neuroprotection, motor improvement in early stage eMSA (Bassil et al., 2016) | – | Efficacy shown in early stage disease in eMSA model only. |
| CLR01        | α-Synuclein | Experimental | PLP-α-syn mouse; treatment initiation at symptom onset (6 mo of age); treatment duration – 1 mo; intracerebroventricular application; GCI reduction, functional improvement (oral communication, Stefanova et al., 2017) | – | Development of drug formulations with better blood-brain-barrier permeability needed. |
| MPLA         | α-Synuclein | Repurposing | PLP-α-syn mouse; treatment initiation at motor symptom onset (6 mo of age); treatment duration – 3 mo; GCI reduction, neuroprotection, motor improvement in eMSA when therapy started at the time of motor symptom onset. (Venezi et al., 2017) | – | Efficacy shown when therapy started at the time of motor symptom onset in eMSA model. |
| Minocycline  | Neuroinflammation | Phase II completed | PLP-α-syn mouse; treatment initiation before motor symptom onset (2 mo of age); treatment duration – 2 mo; Reduction of microglial activation, neuroprotection, no functional readout in early eMSA (Stefanova et al., 2007) | Reduction of microglial activation, no change in rate of progression (Dodel et al., 2010) | First indication of predictive validity of the PLP-α-syn model regarding target engagement, i.e. effects on microglial activation. Difference between initiation of therapy in eMSA and in patients. Difference between preclinical and clinical outcome measures. |
| Fluoxetine   | Neuroinflammation | Phase II completed | MBP-α-syn mouse; treatment initiation at motor symptom onset (6 mo of age); treatment duration – 1 mo; Increase of GDNF and BDNF, reduction of astrogliosis, reduction of demyelination, reduction of GCI, neuroprotection, motor improvement (Ubhi et al., 2012) | No change in rate of progression (NCT01146548) | Difference between preclinical and clinical outcome measures. |
| AZD3241     | Neuroinflammation | Phase I completed | PLP-α-syn mouse + 3-nitropropionic acid model; Reduction of microglial activation, neuroprotection in early eMSA; Reduction of microglial activation, no neuroprotection in advanced eMSA (Stefanova et al., 2012a; Kaindlstorfer et al., 2015) | – | Experimental data indicate the role of initiation of therapy (early versus late) on the outcome of therapy. |
| Exendin-4   | Brain insulin resistance | Repurposing | PLP-α-syn mouse; treatment initiation before motor symptom onset (2 mo of age); treatment duration – 3 mo; Neuroprotection in SNc, reduction of monomeric α-syn, no significant motor improvement in early stage eMSA (Bassil et al., 2017a) | – | Biological activity shown in early stage disease in eMSA model, without significant motor improvement. |
| NaPB         | Histone acetylation | Repurposing | PLP-α-syn mouse; treatment initiation after motor symptom onset (9 mo of age); treatment duration – 2 mo; GCI reduction, neuroprotection, motor improvement in eMSA when therapy started at the time of motor symptom onset. (Sturm et al., 2016) | – | Efficacy shown in eMSA model when therapy started after the motor symptom onset. |

(continued on next page)
Efficacy shown with high but not low dose when therapy initiated in early stage disease in eMSA model. Difference between efficacious drug doses shown in preclinical and low dose used in clinical setting. Efficacy of low dose, however, when compared to high dose, in the eMSA model was not shown. When therapy started in advanced stage disease, efficacy of low dose was shown. No change in rate of progression with low dose treatment (Poewe et al., 2015). Difference between efficacious drug dose in preclinical and the low dose used in the clinical trial may be due to the preclinical data being performed on an embryonic mouse model of disease, whereas the clinical trial was performed on adult human patients.

Neuroprotection, motor improvement in early eMSA with high dose, but not with low dose treatment. (Stefanova et al., 2008) predicted by the preclinical data. Differences between preclinical and clinical outcome measures of efficacy.

Concerns about the design of the clinical trial. New clinical trial ongoing but its causative role in the pathogenesis of human MSA is unclear (no imaging data on early demyelination in MSA, only post-mortem evidence of demyelination available). Differences between therapeutic approaches have already been tested in eMSA with high dose, however its efficacy to reduce the motor deficits and the neuronal loss in the striatonigral and the olivopontocerebellar systems was strongly dependent on the time of initiation of the treatment. The drug was only able to potentiate the efficacy of the single interventions.

Targeting the toxic pro-inflammatory microglial responses has been considered an alternative approach to mitigate the disease progression in MSA (Fellner et al., 2013). The myeloperoxidase inhibitor AZD3241 was shown to successfully suppress microglial activation in eMSA, however its efficacy to reduce the motor deficits and the neuronal loss in the striatonigral and the olivopontocerebellar systems was strongly dependent on the time of initiation of the treatment. The drug was only leading to neuroprotection when applied early in the disease progression but fails to lead to phenotypic improvement when full-blown pathology is already present in MSA mice (Stefanova et al., 2012a; Kaindlstorfer et al., 2015). Therefore, this has been further experimental indication on the role of disease stage for the success of a therapeutic approach targeting microglial activation in eMSA.

An interesting new target has been proposed recently in MSA. Primary observations demonstrated that impaired insulin/insulin-like growth factor-1 signalling and brain insulin resistance may contribute to the pathogenic events in MSA (Bassil et al., 2017). Therefore, treatment with the glaucagon-like peptide-1 analogue exendin-4, a FDA-approved antidiabetic drug was tested in eMSA. Very young PLP-α-syn mice (six-week-old) receiving exendin-4 treatment over a period of 12 weeks showed dopaminergic neuron protection in the SNc and lowering of monomeric α-syn brain levels without significant motor improvement. These primary studies indicate the biological activity of exendin-4 in eMSA, but further studies will be needed to identify the potency of the drug to slow the disease progression as measured by functional indices of motor activity.

In summary, most of the tested strategies (Table 3) show excellent biological activity in pre-clinical models of early stage eMSA with some considerations. Several of the therapeutic approaches have already shown safety and tolerability in phase I clinical trials with variable duration. The successful outcome of future efficacy clinical trials may strongly depend on the stage of initiation of therapy, and the relevance of the outcome measures to the readouts reported in the pre-clinical experiments.

5. Lessons from first translational clinical trials

A few interventions screened in eMSA have already been tested in clinical trials (Table 3). Unfortunately, the outcomes of the clinical
trials in MSA, which measure changes in rate of disease progression, have been mostly negative to date despite the good biological activity demonstrated in eMSA. However, a lot has been learned about the possible problems we still confront in our translational efforts.

The predictive validity of the PLP-α-syn mouse model is partly supported by two clinical trials (though negative in terms of change of disease progression rate). In the first example, minocycline, a tetra-cycline antibiotic that crosses the blood-brain barrier, suppresses microglial activation effectively both in PLP-α-syn mice (Stefanova et al., 2007) and MSA patients (Dodel et al., 2010). Although target engagement has been predicted in MSA mice and confirmed in a clinical trial, minocycline remains inefficient to reduce disease progression in MSA patients when applied a few years after motor symptom onset. However, the experimental evidence show that minocycline can rescue nigral neurons when applied before the motor symptom onset in MSA mice, supporting the notion that early treatment start may be of paramount importance for successful disease modification.

The second example of predictive validity of the PLP-α-syn model is linked to the use of rasagiline. The experimental data suggest that only high dose but not low dose rasagiline has beneficial effect in eMSA (Stefanova et al., 2008). Therefore, the failure of low dose rasagiline treatment in MSA patients to exert changes in disease progression has been predicted, but the low dose of 1 mg/day has been the only feasible dosage to avoid side effects of rasagiline in a clinical setting (Poewe et al., 2015). These results indicate the strong need of preclinical designs that not only have proof-of-concept value related to the biological activity of the intervention, but also address the drug efficacy in a clinically relevant paradigm.

Finally, important insights related to the significance of outcome measures in preclinical studies and clinical trials were gained in the rifampicin trial in MSA. Rifampicin has been suggested to lower α-syn levels in MBP-α-syn mice which has been further associated with neuroprotection in the neocortex and striatum of these mice (Ubbi et al., 2008). The follow-up clinical trial has reported futility of rifampicin to change rates of disease progression in MSA patients (Low et al., 2014). In this specific case no functional improvement has been reported in eMSA, while the major readout in the clinical trial has been the rate of functional deterioration in MSA. The discrepancy in the outcome measures in preclinical versus clinical setting as well as the lack of selective biomarkers that may confirm or discard the biological target engagement (α-syn brain load) in patients, makes the conclusions about the actual efficacy/futility of rifampicin in MSA difficult.

6. Conclusions and future directions

In summary, there is still a serious gap in the translation of preclinical findings into conclusive clinical trials. Deficits can be identified both on the preclinical and the clinical side. We have collected significant knowledge on the α-syn downstream pathogenic mechanisms of MSA and have identified potent targets for disease modification. Currently, we have preclinical models which unequivocally have the potential to replicate the pathology of MSA without being able to reproduce the unknown yet etiological triggers of the disease. One cannot exclude that differences in the biology of the mouse and human CNS may contribute to the divergence between the preclinical and the clinical outcomes. However, the MSA transgenic mice provide a good screening model recapitulating the fingerprint pathology of MSA and the downstream mechanisms that contribute to the disease progression. Predictive validity has partly been shown for the PLP-α-syn mouse model in two independent sets of preclinical experiments and clinical trials. Something, which has been overlooked previously in an effort to provide proof-of-concept data for the feasibility of the tested interventions, is the timing and the dosing in preclinical experiments. Our translational experience postulates that we should design preclinical experiments in a manner relevant to the clinical reality. It should be recommended that experimental data should be provided also for advanced disease and in doses that are applicable in patients before risking failure of a clinical trial (Stefanova et al., 2008; Poewe et al., 2015; Galpern, 2015). Since clinically, we aim slowing of disease progression, it seems critical to include functional readouts (especially indices of rate of motor deterioration) in all relevant preclinical studies. On the other hand, clinical trial design in MSA needs to be improved in a way that: i) the selection of patients is as homogeneous as possible and reflects appropriately the tested target, ii) the disease stage is as early as possible, so that chances of neuronal rescue and disease modification increase, and iii) the primary readouts include feasible progression biomarkers in addition to the evaluation of symptom progression. The lack of suitable biomarkers may lead to claiming false futility of interventions that have positive target engagement, but lack sufficient dose or duration of treatment to reflect into functional changes. Finally, well-estimated risks and reasoned balance should be considered when aiming for a drug dose which may be disease modifying but linked with certain side effects.

Taken together, the cure of MSA will be successfully identified only if preclinical and clinical researchers come together to resolve the current problems in the translational approach and learn from previous experience.

Acknowledgements

This work is supported by grant of the Austrian Science Fund (FWF) I4414.

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