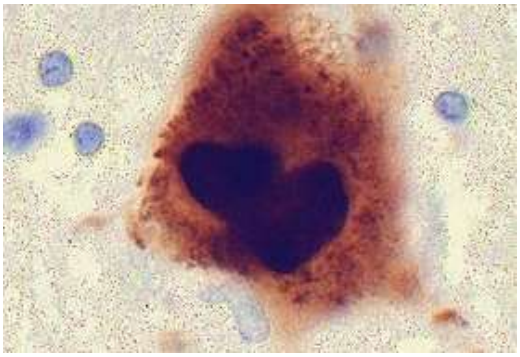
Perceiving Parkinson's

Assaulting Alpha-Synuclein (Day 87)

In 1912, the neurologist Fritz Heinrich Lewy discovered **Lewy bodies** within certain neurons of people with Parkinson's, and since then most researchers have assumed that Lewy bodies contribute to the pathological neuron-killing process in Parkinson's. It is dangerous to make assumptions like this - recall the analogy we used earlier, that the presence of a fire truck at a fire does not necessarily mean that the fire truck contributed to the fire.

Nonetheless, most researchers still believe that Lewy bodies either partially or primarily contribute to neuron loss in Parkinson's. Lewy bodies are microscopic collections of biological material that accumulate within certain neurons of people with Parkinson's, and their major constituent is a misfolded protein called **alpha-synuclein**, a misfolded protein that "aggregates" within each affected neuron.



In this neuron, alpha-synuclein (small dark spots) has aggregated to form Lewy bodies.

Over the last several years, it has been discovered that alpha-synuclein appears to exist not only inside neurons, as **intracellular** aggregates, but also outside neurons, in the **extracellular** space. Due to these findings, researchers who assume that alpha-synuclein is a "bad guy" in Parkinson's believe that:

(1) The **intracellular aggregation** of alpha-synuclein somehow leads to disruption of neuron function, leading to neuron death.

(2) The **extracellular spread** of alpha-synuclein allows alpha-synuclein to "infect" multiple neurons, leading to more intracellular aggregation and more neuron death.

Hence, these researchers are trying to target or "assault" alpha synuclein by developing methods that either block the intracellular aggregation of alpha-synuclein, or limit the extracellular spread of alpha-synuclein. Let's briefly discuss both methods.

Aggregation Blockers - Blocking The Intracellular Aggregation Of Alpha-Synuclein

Proponents of this method believe that **blocking the intracellular aggregation of alpha-synuclein** might allow neurons to avoid neurodegeneration and death in Parkinson's. Currently, two **aggregation blockers** are under very early development. In fact, they still have experimental names:

(1) **ANLE138b** - The first drug, ANLE138b, has been shown to the block intracellular aggregation of alpha-synuclein and extend lifespan in mice. Since it has not yet been tested in humans, the potential side-effects are not known.

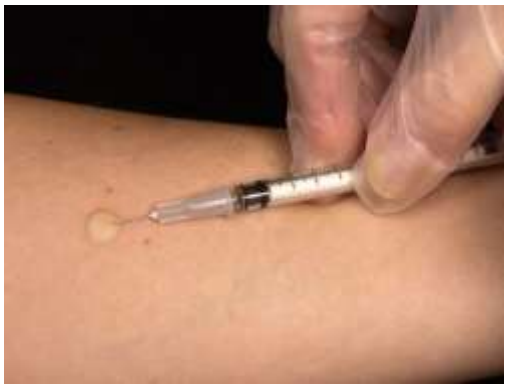
(2) **NPT200-11** - The second drug, NPT200-11, has been shown to block intracellular aggregation of alpha-synuclein *in vitro*, but it has not yet been tested in animals or humans and so any potential side-effects of this drug are completely unknown.

Immunotherapy - Limiting The Extracellular Spread Of Alpha-Synuclein

Proponents of this method believe that **limiting the extracellular spread of alpha-synuclein** might slow down or stop the pathological process that kills neurons in Parkinson's. Currently, researchers are trying to achieve this with **immunotherapy**, which takes one of two forms:

(1) **Active immunotherapy** - In this method, a person is **vaccinated** by injecting them with alpha-synuclein "mimics" so that their immune system will produce antibodies against alpha-synuclein. Mice immunized against alpha-synuclein this way show improved motor and cognitive function, but this has yet to be replicated in humans. However, the side-effects of active immunotherapy in humans have certainly been demonstrated and include a reasonable chance of developing **meningoencephalitis** (brain inflammation).

(2) **Passive immunotherapy** - In this method, a person is conferred **direct immunity** by injecting them with antibodies against alpha-synuclein. Mice immunized against alpha-synuclein this way show improved motor and cognitive function, but human studies are lacking. Since passive immunotherapy circumvents the immune system, many side-effects associated with active immunotherapy are also bypassed. However, passive immunotherapy requires **repeated antibody injections** for life.



Immunizations against Parkinson's? Some researchers believe so.

To sum up, strategies that assault alpha-synuclein make the major assumption that alpha-synuclein contributes to the neuron-killing process in Parkinson's, an assumption that has never been verified and may be flat-out wrong. If so, immunotherapies and aggregation blockers will likely go nowhere towards improving life for people with Parkinson's. However, if alpha-synuclein really does turn out to be a "bad guy" in Parkinson's, immunotherapies and aggregation blockers could become the next big thing in Parkinson's. We'll see.

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References

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