HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

Mov Disord. 2016 February ; 31(2): 225–234. doi:10.1002/mds.26428.

Combination therapies - the next logical step for the treatment of synucleinopathies?

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Abstract

Currently there are no disease-modifying alternatives for the treatment of most neurodegenerative disorders. The available therapies for diseases such as Parkinson's disease (PD), PD dementia (PDD), Dementia with Lewy bodies (DLB) and Multiple system atrophy (MSA), in which the protein alpha-synuclein (α-syn) accumulates within neurons and glial cells with toxic consequences, are focused on managing the disease symptoms. However, utilizing strategic drug combinations and/or multi-target drugs might increase the treatment efficiency when compared to monotherapies. Synucleinopathies are complex disorders that progress through several stages, and toxic α-syn aggregates exhibit prion-like behavior spreading from cell to cell. Therefore, it follows that these neurodegenerative disorders might require equally complex therapeutic approaches in order to obtain significant and long-lasting results. Hypothetically, therapies aimed at reducing α-syn accumulation and cell-to-cell transfer, such as immunotherapy against α-syn, could be combined with agents that reduce neuroinflammation with potential synergistic outcomes. Here we review the current evidence supporting this type of approach, suggesting that such rational therapy combinations, together with the use of multi-target drugs, may hold promise as the next logical step for the treatment of synucleinopathies.

Keywords

Alpha-synuclein; Parkinson's disease; Synucleinopathies; Therapeutics; Combination therapy

Synucleinopathies[1] are a group of neurodegenerative disorders characterized by the abnormal deposition of the protein alpha-synuclein (α-syn) in the form of oligomeric and fibrillary aggregates within neuronal and glial cell populations, this accumulation leading to cell death and subsequent behavioral and motor deficits. A-syn is a protein found in presynaptic terminals that is involved in synaptic transmission[2, 3], and its abnormal accumulation in the form of oligomers and fibrils is toxic[4–6]. Synucleinopathies include Parkinson's disease (PD), PD dementia (PDD), Dementia with Lewy bodies (DLB) and

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Conflict of interest

The authors declare that they have no conflict of interest, support or financial issues.

Multiple system atrophy (MSA). Specific neuronal populations degenerate in each of these disorders[7]: dopaminergic neurons in the substantia nigra, midbrain, nucleus basalis of Meynert and brainstem are affected in PD; in DLB, both dopaminergic and cholinergic neurons in the nucleus basalis of Meynert and limbic system degenerate; and finally, the pattern of neurodegeneration in MSA (putamen, middle cerebellar peduncle, pons, and/or cerebellum) is characteristic for each subtype (MSA-P or MSA-C)[8]. Moreover, in MSA α-syn accumulates not only within neurons but also within oligodendroglial cells[9, 10], leading to demyelination and the loss of trophic support to neurons, which translates into secondary neurodegeneration. Symptoms of synucleinopathies include a chronic and progressive decline in motor (ataxia, parkinsonism), cognitive (memory loss) and behavioral functions (depression, anxiety, REM sleep disorder)[11], and dysautonomia, depending on the distribution of the lesions. The incidence rate of synucleinopathies is 21 per 100,000 persons per year, and increases with age[12]. PD is the most prevalent synucleinopathy and the second most common neurodegenerative disorder after Alzheimer's disease (AD), affecting 1.5 million people in the US and 1% of people over 60 years old. The prevalence of Lewy body dementias in the US is estimated to be 1.3 million[13]. Finally, MSA affects approximately 14,000 people in the US.

Synucleinopathies are complex diseases that progress through several stages[14–16] (Figure 1), and increasing evidence suggest that an early diagnosis would increase the efficacy of the therapeutic intervention. A rational approach for the treatment of synucleinopathies dictates that preventive efforts aimed at protecting from neurodegeneration and stopping the early deposition of α-syn would be more effective if administered before or during the pre-symptomatic stage (Figure 1). However, the diagnosis usually occurs during the symptomatic stage, once α-syn deposition is already established, neuroinflammation is widespread, and approximately 75% of dopaminergic neurons have died[17]. At this point, restoring neurotransmitter signaling (dopamine, acetylcholine) and reducing inflammation may help alleviating symptoms and preventing further neuronal loss. Finally, late disease stages are characterized by extended neurodegeneration and loss of the neurotrophic support, and in this period the use of regenerative therapies and neurotrophic factors[18, 19] can help delaying neurodegeneration and palliating its behavioral and motor correlates (Figure 1). From the analysis of these disease stages it can be concluded that developing therapies that make use of the natural windows of therapeutic intervention by targeting the most relevant events in each disease period may stop degenerative and inflammatory cascades from progressing further. For example, early stage interventions should be focused on prevention by reducing α-syn synthesis, propagation and accumulation; during the symptomatic stages, when the majority of α-syn deposition has already occurred and behavioral and motor symptoms are significant, treatments should be aimed at reducing neuroinflammation and preventing further neuronal death; and finally, slowing down neurodegeneration and restoring trophic support should be the main therapeutic goal at late stages.

Therapeutic alternatives for synucleinopathies

Currently there are no disease-modifying treatments for synucleinopathies, and existing therapies are directed at managing the symptoms of the disease. Drugs that restore dopamine

signaling such as L-DOPA[20–22] (L-3,4-dihydroxyphenylalanine, levodopa), dopamine agonists (ropinirole[23], pramipexole[24, 25]) and dopamine reuptake inhibitors (amantadine[26]) are widely used to treat parkinsonian symptoms in PD patients. Moreover, drugs used to treat PD symptoms may also be prescribed for other synucleinopathies such as MSA; however, these treatments may show reduced efficiency when used for other disorders, and for example approximately one third of MSA patients do not respond to levodopa therapy[27]. Apart from dopamine signaling, cholinesterase inhibitors such as donepezil[28, 29], rivastigmine[30] and galantamine[31] are used to slow or prevent the decline of cognitive function in DLB and PDD. Low blood pressure, urinary incontinence, REM sleep disorder, dystonia and impotence are also targets for pharmacological intervention in synucleinopathies[32]. Nevertheless, none of these therapies is able to slow down the neurodegeneration cascades that affect the diseased brain.

Therefore, in order to effectively delay or halt the progression of the disease it is necessary to develop effective disease-modifying alternatives. The vast majority of research efforts towards the development of disease-modifying therapies are focused on targeting α-syn deposition in the brain, since it seems to be a critical step in the development of synucleinopathies. Abnormal α-syn accumulation occurs early in the disease progression and spreads following a quite defined pattern through the brain[14], suggesting that it is the driving force in PD pathogenesis[5, 33]. And, as it occurs with the accumulation of other toxic proteins[34], the intracellular build-up of α-syn can be reduced by either 1) inhibiting α-syn synthesis, 2) blocking its aggregation, and/or 3) increasing its degradation and clearance (Figure 2). Postmortem brain samples of sporadic PD patients have higher levels of α-syn mRNA, which is relatively specific to neurons[35]. In the special case of MSA, the mRNA levels of α-syn are 1.5 higher in oligodendrocytes that in neurons[36], suggesting that increased expression rates may be involved in the oligodendroglial α-syn accumulation observed in this synucleinopathy. Furthermore, duplications and triplications of the α-syn gene (*SNCA*) are associated with familial PD[37–39], and genome-wide association studies (GWAS) show that *SNCA* single-nucleotide polymorphisms are risk factors for sporadic PD[40], indicating a mechanistic role of increased α-syn in the origin of the pathology. Levels of α-syn expression can be therapeutically reduced using siRNAs[41] or miRNAs[42, 43]. However, given that this protein is involved in normal synaptic transmission, successfully modulating α-syn synthesis in sporadic cases can be challenging. High intracellular levels of α-syn may increase its tendency to aggregate, together with other factors such as protein misfolding[44, 45], limited proteolysis[46], mutations[47–49], and post-transcriptional modifications such as phosphorylation[50, 51] and truncation[52, 53]. The processes of α-syn aggregation and fibrillation can be used as therapeutic targets for the development of drugs that act as conformational stabilizers and anti-aggregation agents (e.g., small molecules[54], rifampicin[55]). Interestingly, the recent discovery that different α-syn conformations ("strains") are specific of different synucleinopathies[56] suggests that conformation-specific anti-aggregation agents may be more effective at reducing aggregation than more generic alternatives. Finally, the increased tendency of α-syn to propagate from cell to cell and to accumulate within neurons and glial cells might be due to deficits in protein clearance mechanisms in donor and/or acceptor cells. Autophagy impairments have been associated to PD and other synucleinopathies[57, 58], and dysfunctions in other clearance mechanisms such

as proteolysis and unfolded protein response have also been reported[59, 60]. Increasing α-syn degradation using autophagy inducers, unfolded protein response inducers[61] and enzymes such as kallikrein-6 (neurosin)[62, 63], MMP9[64] or cathepsin D[65, 66] could help reduce both α-syn propagation and accumulation.

Importantly, it has been suggested that cell-to-cell propagation of α-syn aggregates plays a pivotal role in the mechanism of α-syn toxicity (Figure 3), and it is responsible for the prion-like spreading of the disease through the brain. Propagating α-syn aggregates, once taken up by acceptor cells, may act as seeds for further α-syn deposition within recipient cells, thus explaining the neurodegeneration pattern observed at different stages[14, 67]. It follows that α-syn-reducing agents that target extracellular α-syn or inhibit its endocytosis may inhibit propagation and therefore stop or delay the progression of the disease. One of such approaches is the use immunotherapy against toxic conformations of α-syn. Active and passive immunotherapeutic approaches have been effective at reducing toxic α-syn aggregates (dimers, oligomers) and improving behavioral deficits in transgenic (tg) mouse models of PD and MSA[68–73]. Active immunization with full human α-syn[68] or with peptides (AFFITOPEs®) that mimic the C-terminus region of α-syn[70, 71] results in the production of high relative affinity antibodies, decreased accumulation of α-syn aggregates and reduced neurodegeneration. Antibodies produced by immunized mice recognize abnormal α-syn and promote its degradation, probably via microglial lysosomal pathways. In this sense, clinical trials using the AFFITOPE® PD03A for PD and MSA are currently undergoing. Likewise, passive immunization with antibodies against the C-terminus of α-syn are able to cross into the CNS, attenuate synaptic and axonal pathology and reduce the accumulation and propagation of C-terminus-truncated α-syn[69, 72], thus improving behavioral and motor functions in a mouse model of PD. Finally, the clearance of extracellular α-syn can also be achieved by targeting extracellular chaperones such as Hsp70[74] and enzymes such as neurosin[63].

The late stages of most neurodegenerative disorders are characterized by significant neuronal loss, which drastically reduces the effectiveness of therapies prescribed for earlier stages. Once neurodegeneration is widespread, behavioral and motor impairments can only be reverted by either restoring neuronal populations or compensating for their loss. In this case, disease-modifying efforts are focused on the use of neurotrophic factors (BDNF, GDNF)[75–78] or neurotrophic factor inducers[79], drugs that enhance neurogenesis[80], or regenerative cell therapy with stem cells[81]. However, it is important to consider that α-syn propagation still occurs at late stages, and regenerative efforts may be hindered if the propagation of α-syn aggregates from surrounding diseased tissues is not inhibited[82, 83].

Finally, mutations in genes other than *SNCA*, namely *LRRK2*, *PARK2* (parkin), *PINK1*, *PARK7* (DJ-1), *ATP13A2*, *VPS35*, *EIF4G1*, *GBA* (β-Glucocerebrosidase) and *UCHL1*[84–94], have been considered as potential therapeutic targets, as mutations on those genes are associated with an increased risk of developing PD. Other genes of susceptibility for synucleinopathies are *COQ2* for MSA[95, 96], and *PARK11*[97] and *GBA*[98] for DLB. Interestingly, most of the proteins encoded by these genes are involved in lysosomal and mitochondrial functions, highlighting the crucial role of mitochondria and cell metabolism in the origin and progression of these disorders. For example, mutations that induce a gain

on function on LRRK2 could be managed using LRRK2 kinase inhibitors such as sorafenib[99], GW5074[99] and staurosporine[100–102]. However, as most of these mutations lead to a loss of function, gene therapy has been suggested for *PARK2*[103, 104] and *GBA*[105]. The potential use of the DJ-1 products glycolate and D-lactate, that are neuroprotective, has been explored as well[106]. In the case of MSA, mutations in the coenzyme Q10 encoding gene *COQ2* have been associated with an increase risk of suffering this disease[95, 96]; however treatment with coenzyme Q10 did not slow down the progression of PD in a Phase III study[107], suggesting that its efficacy may be limited by other factors. Although therapies focused on these proteins might prove useful for synucleinopathies, potential treatment are still on the validation stage. Importantly, mutations in these genes can be used as biomarkers for prevention in pre-symptomatic stages, in which the use mitochondrial agents and neuroprotective compounds could prevent or delay the onset of the disease.

Neuroinflammation as therapeutic target in synucleinopathies

Synucleinopathies are complex disorders and, as mentioned before, using the opportunity of available windows for therapeutic intervention, although not without its challenges, may drastically affect the outcome of the pharmacological intervention (Figure 1). While early pre-symptomatic stages are characterized by an increased production, propagation and accumulation of α-syn, more advanced, symptomatic stages are characterized by the onset of non-autoimmune neuroinflammation. Neuroinflammation in synucleinopathies is characterized by microglial and astroglial activation with α-syn accumulation, cytokine dysregulation and immune cell infiltration into the brain[108]. Neuroinflammation is linked to memory retrieval dysfunction[109, 110], and it is responsible for some of the cognitive impairments observed during the symptomatic stages of the disease[111, 112]. Importantly, only removing the initial neuroinflammatory stimulus (e.g., α-syn) would not be enough to put a stop to neuroinflammatory cascades once initiated[113]. Inflammatory mediators released by activated glial cells self-perpetuate their activation in a positive feedback loop manner, leading to over-production of pro-inflammatory cytokines and reactive oxygen species (ROS), oxidative stress and secondary neurodegeneration. Pro-inflammatory cytokines such as TNFα, IL-1β and IL-6 are elevated in the brain of PD patients[114, 115], and are important mediators of inflammatory cascades and glial activation (Figure 3). Importantly, the presence of unaddressed neuroinflammation may be one of the reasons why effective anti-aggregation and α-syn-reducing agents have shown suboptimal results at reducing the pathology when used autonomously, and other disorders that accumulate toxic proteins, such as AD, have yielded similar results. In the case of AD, it has been shown that reducing amyloid beta levels using immunotherapy does not significantly improve memory deficits in humans[116, 117], suggesting that factors other than toxic protein accumulation, such as neuroinflammation, may be responsible for behavioral outcomes in these neurodegenerative disorders.

Consequently, recent research efforts have been devoted to targeting neuroinflammation as a palliative treatment for synucleinopathies. Preclinical and clinical anti-inflammatory efforts have included nonsteroidal anti-inflammatory drugs (ibuprofen, indomethacin)[118, 119], TNFα inhibitors (XPro1595, immunomodulatory drugs)[120, 121], antidepressants (fluoxetine)[80, 122, 123], antioxidants (coenzyme Q10, quercetin, curcumin)[124–128],

polyphenols (apigenin, luteolin)[129, 130] and others. However, several clinical trials have shown that anti-inflammatories do not significantly reduce behavioral and motor deficits. In this sense it is important to note that most anti-inflammatories do not reduce extracellular α-syn levels, which constitutes a significant pro-inflammatory stimulus for glial cells in synucleinopathies[131–133]. However, treatment with some of these anti-inflammatory compounds can have more than one beneficial outcome and even disease-modifying properties, thus increasing their potential as therapeutic alternatives. For example, the antidepressant fluoxetine reduces neuroinflammation, increases neurogenesis, and inhibits α-syn propagation and accumulation in a tg model of MSA[122, 123]. It follows that approaches using similar multi-target drugs might be viable choices for the treatment of neurodegenerative disorders.

Combination therapies – a rational approach for the treatment of synucleinopathies

However, despite the considerable effort devoted to developing therapies that stop or delay the progression of synucleinopathies, substantially effective treatments have not been identified yet. This lack of success raises the question of whether conventional drug development approaches are appropriate for neurodegenerative diseases. Monotherapies, although effective for numerous diseases and with fewer side effects, might not be enough to induce significant improvements in patients with neurodegenerative disorders such as PD. Because of the complexity of these disorders, it may take a combination of therapies and/or the use of multi-target drugs to help stop the progression of the disease. Moreover, the need for combination therapies is being increasingly recognized due to the failure, or marginally protective effects, observed when using single-target agents[134].

Among the reasons supporting the use of a logical combination of therapies for the treatment of neurodegenerative disorders is that utilizing drugs that target different signaling pathways that complement each other, or the same pathway at different levels, might have synergistic effects. For example, anti-inflammatories inhibit pro-inflammatory cascades while immunotherapy against α-syn reduces the levels of aggregated α-syn, which in turn may act as a pro-inflammatory stimulus for glial cells[131, 132]. Likewise, some anti-inflammatories are also able to reduce α-syn accumulation[123], probably by stimulating the clearance of extracellular α-syn by physiologically-activated microglial cells (M2 polarized microglia)[135]. However, among the potential weaknesses of combining drugs is that it might lead to negative interactions among metabolites, resulting in a reduction in the positive outcome of the treatment, or even to increased side effects and/or hepatic toxicity. In this sense, some chronic diseases known to have competing therapies include diabetes, heart failure, high blood pressure, high cholesterol, and osteoarthritis[136, 137]. In synucleinopathies, some anti-TNFα and anti-inflammatory therapies might hypothetically interfere with responses to active immunization, as they modulate immune cell activation[138, 139]. Therefore, it is important to perform an in-depth analysis of each drug combination in order to prevent potential undesired effects.

The combination of therapeutic approaches has been successfully explored for other ailments such as autoimmune diseases and cancer[140, 141]. In the case of synucleinopathies

some combinations have been recently suggested, including lithium plus levodopa/carbidopa[142], rasagiline and levodopa[143], and creatine plus coenzyme Q10, that produce additive neuroprotective effects in models of PD[128]. However, due to the inherent complexity of neurodegenerative disorders, patients are usually prescribed with more than one medication and, for example, it is not uncommon to combine the use of antidepressants with treatments aimed at managing the disease symptoms, such as parkinsonism and ataxia. Such unintended combinations have yielded some interesting results. For example, simultaneous treatment with rasagiline (monoamine oxidase (MAO) inhibitor) and an antidepressant has been associated with a reduced worsening of non-motor symptoms in PD patients[144], encouraging further studies in this direction. Yet, the combination of pharmacological therapies has not been as extensively explored as monotherapeutic approaches. More frequent is the mix of pharmacological treatments with non-pharmacological approaches such as deep brain stimulation[145–147] or physical exercise[148] for the treatment of motor and cognitive symptoms in synucleinopathies.

As mentioned before, more research is needed for elucidating how drugs interact, and how we could use their synergy to our advantage. Following a rational approach focused on complementary targets and mechanisms of action, researchers are able to design specific therapeutic combinations to be explored for the treatment of PD and related disorders. For example, one of such combinations might be the use antidepressants with anti-inflammatory activity (e.g., fluoxetine) together with immunotherapy against toxic α-syn conformations. The rationale for this combination is that it would achieve a reduction in α-syn propagation and accumulation (immunotherapy) together with a reduction in neuroinflammation and secondary neurodegeneration (antidepressant). Both active and passive immunotherapies reduce α-syn levels, most likely by stimulating microglia to clear out extracellular antibody-α-syn complexes[70–72]. Additionally, antidepressants not only stabilize mood changes and anxiety, but also reduce microglial and astroglial pro-inflammatory cytokine responses[123, 149]. Furthermore, additional α-syn reduction and increased neurogenesis can be achieved using specific antidepressants (e.g., fluoxetine)[150]. Together, these results suggest that this or similar combinations would yield better results than using each drug separately, specially if administered at pre-symptomatic or early symptomatic stages, when α-syn is actively propagating (Figure 1). Another example would be combining the use of TNFα inhibitors such as lenalidomide, together with passive immunization against the C-terminal end of α-syn. Lenalidomide reduces microgliosis and inhibits the expression of pro-inflammatory cytokines in a tg mouse model of PD[120], while antibodies against the C-terminal site of α-syn reduce its propagation, ameliorate the pathology and improve behavioral and motor functions in the same mouse model-term[72]. Such complementary modes of action suggest that combining both drugs may lead to synergistic results. However, at late disease stages, once neuroinflammation and neurodegeneration are widespread, α-syn-reducing agents would be less effective. In this situation, mixing anti-inflammatory approaches with regenerative therapy might lead to improved cognitive and motor functions. Other specific examples of rational therapy combinations are: anti-inflammatory and anti-oxidant molecules such as curcumin or derivatives, together with L-DOPA for PD; or minocycline[151], an antibiotic that modulates microglial activation, combined with an α-syn endocytosis inhibitor for MSA. However, although the possibilities are multiple, a rational

approach must be followed for designing such combination therapies. Logical pairings would include a) drugs that have different targets that complement each other (eg. TNFα inhibitors plus α-syn-reducing agents); b) drugs that act on the same pathway but targeting different mechanisms (eg. antidepressants that reduce α-syn propagation plus immunotherapy against α-syn); or c) multi-target drugs that inhibit several pathways, or one pathway at different levels (e.g., lenalidomide actions on several members of the NF-κB pathway and on TNFα mRNA stability).

Closing remarks

In conclusion, there is an urgent need for the development of new, effective therapeutic alternatives for the treatment of neurodegenerative disorders. This includes not only the development of reliable predictive and early diagnostic tools for synucleinopathies, but also of novel therapeutic alternatives that significantly down the progression of the disease at later stages. Available therapies to date are focused on managing disease symptoms, and a therapeutic breakthrough is sorely needed for PD and related disorders. In this sense, recent clinical trials have yielded suboptimal results, suggesting that a combination of two or more therapies may be needed in order to achieve significant improvements and disease modification. Taking advantage of the potential synergistic effects derived from combining therapies could be the next logical step for the treatment of synucleinopathies.

ACKNOWLEDGEMENTS

This work was funded by the National Institutes of Health (NIH) grants NS044233, AG18440, NS047303, AG022074 and NS057096.

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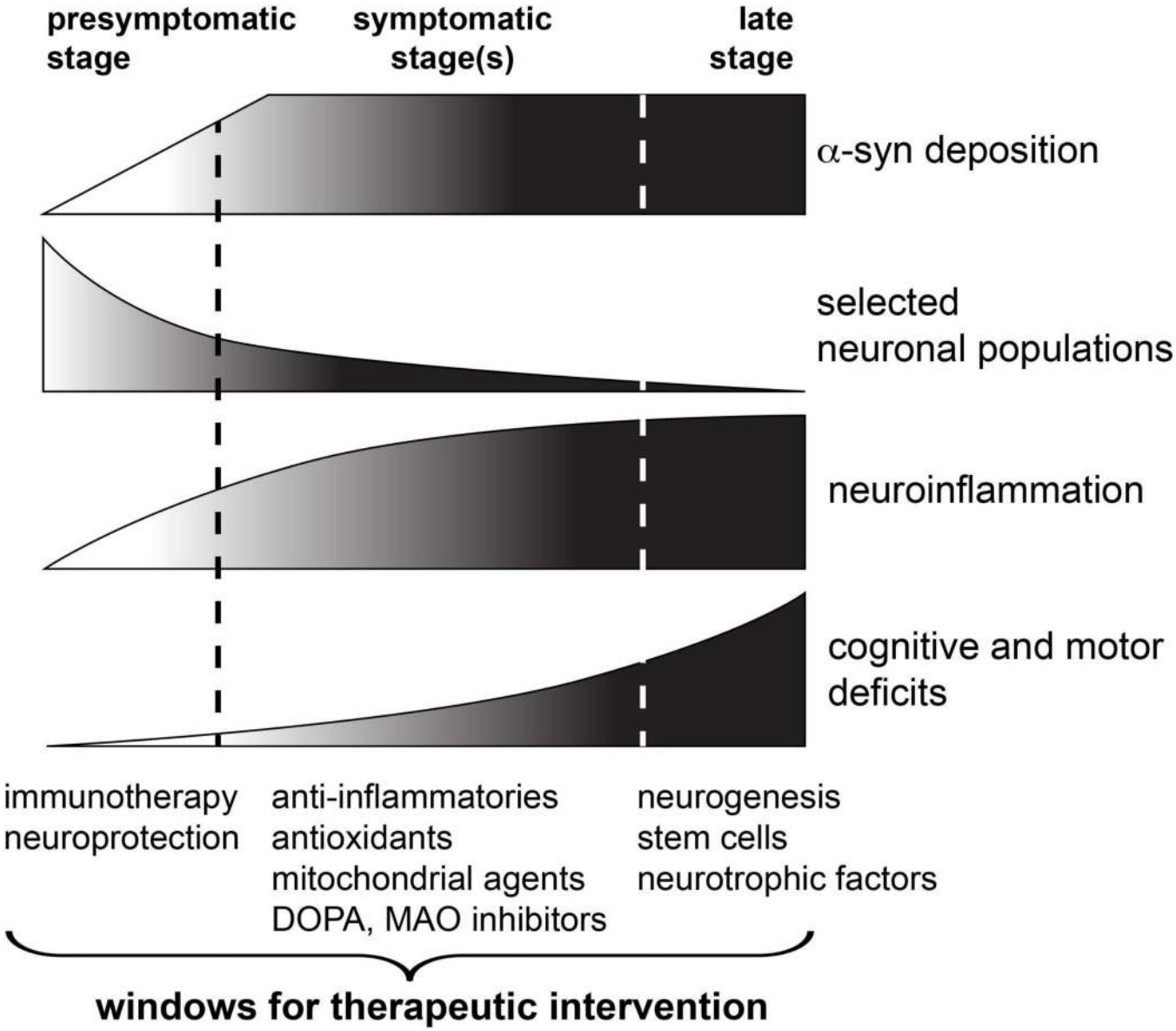

Figure 1. Windows for therapeutic intervention in synucleinopathies

Hypothetical disease progression in stages postulated for PD and other synucleinopathies, including α-syn deposition, death of selected neuronal populations, neuroinflammation and cognitive and motor deficits. Suggested treatments that could be suitable for each therapeutic window of opportunity are depicted below.

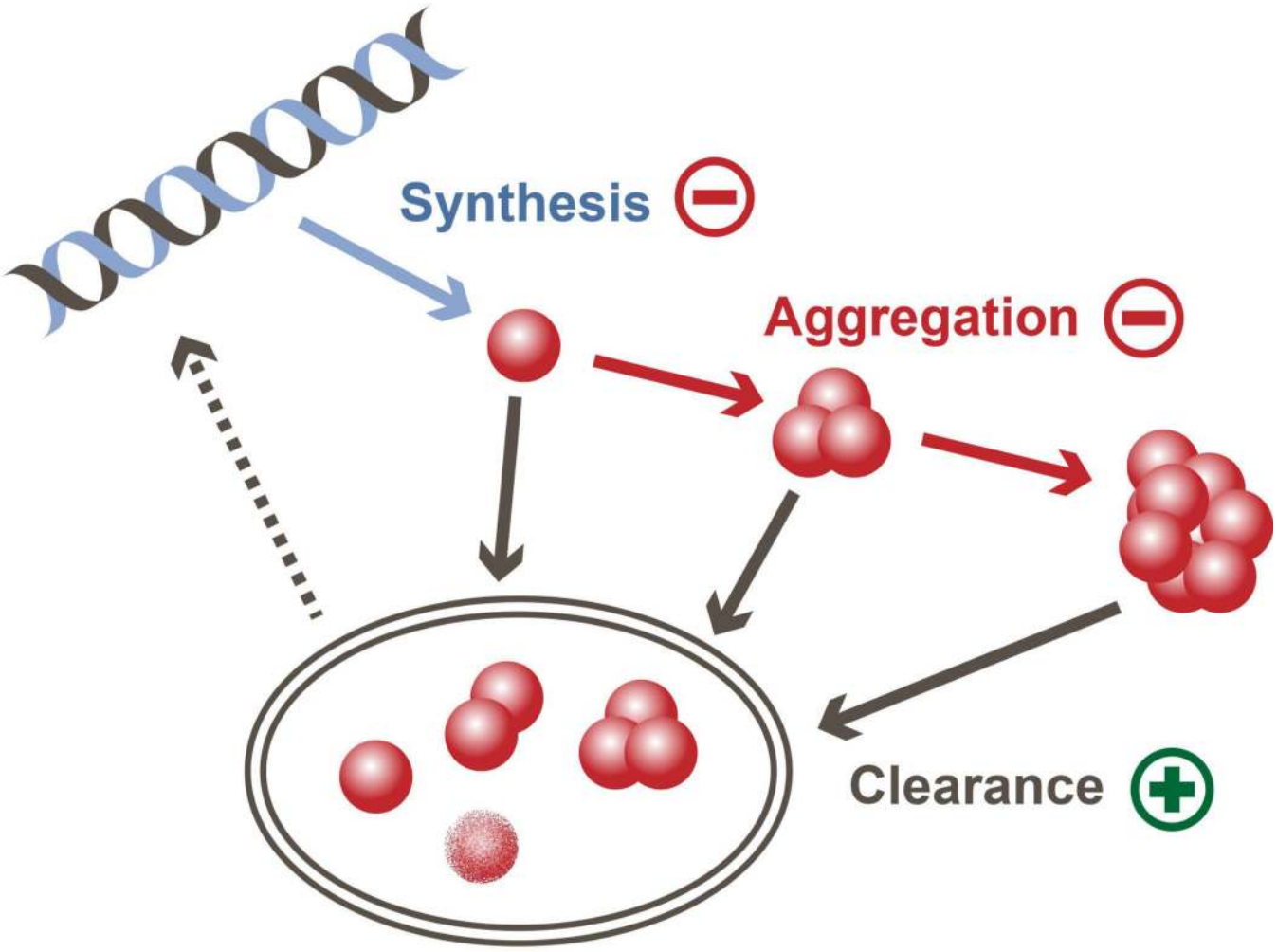

Figure 2. Disease-modifying therapeutic strategies focused on intracellular α-syn accumulation

Intracellular α-syn levels are regulated by the balance between α-syn synthesis, aggregation and clearance. Strategies to reduce α-syn accumulation include decreasing its synthesis (−) with siRNA or miRNAs, reducing its aggregation (−) using anti-aggregation agents or post-translational modifications, and/or activating clearance mechanisms (+) such as autophagy.

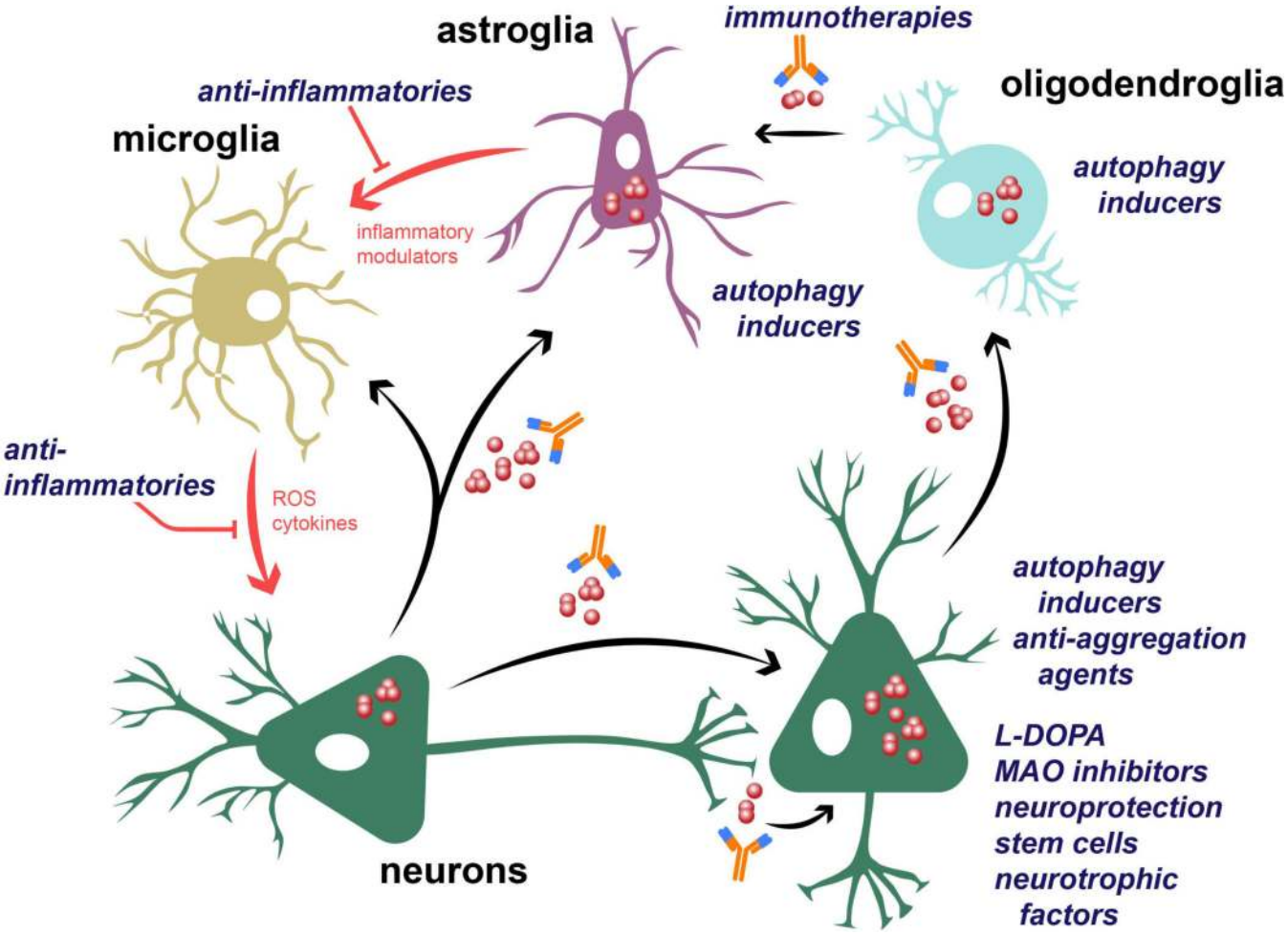

Figure 3. Potential therapeutic interventions for the treatment of synucleinopathies

α-syn aggregation can take place either in the cytoplasm or in association with the cellular membrane of neuronal cells. Interestingly, α-syn oligomers and fibrils, as well as the monomers, can be transferred between cells and induce disease spreading to other brain regions. Propagation of α-syn to astroglial and microglial cells can induce glial activation and neuroinflammation. In MSA, α-syn also accumulates within oligodendrocytes and propagate from these cells to astroglia. Potential therapeutic interventions include immunotherapy against extracellular α-syn; the use of anti-inflammatories to reduce glial neuroinflammation; autophagy inducers to stimulate the clearance of intracellular α-syn; and mechanisms to reduce or compensate neurodegeneration such as L-DOPA, MAO inhibitors, neuroprotective compounds, neurotrophic factors (BDNF, GDNF) or regenerative therapy with stem cells.