

Clinical trials in MSA

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What is a clinical trial?

Research study involving human patients to determine the effects of an intervention on the human's health

- ✓ Research studies – not standard of care
- ✓ Humans – not animals
- ✓ Human's health – can be symptoms or disease progression

Which one of these is a clinical trial?

- A. A doctor prescribing iron to treat anemia in a patient
- B. A study to test if aspirin can prevent cancer in rats
- C. A company selling stem cells for the treatment of neurological disorders in patients
- D. A study to define kidney abnormalities in Parkinson disease

Why do we need clinical trials?

Proving that a drug is effective to improve health outcomes in patients is the only way for a drug to be **FDA-APPROVED** for that condition

FDA-APPROVAL implies that the insurance company will cover the cost of the medication for the specific indication

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Investor Announcement

Prana receives Orphan Designation for PBT434 for treatment of MSA

JANUARY 20, 2019

Prana Biotechnology Ltd (ASX: PBT, NASDAQ: PRAN) has today announced the US Food and Drug Administration (FDA) has granted Orphan Drug designation for its lead molecule, PBT434, for the treatment of Multiple System Atrophy (MSA). This is the first time the FDA has granted orphan designation to a drug for the treatment of MSA.

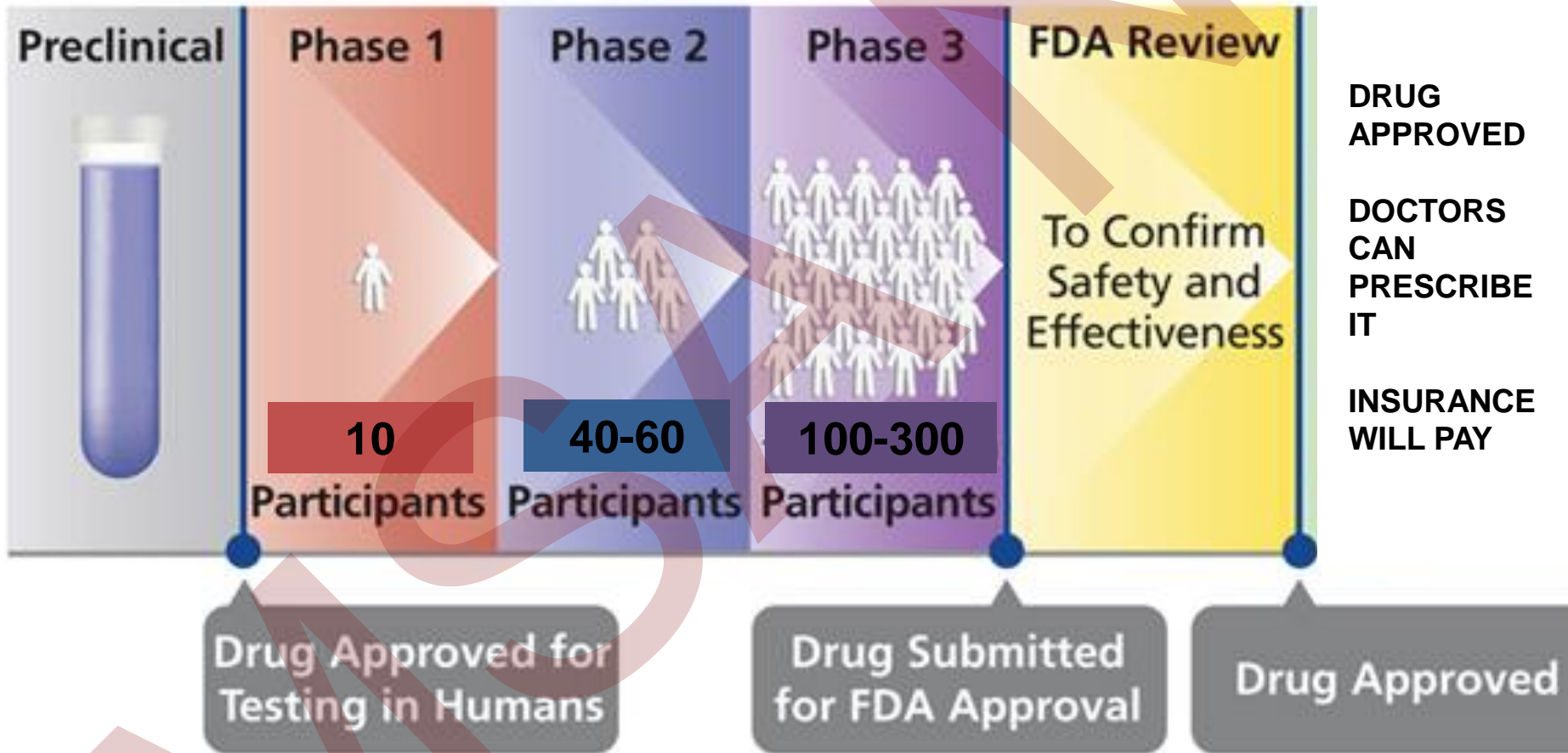
Orphan Drug designation by the FDA entitles Prana to seven years of market exclusivity for the use of PBT434 in the treatment of MSA and qualifies the sponsor of the drug for various development incentives of the Orphan Drug Act, including qualified clinical testing.

**THIS IS NOT FDA-APPROVAL
NO CLINICAL TRIALS SHOWING EFFICACY**



Animals

Clinical Trials



Two types of trials

1. Clinical trials to test if a drug can improve symptoms (**symptomatic therapy**)

- ✓ Neurogenic orthostatic hypotension
- ✓ Neurogenic bladder
- ✓ Constipation
- ✓ Depression
- ✓ Tremors

Two types of trials

2. Clinical trials to test if a drug can slow the progression of the disease (**disease modifying therapy**)

- ✓ Symptoms may or may not improve (may worsen)
- ✓ Think of this as a cancer drug

Which of these is FDA-approved to slow the progression of MSA?

A. Stem cells

B. Hyperbaric oxygen

C. Medical marijuana

D. Nilotinib

E. Cerezyme Q10

F. Intravenous Immunoglobulin (IVIG)

✓ Safety and efficacy in MSA not proven
✓ Not FDA approved
✓ You will have to pay for them out of pocket

Pros and cons of participating in a trial

PROS

- ✓ Possibility of receiving a new and potentially useful drug for free
- ✓ Being evaluated by experts
- ✓ Contributing to the development of new medicines

CONS

- ✗ You may receive a placebo instead of the drug you want
- ✗ The drug may be ineffective or cause side effects
- ✗ Trials require time and effort commitment, months or years



Where to find legit clinical trials

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 300,807 research studies in all 50 states and in 208 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

Before participating in a study, talk to your health care provider and learn about the [risks and potential benefits](#).

Find a study (all fields optional)

Status ⓘ

- Recruiting and not yet recruiting studies
- All studies

Condition or disease ⓘ (For example: breast cancer)

Other terms ⓘ (For example: NCT number, drug name, investigator name)

Two trials for MSA now at NYU

- To test if a drug is effective to treat neurogenic orthostatic hypotension (TD-9855, Amprexetine)
 - New investigational drug
 - Phase 3 study
 - Pharmaceutical company (Theravance)
- To test if a drug is effective to slow the progression of MSA (sirolimus)
 - FDA-approved drug to treat organ transplant rejection
 - Phase 2 study
 - NIH-sponsored

Theravance Trial

- Most patients with MSA have neurogenic orthostatic hypotension
- Currently approved treatments (midodrine, fludrocortisone, Northera®) are not satisfactory in ~30% of patients
- Ampreloxetine (TD-9855) has a completely different mechanism

Theravance Trial

- Phase 2 studies showed that the drug is safe and potentially effective to improve symptoms of nOH and increase BP when standing
- A Phase 3 study is now in place and actively enrolling patients.

Theravance trial for nOH

- **Where?** Several sites in the U.S. – NYU the only one in the U.S. East Coast
- **How many people?** ~200 subjects
- **How is the drug given?** Oral tablets, once a day, for **1 month.**
- **Could I get placebo?** Yes – 50% chance
- **How do you determine the efficacy of the drug?**
Symptoms of nOH and blood pressure
- **Do I have to pay to be enrolled?** No, not at all.
- **Are patients reimbursed for travel/time?** Yes

Theravance trial for nOH

- ***What are the main inclusion criteria?***
 - nOH caused by MSA, PD or PAF
 - Symptoms of dizziness/lightheadedness have to be moderate
- ***What are the main exclusion criteria?***
 - Renal failure
 - Dementia
 - Patients need to stop midodrine or Northera

Possibility of receiving the study drug for 6 more months after the first month of the trial

Theravance trial for nOH

Interested? Questions?

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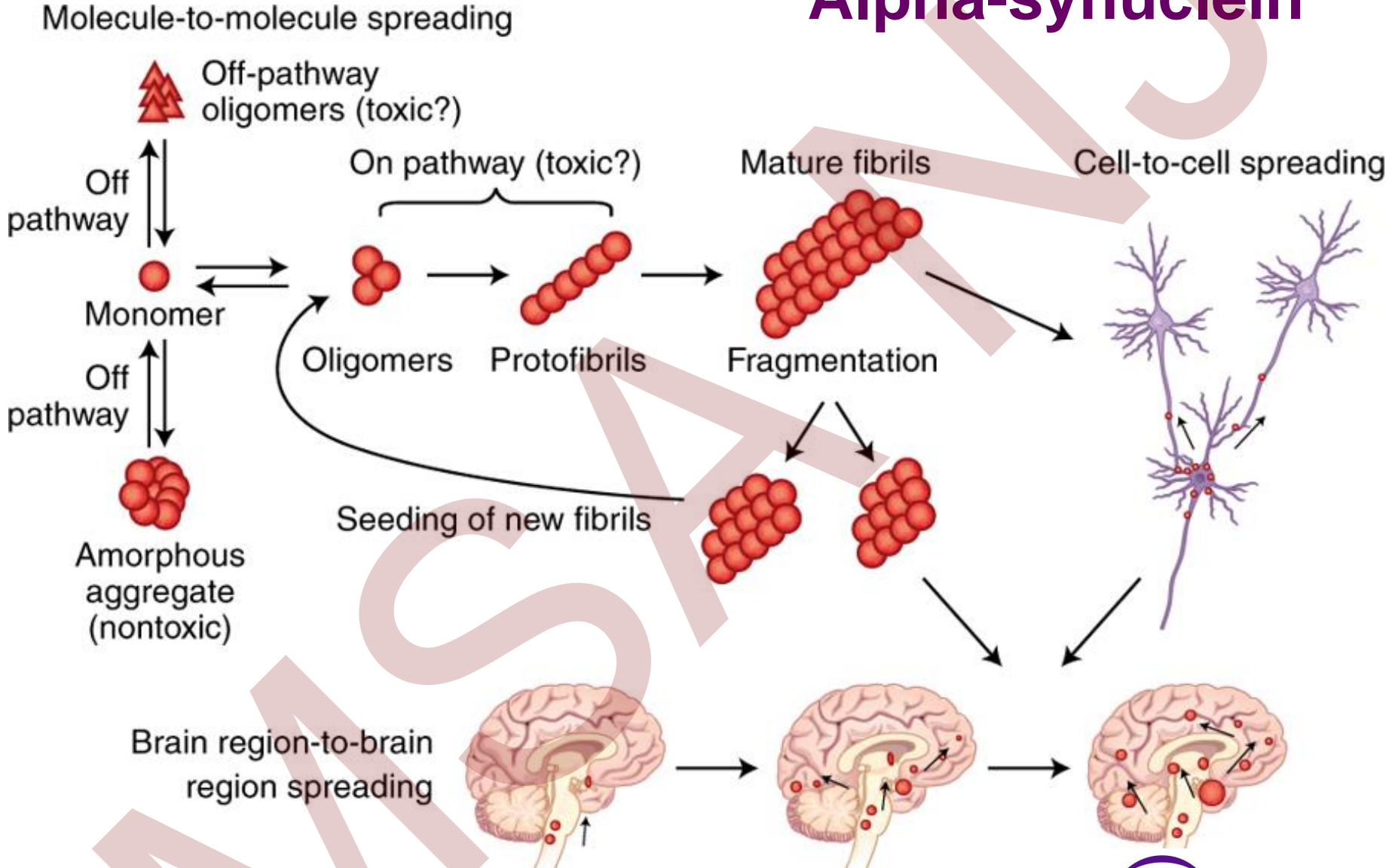
Sirolimus in MSA

- Sirolimus (Rapamycin) is a potent immunosuppressant approved by the FDA for over 2 decades for the treatment of various disorders:
 - Prevention of organ transplant rejection
 - Lymphangiomyomatosis
 - Rare pediatric cancers

Sirolimus in MSA

- Sirolimus (Rapamycin) is also a potent activator of **autophagy**
- Autophagy: the process by which the organism eliminates proteins that are excessively accumulated
- MSA is caused by excessive accumulation of the protein alpha-synuclein

Alpha-synuclein



Soto C, Pritzkow S. Nat Neurosci. 2018 Oct;21(10):1332-1340.

Sirolimus in MSA

- When used **in cellular and animal models** of Parkinson disease, MSA and other neurodegenerative disorders, treatment with sirolimus:
 - Stopped and prevented the deposition of alpha-synuclein
 - Stopped neurodegeneration
 - Improved motor function
 - Prevented aging

Alpha-synuclein clumps

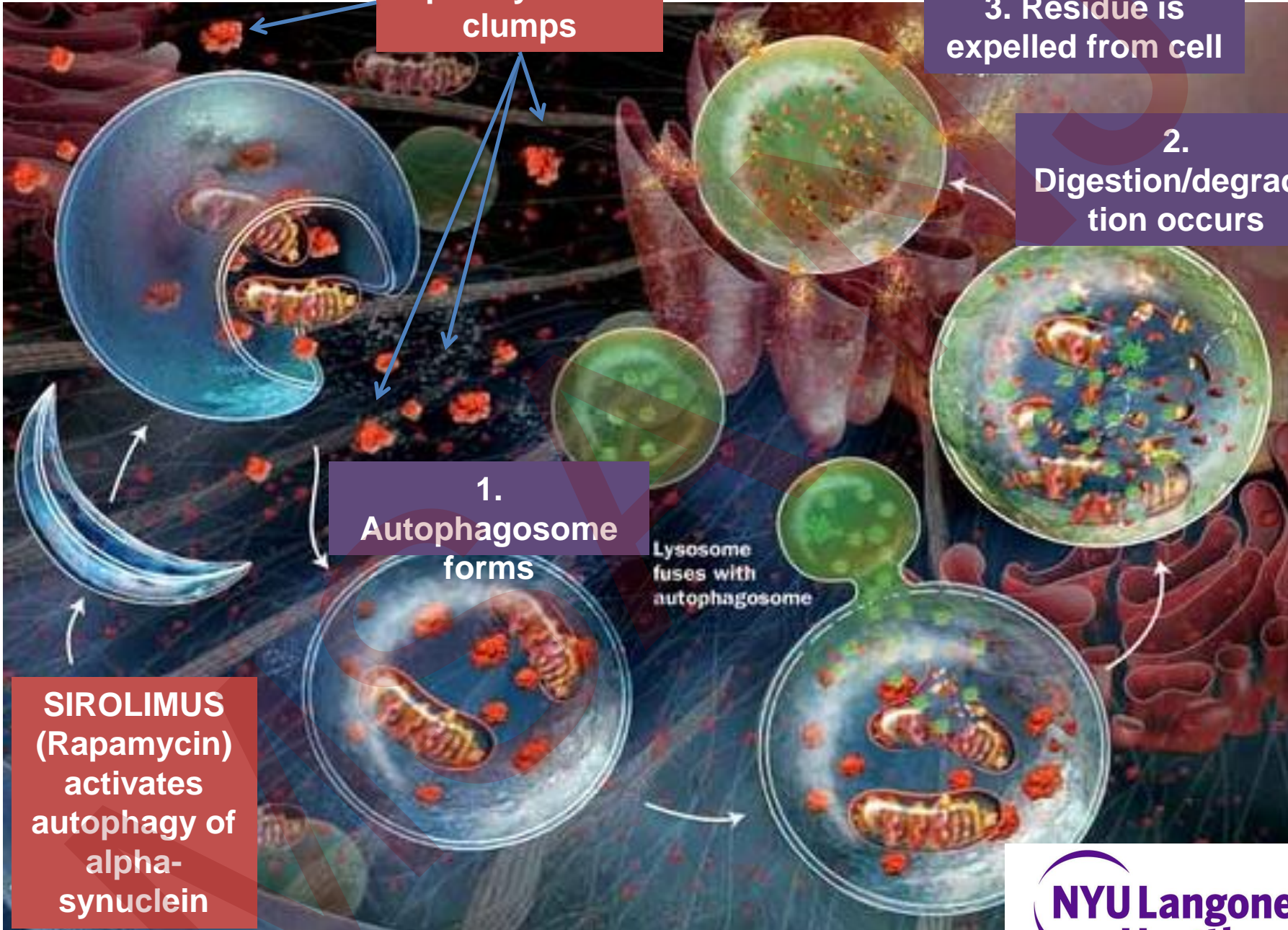
3. Residue is expelled from cell

2. Digestion/degradation occurs

1. Autophagosome forms

Lysosome fuses with autophagosome

SIROLIMUS (Rapamycin) activates autophagy of alpha-synuclein



Sirolimus in MSA

- Good and promising data in cells and animal models
- Sirolimus has never been tested in humans to treat a neurodegenerative disease
- We need a clinical trial!

Sirolimus trial for MSA

- **Where?** Only at NYU – this is a single-center trial
- **How many people?** 56 subjects
- **How is the drug given?** Oral tablets, once a day, for 1 year.
- **Could I get placebo?** Yes: 42 will receive sirolimus and 14 will receive placebo.
- **How do you determine the efficacy of the drug?** UMSARS, brain MRI and retinal scan
- **Do I have to pay to be enrolled?** No, not at all.
- **Are patients reimbursed for travel/time?** Yes

Sirolimus trial for MSA

- ***What are the main inclusion criteria?***
 - MSA diagnosed within 4 years
 - Patient is able to walk (with or without a cane/walker)
 - Patient is less than 80 years old
- ***What are the main exclusion criteria?***
 - Immunosuppression
 - Chronic infection such as HIV, hepatitis or tuberculosis
 - Extremely high cholesterol or major disease (i.e., renal failure, cardiac failure, severe diabetes, etc.)
 - Pacemaker (incompatible with MRI)

Sirolimus trial for MSA

Interested? Questions?

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Summary

- ✓ Clinical trials are needed to prove if a drug works or not
- ✓ FDA requires clinical trials before approving a drug - insurance
- ✓ Getting involved in clinical trial has pros and cons
- ✓ Clinical trials for MSA are now open at NYU