THE RESEARCH RADAR

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WELCOME

A warm welcome to our first Defeat MSA Alliance research-focused newsletter: ***The Research Radar***. Defeat MSA Alliance is a charity that aspires to balance support for patients, educate medical professionals, raise public awareness, nurture promising research, and advocate for the MSA community.

The ***Research Radar*** aims to break down the – often complex – science behind MSA and act as a source for sharing key events and information with the global MSA community.

While there is currently no cure for MSA, much research is ongoing to find treatment strategies for MSA. In this first issue, we focus on alpha-synuclein modifying treatments. What is alpha-synuclein? How is it linked to MSA? And how can alpha-synuclein be targeted in MSA treatments? Inside, we dive into these questions and share the latest MSA-related announcements and clinical trial information.

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Find **Defeat MSA** on:

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IN THE NEWS

NEW DRUG GIVEN ORPHAN DESIGNATION

ATH434, a drug being researched by Alterity Pharmaceuticals as a treatment for multiple system atrophy, receives orphan designation in the US and the EU. Further information can be found at the Alterity Pharmaceuticals website (**www.alteritytherapeutics.com**).

FUNDED MSA RESEARCH GRANTS AWARDED FOR 2022

The Board of Directors of Defeat MSA Alliance (US), Defeat MSA/Vaincre AMS Canada, and Defeat MSA Australia and New Zealand have approved several grants to fund promising new research. Together with two other charities, La Asociación Española Síndrome Shy Drager – Atrofia Multisistémica (Spain) and Combattiamo l'Atrofia Multisistemica (Italy), the charities formed a new research consortium in 2020.

The MSA United Consortium awarded the following researchers with the 2021 research grants:

Woojin Kim, PhD
(University of Sydney, NSW, Australia)

Naveen Kondru, PhD
(Mayo Clinic, FL, United States)

Suzanne Bechstedt, PhD
(McGill University, Montreal, QC, Canada)

Yuhong Fu, PhD
(University of Sydney, NSW, Australia)

Tomasz Brudek, PhD
(Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark)

Researchers interested in future grants are kindly requested to submit their contact and professional details through the form at the following link: **www.msaunited.org/researcher-form/**.

Defeat MSA Alliance (USA)
www.defeatmsa.org

Defeat MSA Australia & New Zealand (Defeat MSA Down Under)
www.msadownunder.org.au
www.msadownunder.org.nz

Defeat MSA Awareness Shoe
www.msashoe.org

Defeat Multiple System Atrophy – Vaincre L'Atrophie Multisystématisée (Canada)
www.msacanada.ca

La Asociación Español Síndrome Shy Drager Atrofia Multisistémica
www.asyd.es

Combattiamo l'Atrofia Multisistemica (MSA-Italia)
www.msa-italia.org

DEEP DIVE: WHAT ARE ALPHA-SYNUCLEIN MODIFYING TREATMENTS?

Alpha-synuclein – a key protein linked to multiple system atrophy (MSA) – has emerged as a potential target for treating MSA. Here, we look at what alpha-synuclein is and what tactics researchers are developing in hope of treating MSA.

Alpha-synuclein is a protein found naturally in healthy neurons, where it typically exists as a single molecule. However, under certain conditions, multiple alpha-synuclein proteins can join together to form clusters (or 'aggregates'). These aggregates have been linked to various neurodegenerative diseases, including multiple system atrophy (MSA)[1].

Alpha-synuclein aggregates can damage cells through a variety of processes. For example, aggregates can kill cells by puncturing holes in the membrane that surrounds a cell. The harmful effects alpha-synuclein aggregates have on cells can trigger diseases, such as MSA.

Alpha-synuclein as a marker of MSA

Aggregate forms of alpha-synuclein are a key marker of MSA—other markers can include inflammation and damaged or loss of neurons. Alpha-synuclein aggregates form structures called glial cytoplasmic inclusions (GCIs) inside neurons and oligodendrocytes (a type of brain cell)[2]. These GCIs have been linked to MSA, for example:

- Alpha-synuclein is not found in healthy oligodendrocytes, but alpha-synuclein aggregates can be found in the oligodendrocytes of MSA patients.
- Higher levels of GCIs have correlated with higher levels of loss of neurons in MSA patients.

However, some regions of the central nervous system can have high levels of neuron damage and loss without high levels of GCIs, suggesting the relationship between alpha-synuclein and MSA is not clear cut[2]. Alpha-synuclein aggregates found in neurons may also be linked to MSA development or progression[3].

Diagnosis of MSA relies on patients having GCIs present, making disease-causing or pathological forms of alpha-synuclein potential targets for MSA treatments[2].

Why and how do alpha-synuclein aggregates form and accumulate?

The processes that trigger alpha-synuclein aggregates to develop and form are not fully understood. Researchers have put forward multiple theories on what leads to alpha-synuclein accumulating in cells—particularly in oligodendrocytes, where alpha-synuclein is not typically detected in healthy cells.

One possibility is that oligodendrocytes take up alpha-synuclein from their surroundings or from other cells that generate alpha-synuclein (such as neurons). This passing of pathological forms of alpha-synuclein from cell to cell helps GCIs to spread between cells, contributing to neurodegeneration.

Alpha-synuclein may also accumulate in cells because faults in processes that prevent alpha-synuclein

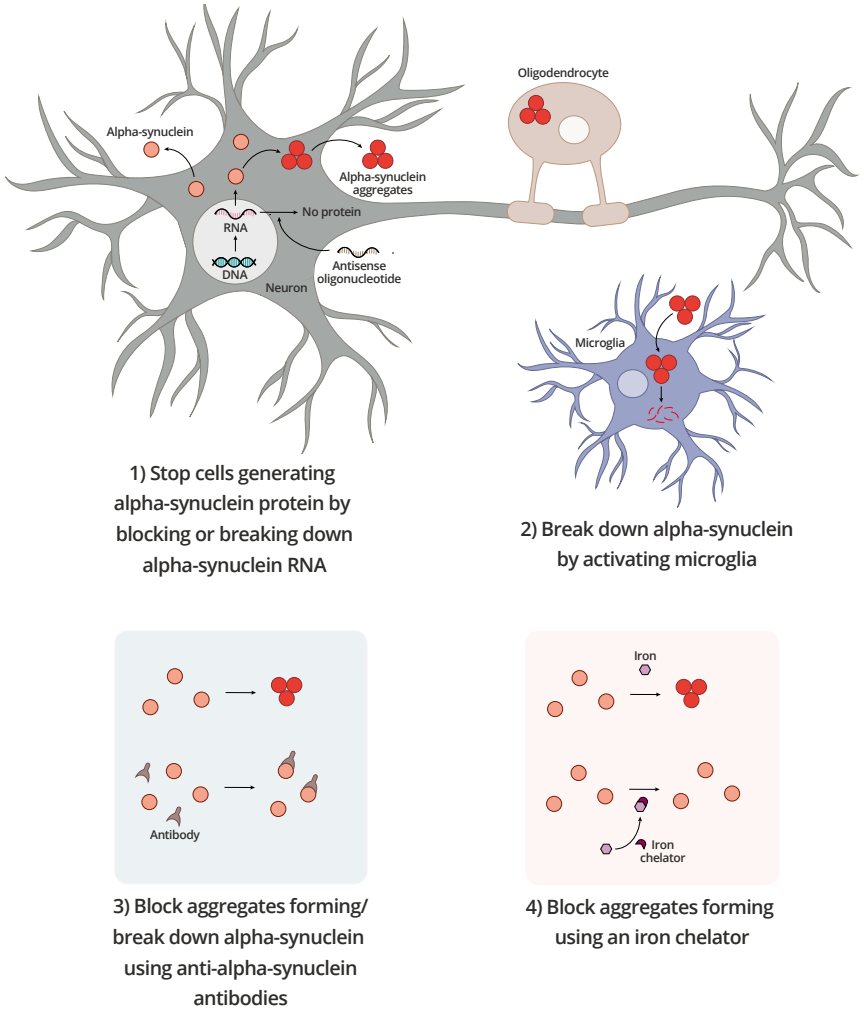

Figure 1. Potential alpha-synuclein modifying treatments being studied in MSA research.

from being broken down. Potentially, other proteins – such as 'TPPP' - may also play a role in triggering alpha-synuclein to accumulate in oligodendrocytes[2].

How can we target alpha-synuclein for MSA treatment?

Despite there being no cure for MSA, many drugs are being investigated in pre-clinical and clinical studies. As alpha-synuclein aggregates are a key marker of MSA, targeting alpha-synuclein is one strategy researchers are taking in hope of treating MSA. These strategies may involve: 1) stopping the cells from generating alpha-synuclein and 2) stopping alpha-synuclein from aggregating and accumulating (see **Figure 1**).

1) Stopping cells from generating alpha-synuclein

As MSA is linked to alpha-synuclein accumulating in cells, reducing alpha-synuclein levels may offer a way to help treat MSA.

To generate an alpha-synuclein protein, cells convert the DNA of the alpha-synuclein gene (known as *SNCA*) into RNA, which is then converted into the alpha-synuclein protein. Techniques such as *antisense therapy* can stop RNA from being turned into a protein. In antisense therapy, small sections of RNA (known as antisense oligonucleotides) stick to the alpha-synuclein RNA, resulting in the cell breaking down the RNA or stopping the RNA from being converted into a protein, reducing alpha-synuclein protein levels in the cell. As alpha-synuclein is needed for healthy neurons, levels of alpha-synuclein need to be sufficiently reduced to cause a therapeutic response but without causing damage or stopping cells from working properly.

2) Stopping alpha-synuclein from aggregating and accumulating

Antibodies are proteins that form a key part of our immune system; by tagging disease-causing molecules, antibodies allow immune cells to find and remove harmful substances from the body. Antibodies can also block molecules from sticking to other molecules or working as normal. Scientists can generate antibodies in the lab to target alpha-synuclein—known as anti-alpha-synuclein antibodies. These antibodies can stick to alpha-synuclein molecules, blocking multiple alpha-synuclein from joining together to form aggregates and accumulating in cells.

Small sections of proteins – called peptides – could be used in vaccines to trigger anti-alpha-synuclein antibodies to be produced in the body. Peptides can be generated to mimic a section of aggregated alpha-synuclein protein. The antibodies can, as above, then block alpha-synuclein aggregates from forming and accumulating in cells.

A separate strategy that may help target alpha-synuclein accumulation in MSA involves immune cells. Immune cells in the brain – called microglia – can help break down and remove alpha-synuclein. Microglia have proteins at the cell surface called toll-like receptors, which are involved in the immune response. Activating a particular toll-like receptor, called TLR4, has been shown to trigger microglia to break down alpha-synuclein from the brain. Balancing activation of TLR4 is important as too much can cause toxic inflammation. A mouse model has shown that a molecule, monophosphoryl lipid A, activates TLR4 and leads to alpha-synuclein being broken down in a mouse model of MSA, without causing harmful inflammation[4].

Another potential strategy for stopping alpha-synuclein aggregates from forming is through using molecules that combine with metals – such as iron – called metal chelators[5]. Iron can encourage alpha-synuclein aggregates to form and so introducing metal chelators could help stop alpha-synuclein aggregates from forming[6].

Progress in alpha-synuclein modifying treatments

There are a variety of alpha-synuclein modifying treatments currently in clinical trials. Some of these studies are currently recruiting patients; for further information, see page 8.

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CURRENTLY ENROLLING CLINICAL TRIALS

A variety of clinical trials are currently recruiting MSA patients across the globe. Researchers are using different approaches in hope of treating MSA and/or MSA-related symptoms—such as alpha-synuclein modifying treatments, neuroprotective therapies, and symptomatic treatments.

The following pages provide details on clinical trials that are currently enrolling MSA patients, including studies using alpha-synuclein modifying treatments (see Lu AF82422, ATH434, and ION464 below).

Lu AF82422

A phase 2 clinical trial (NCT05104476) is using antibodies to target alpha-synuclein in MSA patients, assessing the effects of an antibody (Lu AF82422) on disease progression. Lu AF82422 binds to monomeric and oligomeric forms of alpha-synuclein, with previous studies showing that the antibody blocks the "seeding of alpha-synuclein aggregation", potentially working by attaching to disease-causing forms of alpha-synuclein located outside the cell[1].

Recruiting in the US and Japan

www.clinicaltrials.gov/ct2/show/NCT05104476

ATH434

An active phase II clinical trial (NCT05109091) is testing a metal chelator (ATH434), which combines with iron, in MSA patients. ATH434 (formerly PBT434) has been shown to reduce alpha-synuclein aggregation and "improved motor function" in mice[2].

Recruiting in New Zealand and the UK

https://clinicaltrials.gov/ct2/show/NCT05109091

ION464

An active phase I clinical trial (NCT04165486) is testing the safety of multiple doses of an antisense oligonucleotide, ION464 (also known as BIIB101), in MSA patients. BIIB101 attaches to alpha-synuclein mRNA (messenger RNA), aiming to reduce alpha-synuclein levels[3].

Recruiting in Austria, France, and Germany

https://clinicaltrials.gov/ct2/show/NCT04165486

AAV2-GDNF

AAV2-GDNF – adeno-associated virus serotype 2-glial cell line-derived neurotrophic factor – gene therapy works by delivering a gene (such as GDNF) into a cell, allowing the cell to produce a protein that helps manage or treat disease. GDNF may be able to protect nerve cells from damage and stimulate nerve cells to grow[4]. An active phase I clinical trial (NCT04680065) aims to assess the safety and effects of AAV2-GDNF in MSA patients.

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT04680065

Exenatide

Exenatide is a drug that mimics a molecule in the body called GLP-1 (glucagon-like peptide 1) that can trigger cells to release insulin—a hormone important for regulating blood glucose levels. Insulin plays a variety of roles in the brain, such as helping build and maintain neurons[5,6]. An active phase II clinical trial (NCT04431713) is assessing whether exenatide can alter disease progression in MSA patients.

Recruiting in the UK

https://clinicaltrials.gov/ct2/show/NCT04431713

Stem Cells

1) Autologous Mesenchymal Stem Cells

Mesenchymal stem cells (or MSCs) generate proteins that may have neuroprotective and immune-regulating roles[7]. An active phase II clinical trial (NCT05167721) is investigating the safety and effectiveness of autologous mesenchymal stem cells (cells collected from the same individual) delivered into the spinal fluid of MSA patients, as well as the optimal dose.

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT05167721

2) Autologous and Allogeneic Mesenchymal Stem Cells

Another active study (NCT04876326) aims to assess the clinical effects of autologous (cells collected from the same individual) and allogeneic (cells collected from a different individual of the same species) mesenchymal stem cells in MSA patients.

Recruiting in Indonesia

https://clinicaltrials.gov/ct2/show/NCT04876326

3) Autologous Stem Cells

A separate study (NCT02795052) aims to investigate the whether autologous stem cells can improve neurological function in patients with neurological conditions.

Recruiting in the US and the United Arab Emirates

https://clinicaltrials.gov/ct2/show/NCT02795052

Tllsh2910

Tllsh2910 regulates NDMA, which is a receptor involved in different processes, such as memory and motor learning. A phase III clinical trial (NCT03901638) aims to assess the efficacy of Tllsh2910 to treat patients with ataxia, while also assessing changes in the gut microbiota—the community of microorganisms that live in the gut.

Recruiting in Taiwan

https://clinicaltrials.gov/ct2/show/NCT03901638

Midodrine and Droxidopa

The effects of droxidopa and midodrine on the veins of the abdomen of MSA patients are being assessed in an active phase I clinical trial (NCT02897063). Both midodrine and droxidopa have been shown to be used in treating orthostatic hypotension, where both molecules can be converted in the body into forms that can activate adrenoreceptors, activating sympathetic nervous system actions[8,9].

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT02897063

Abdominal Binder

1) Automated Abdominal Binder

Abdominal binders may improve blood flow back to the heart by compressing veins, encouraging blood flow[10]. An active phase I/II clinical trial (NCT03482297) is assessing the effectiveness and safety of an automated inflatable abdominal binder to treat orthostatic hypotension in MSA patients with autonomic failure.

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT03482297

2) Abdominal binder

In addition, a separate active study (NCT049205524) is assessing the effectiveness of abdominal binders to manage orthostatic hypotension in patients with Parkinson's disease or MSA.

Recruiting in Austria

https://clinicaltrials.gov/ct2/show/NCT04920552

Deep Brain Stimulation

1) Deep Brain Stimulation

Deep brain stimulation involves electrodes being implanted into the brain that can generate impulses to correct impaired brain signalling[11]. An active phase I clinical study (NCT05011773) aims to assess whether sleep can be improved using deep brain stimulation, providing specific stimulating patterns to the brain of patients during sleep.

Enrolling by invitation

https://clinicaltrials.gov/ct2/show/NCT05011773

Deep Brain Stimulation (continued)

2) Motion Adaptive Deep Brain Stimulation

An active study (NCT05197816) aims to develop a new, patient-tailored deep brain stimulation technique for symptomatic treatment of MSA.

Recruiting in the UK

https://clinicaltrials.gov/ct2/show/NCT05197816

3) Deep Brain Stimulation

An active study (NCT03593512) aims to assess deep brain stimulation for treating MSA symptoms, such as gait and autonomic symptoms.

Recruiting in the UK

https://clinicaltrials.gov/ct2/show/NCT03593512

Swallowing Therapy

An active clinical trial (NCT04782284) aims to assess how effective swallowing therapy is in MSA patients.

Recruiting in the Republic of Korea

https://clinicaltrials.gov/ct2/show/NCT04782284

Expiratory Muscle Strength Training

An active clinical trial (NCT05139342) is looking at dysphagia treatment using expiratory muscle strength training (EMST), which is a technique that is taught to study participants by speech and language therapists.

Recruiting in Germany

https://clinicaltrials.gov/ct2/show/NCT05139342

Zoledronic Acid

Patients with MSA can be at risk of fractures[12]. An active clinical trial (NCT03924414) is assessing whether a drug, zoledronic acid, can help prevent fractures in MSA patients. Zolendronic acid may inhibit bone resorption, a complex process where bone is being broken down in the body. Blocking bone resorption can help strengthen bones and reduce risk of fractures[13,14].

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT03924414

Continuous Positive Airway Pressure

A continuous positive airway pressure (CPAP) machine is a device that blows air into a tube connected to a mask placed over the nose or nose/mouth. An active study (NCT03312556) aims to assess whether CPAP can decrease blood pressure in MSA patients with supine hypertension.

Recruiting in the US

https://clinicaltrials.gov/ct2/show/NCT03312556

Spinal Cord Stimulation

An active study (NCT05171205) is assessing the effects of spinal cord stimulation on MSA symptoms. Spinal cord stimulation is a technique where signals are directed towards the spinal cord, which can help manage pain[15].

Recruiting in China

https://clinicaltrials.gov/ct2/show/NCT05171205

Deep Brain Stimulation and Spinal Cord Stimulation

Deep brain stimulation is also being tested in combination with spinal cord stimulation. An active clinical trial (NCT04617873) aims to assess the efficacy of deep brain stimulation and spinal cord stimulation to alleviate symptoms, such as freezing of gait, in MSA patients.

Recruiting in China

https://clinicaltrials.gov/ct2/show/NCT04617873

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is a non-invasive technique, where a coil is placed on the scalp and sends a magnetic pulse through the skull[16]. An active study (NCT04313530) aims to assess the effects of transcranial magnetic stimulation on fatigue in MSA patients.

Enrolling by invitation

https://clinicaltrials.gov/ct2/show/NCT04313530

For further information on MSA clinical trials, visit
www.clinicaltrials.gov **or**. www.defeatmsa.org/msa-research/pipelines

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RESOURCES

WORLD MSA RESEARCH REGISTRY

The MSA Research Registry is designed as a way for patients and caregivers to connect with vital research opportunities worldwide and receive information about resources.

To register, visit: **https://defeatmsa.org/research-registry/**

BRAIN DONATIONS

Brain donations could help researchers better understand MSA, potentially improving diagnosis and finding cause/s and new treatments for MSA. A brain donation does not hinder the funeral or any burial plans. In some cases, associated costs can be offset by a grant from an institution or charity.

There are many institutes across the globe that are currently performing MSA research. Defeat MSA Alliance can help facilitate a brain donation for families in the US and Canada.

For more information, visit:
https://defeatmsa.org/msa-research/#brain-donations.

NEED HELP FINDING A SPECIALIST?

See below for a list of directories to help find specialists. The following directories are provided for informational purposes from Defeat MSA Alliance's friends and allies.

Find a movement disorder specialist at the International Movement Disorders Society (IMDS):
https://mds.movementdisorders.org/directory/

Find an autonomic disorders specialist at the American Autonomic Society (AAS):
https://americanautonomicsociety.org/physician-directory

Email Defeat MSA Alliance if you are seeking a neurologist—we may be able to help with a list of possible doctors in your area:
neuro-list@defeatmsa.org

DEFEAT MSA ALLIANCE

ROADMAP

Defeat MSA Alliance and its affiliated organizations within MSA United International are committed to the Global MSA Research Roadmap that was developed out of an international meeting in Las Vegas, Nevada in 2014. Meeting attendees included MSA experts, MSA advocacy organization leaders (including Defeat MSA Alliance), pharmaceutical industry representatives, and other important stakeholders in the global MSA community. The Roadmap set forth a robust global research strategy. In 2018, the Roadmap's forward thinking recommendations were included in a report that was published in Neurology, the journal of the American Academy of Neurology (AAN). The entire paper can be read **here** per the courtesy of the AAN.

MISSIONS

Defeat MSA Alliance is a US based 501(c)(3) national charity that aspires to balance support for patients, education of medical professionals, raising public awareness, nurturing promising research and advocacy for the MSA community.

MSA United International is a global consortium of charitable associations united in their dedication to fight MSA. The collective purpose of MSA United aspires to balance community support, medical education and advocacy, public awareness, and scientific research. All the charitable groups in MSA United International are staffed entirely by volunteers and include the following non-profits:

Defeat MSA Alliance (USA)

Defeat MSA Awareness Shoe Campaign (USA)

Defeat Multiple System Atrophy/Vaincre L'Atrophie Multisystématisée (Canada)

Atrofia Multisistémica – ASYD (España)

Combattiamo L'Atrofia Multisistemica (Italia)

Defeat Multiple System Atrophy Australia and New Zealand, Ltd (AU)

Defeat Multiple System Atrophy Australia and New Zealand Trust (NZ)

Landsforeningen Multipel System Atrofi (Denmark)

Want to participate in research trials?
Submit your information on the
World MSA Research Registry
https://defeatmsa.org/research-registry/

Interested in possible new drugs?
https://defeatmsa.org/msa-research/pipelines/

Help Us Defeat MSA! Donate Now!
https://defeatmsa.org/donate-to-us/