Update on therapies for Parkinson's Disease

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Avera Medical Group

Overview

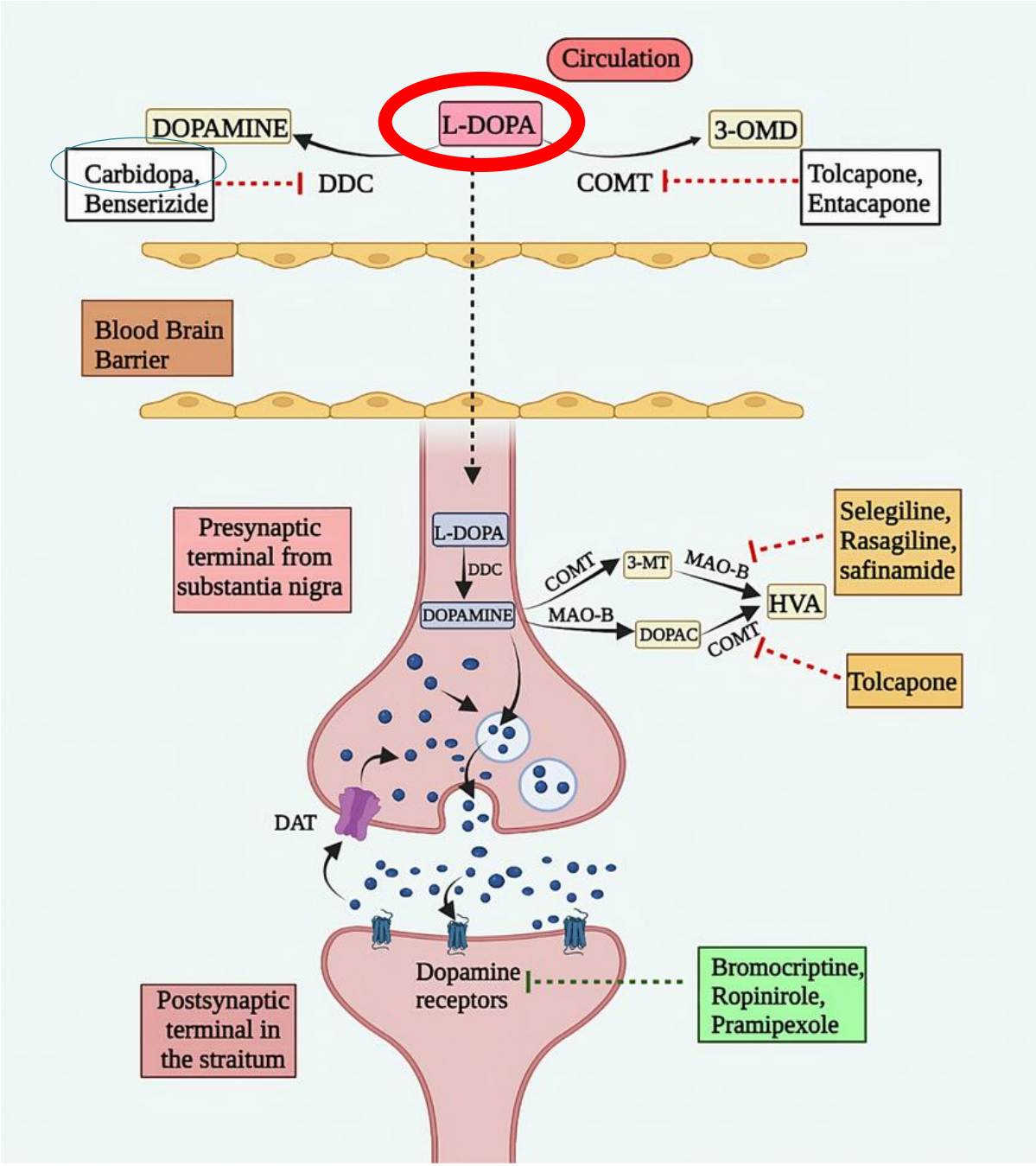
NEW DRUGS AVAILABLE

DBS UPDATE

FUTURE DIRECTIONS

Levodopa

- So far, the BEST option for most people



- Dopamine is missing in PD
  - **Sinemet** (**Levodopa/carbidopa**)
    - L-dopa can cross into brain
    - Carbadopa helps prevent it from becoming Dopaine in the blood stream
      - Nausea prevention
    - REPLACES what is MISSING!
  - Helps stiffness, slowness, tremors, gait
  - Helps mood sometimes

  - Can cause
    - Dyskinesias
    - Hallucinations
    - Sleepiness
    - Nausea
    - Light-headedness

Other L-dopas

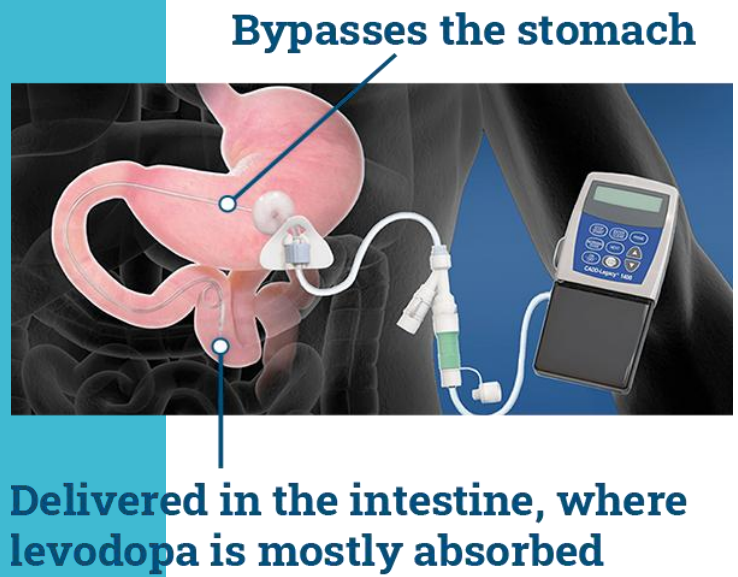
- Sub Cutaneous (Vyalev)
- Through stomach tube (Duopa)
- Longer acting L-dopa (Crexont)

Pumps

- Foscarbidopa/foslevodopa (Vyalev)
  - 24, variable rate infusion into the skin
  - Not currently covered….?

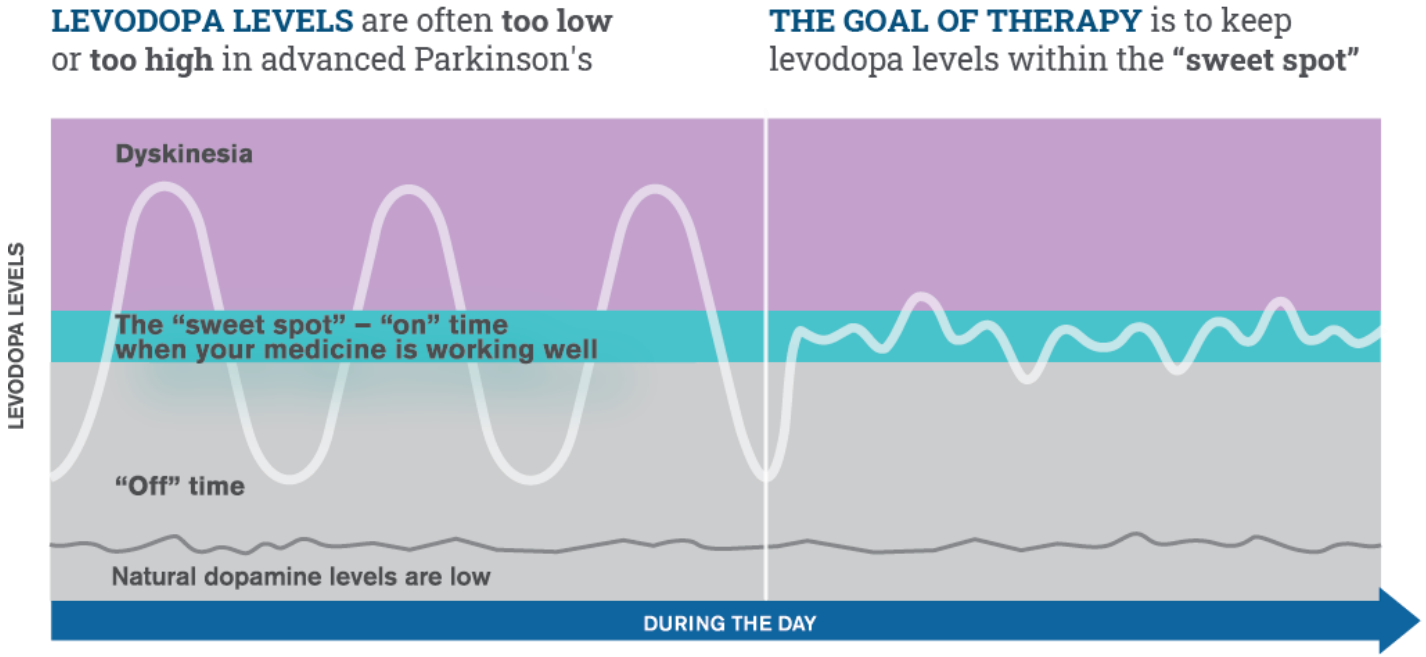
Pumps

- Carbidopa/levodopa enteral suspension (Duopa)
  - 16 hour through a hole in the abdomen
  - Currently covered
  - Refrigerated



Pump Benefits

- Smooth blood level
- Less/not affected by food
- Goal is to be able to stop ALL levodopa (and usually dopamine agonists)

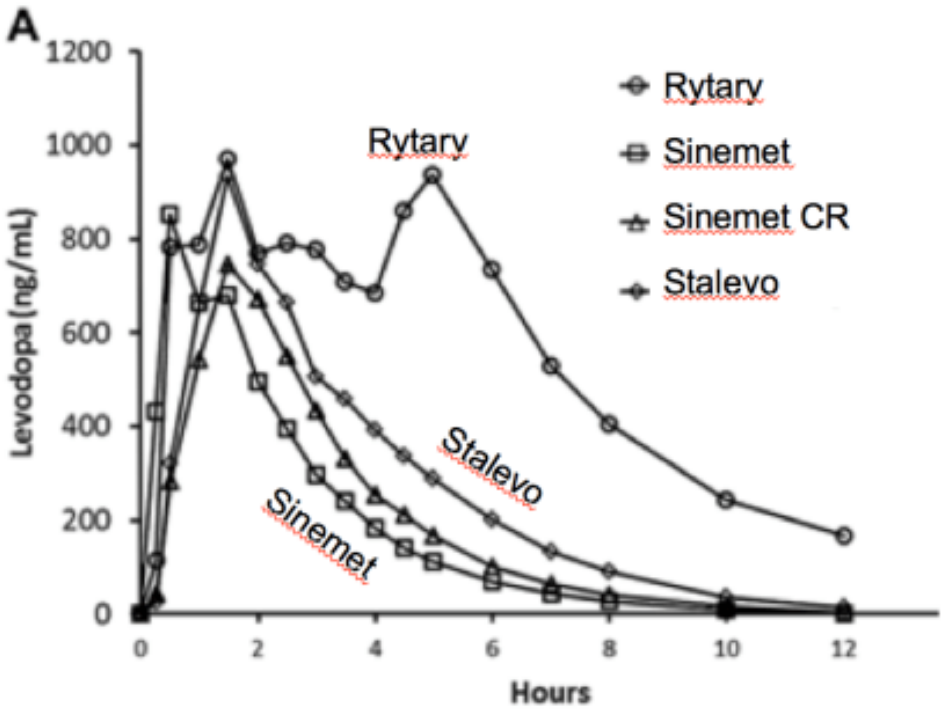


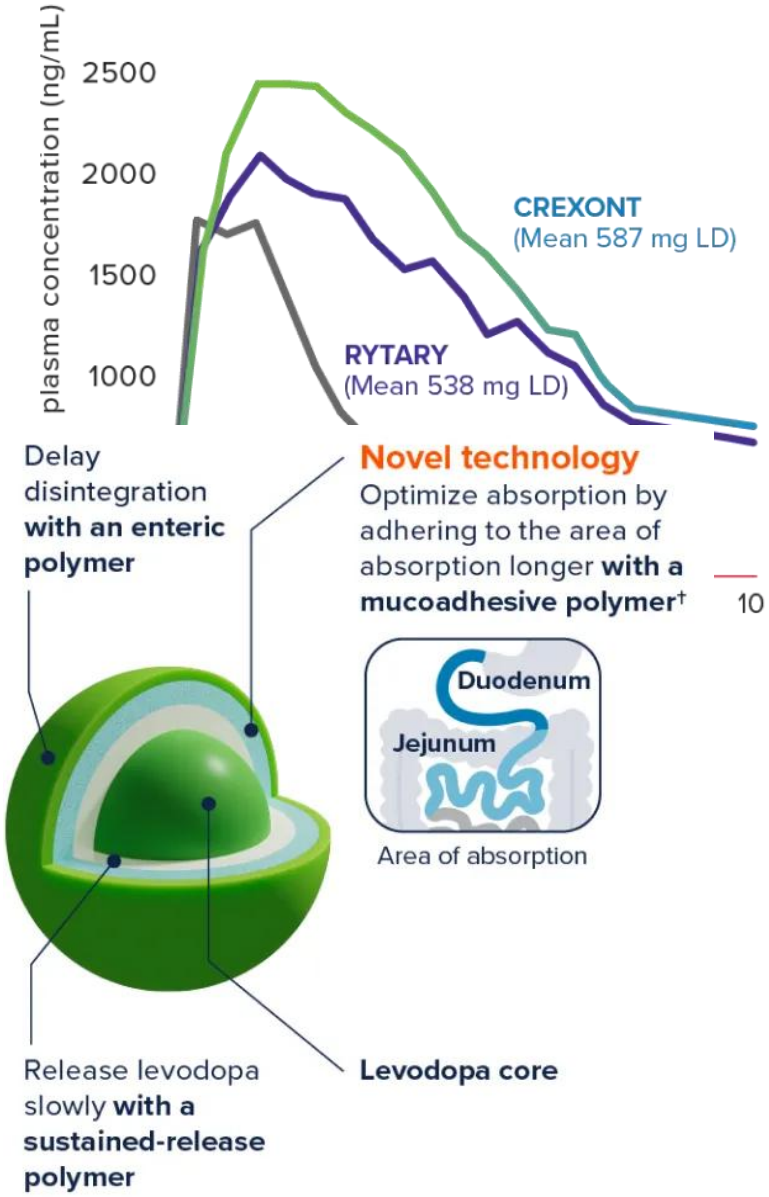
Pump negatives

- More invasive than pills
- Expensive
- No different effects than Sinemet really

Crexont

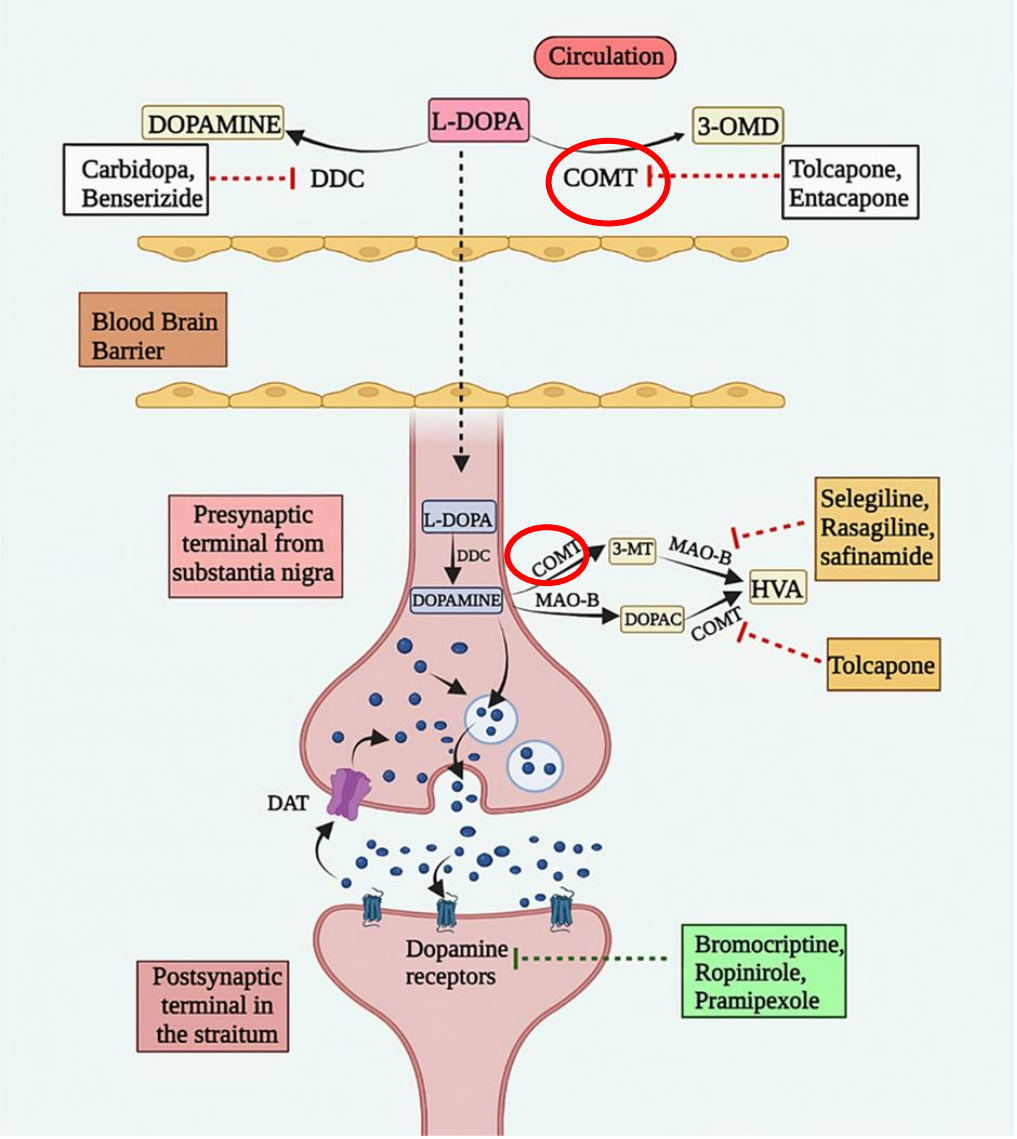
- Less frequent dosing
- Higher dosage per dose though!





Make L-dopa last longer

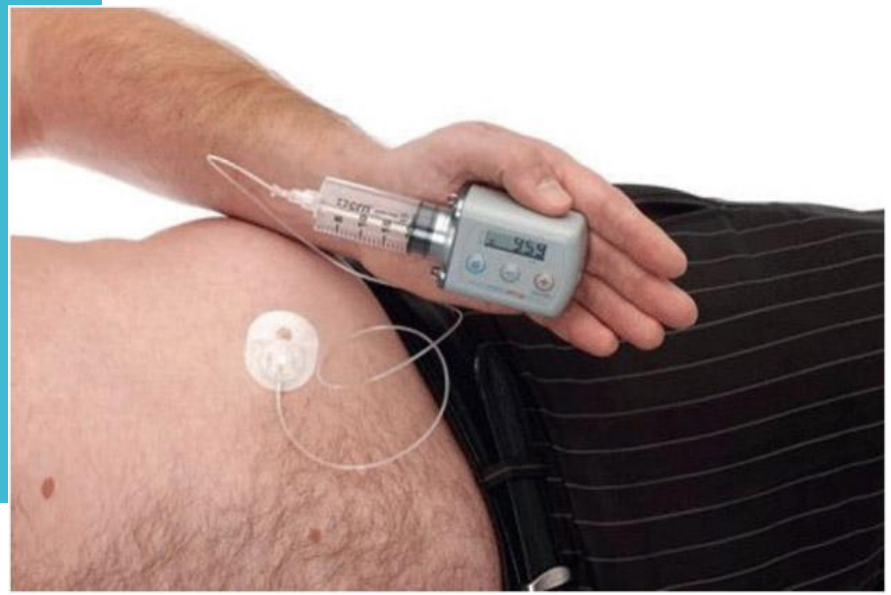
- COMT inhibitors
  - **Opicapone**
  - Entacapone
- MAO-B inhibitors
  - Rasagiline
  - Selegiline

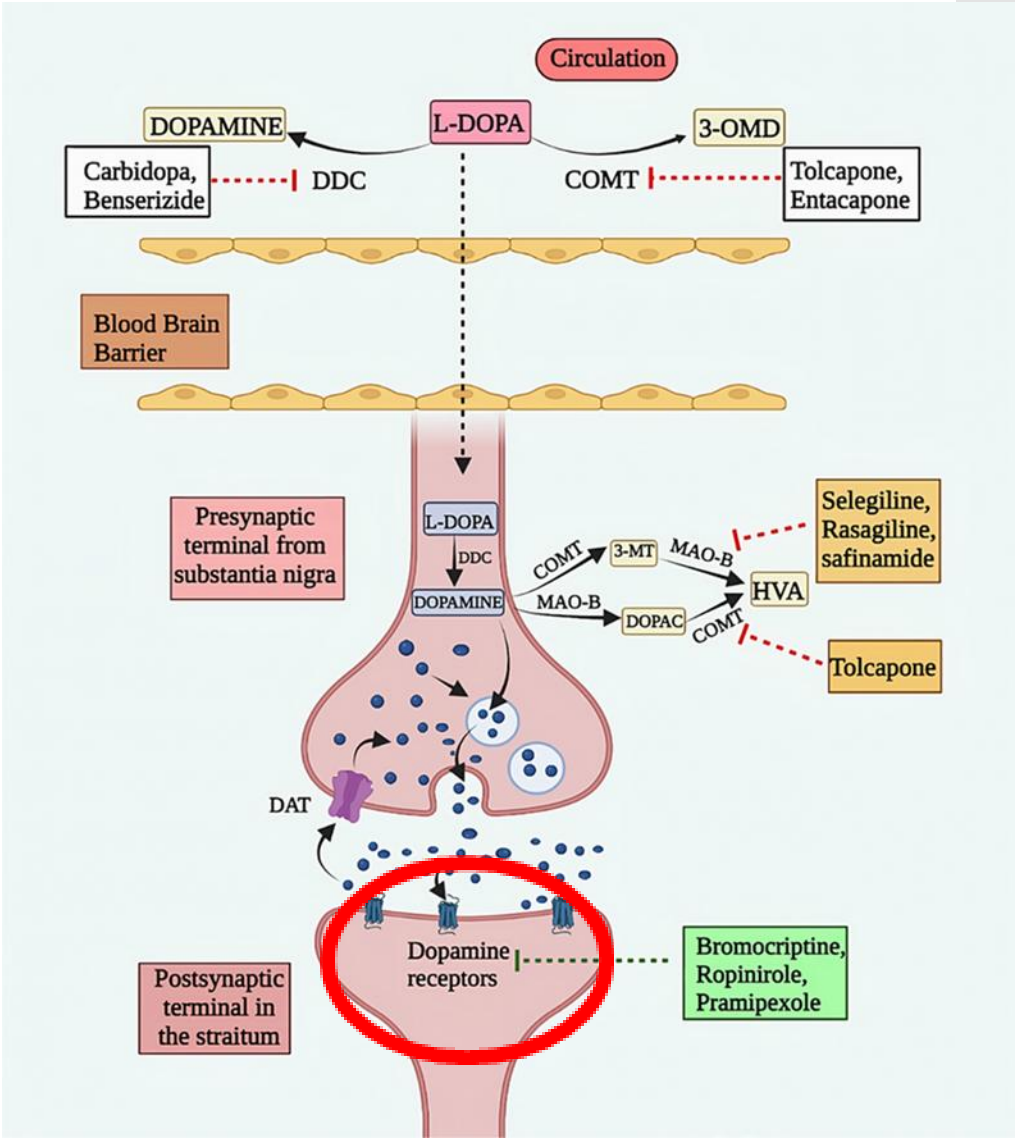


Dopamine Agonists

Apomorphine

- NOT RELATED TO PAIN
- Oral dissolving
- Infusion pump





Dopamine Agonists

Positives

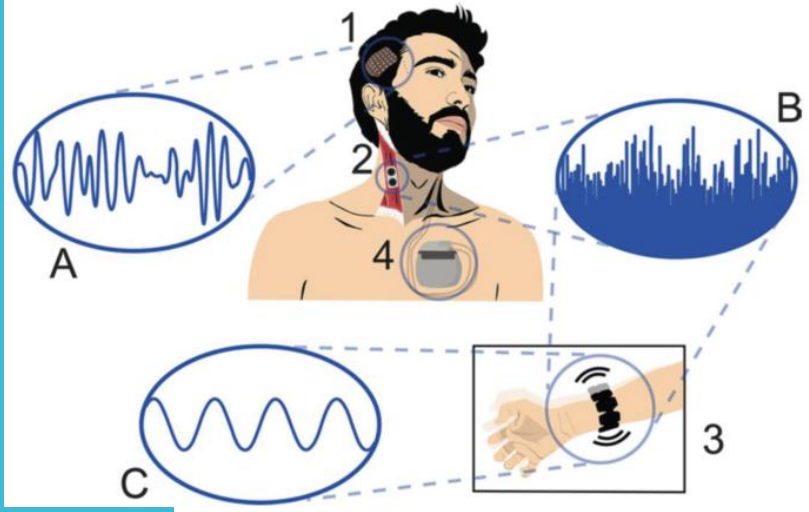
- Smoother
- No dyskinesia (if taken without Sinemet)

Negatives

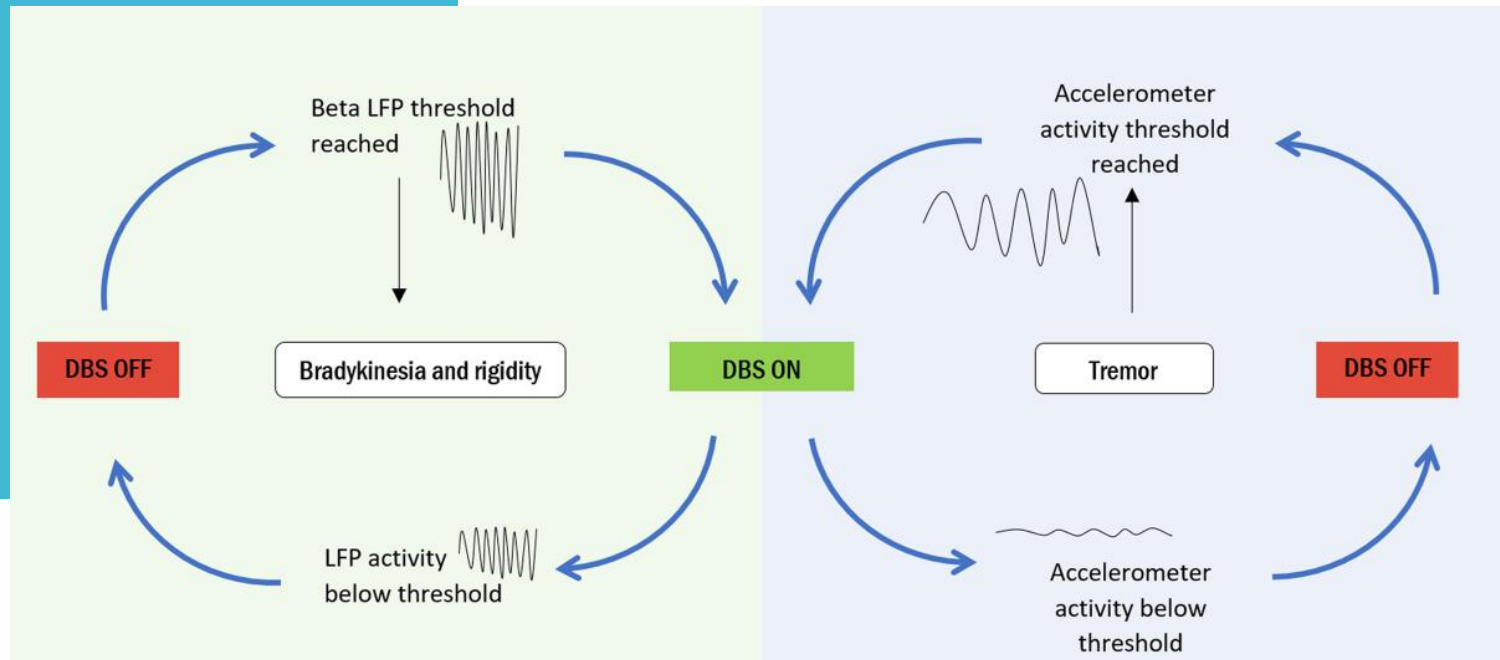
- Somnolence
- OCD like symptoms
- Nausea

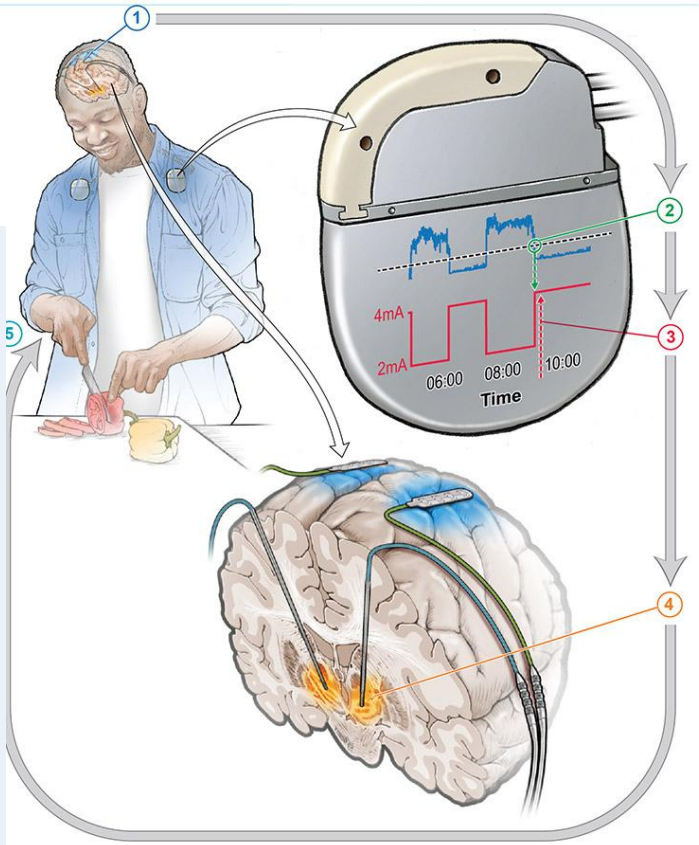
OTHER DOPAMINE AGONISTS
Pramipexole (Mirapex)
Ropinerole (Requip)
Rotigatine (Neupro)

Adaptive closed loop DBS



DBS that listens to your brain or tremor/gait sensors!

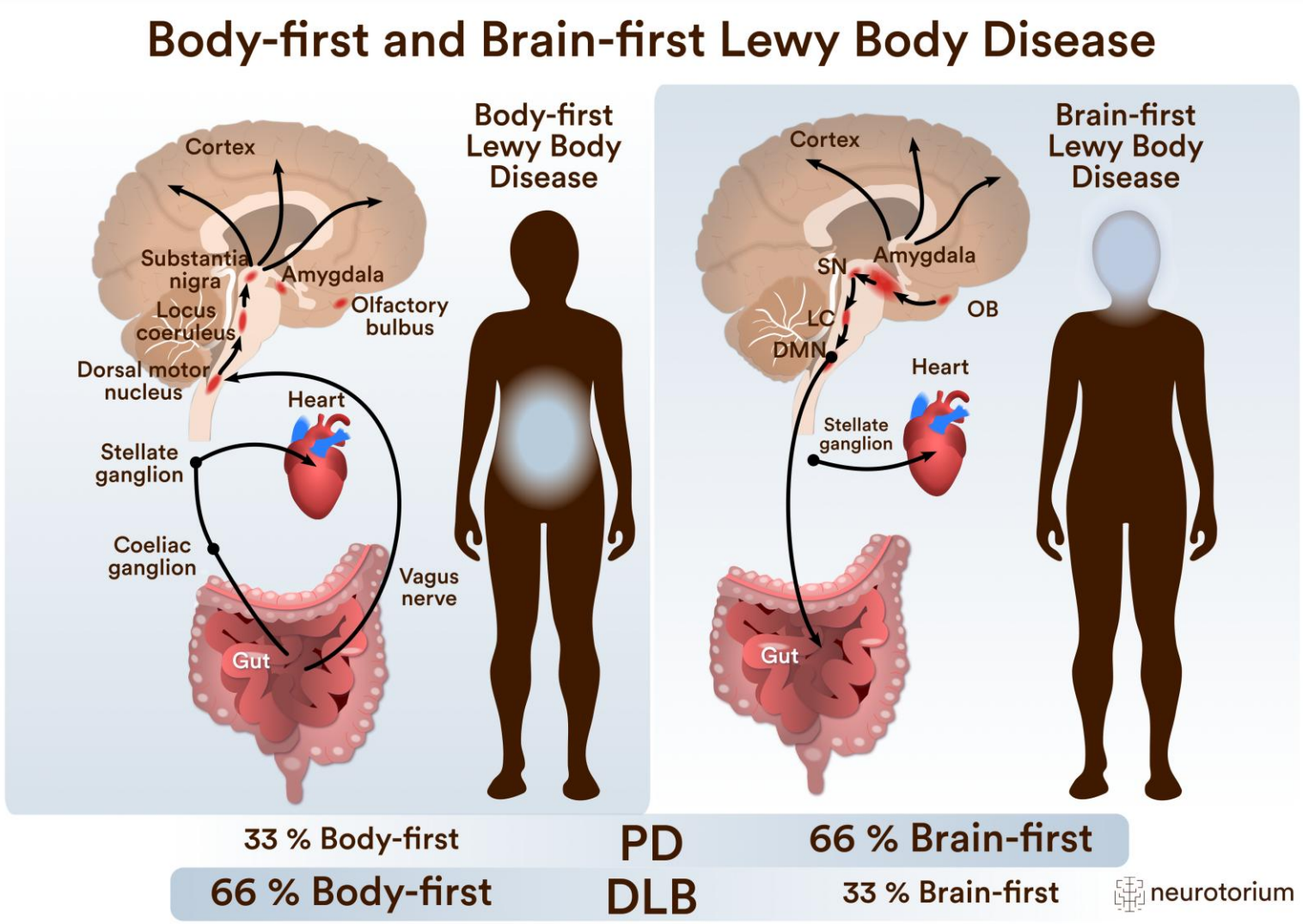




The Crew

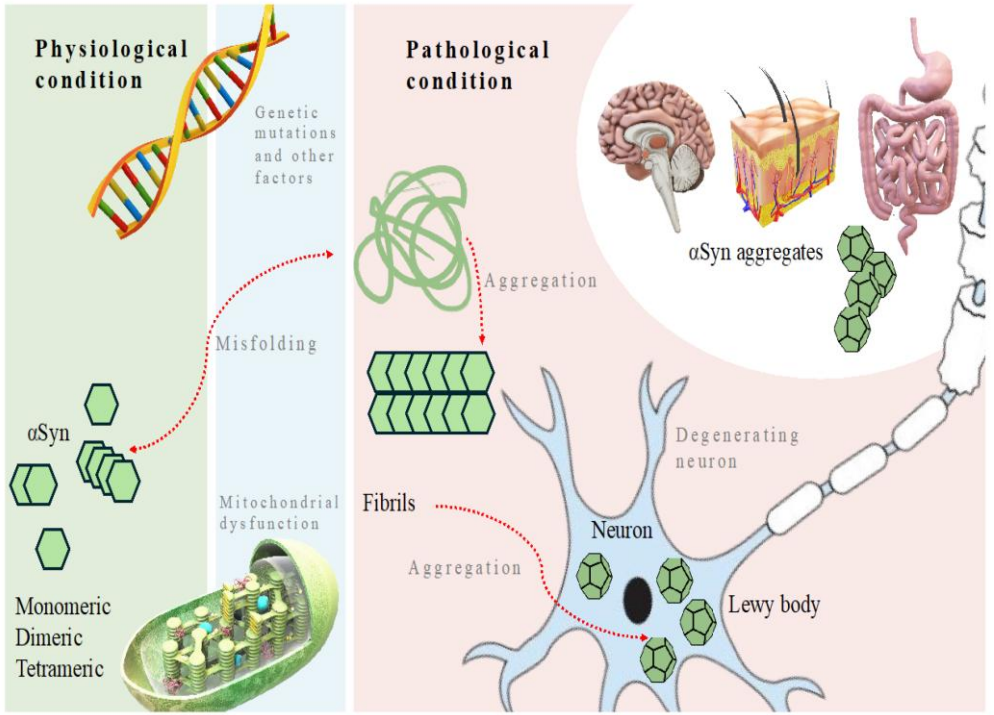
Upcoming research

What happens to CAUSE Parkinsons?



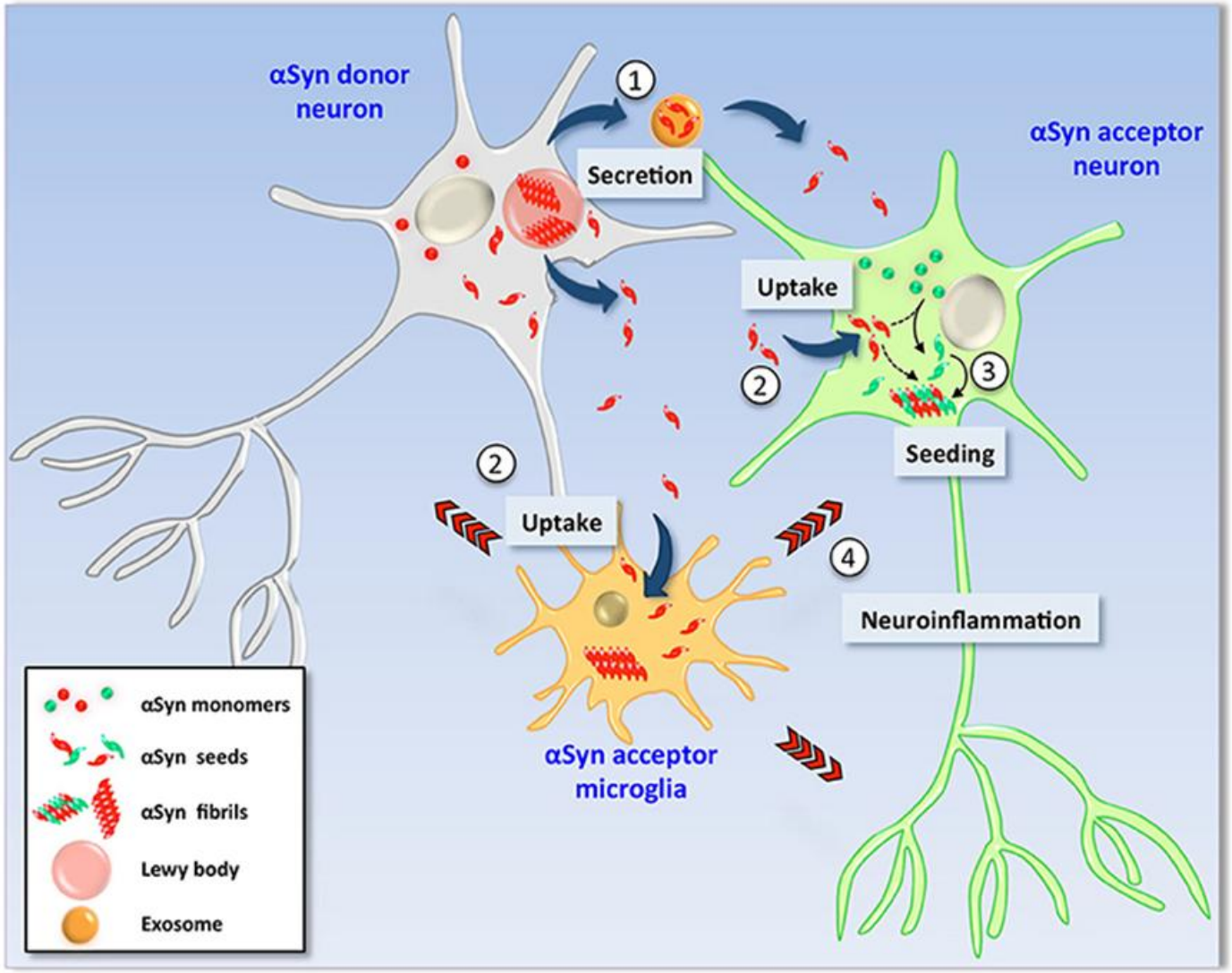
Alpha-synuclein

- A-syn used to control neurotramission
- Misformed proteins can clump up and create Lewy Bodies

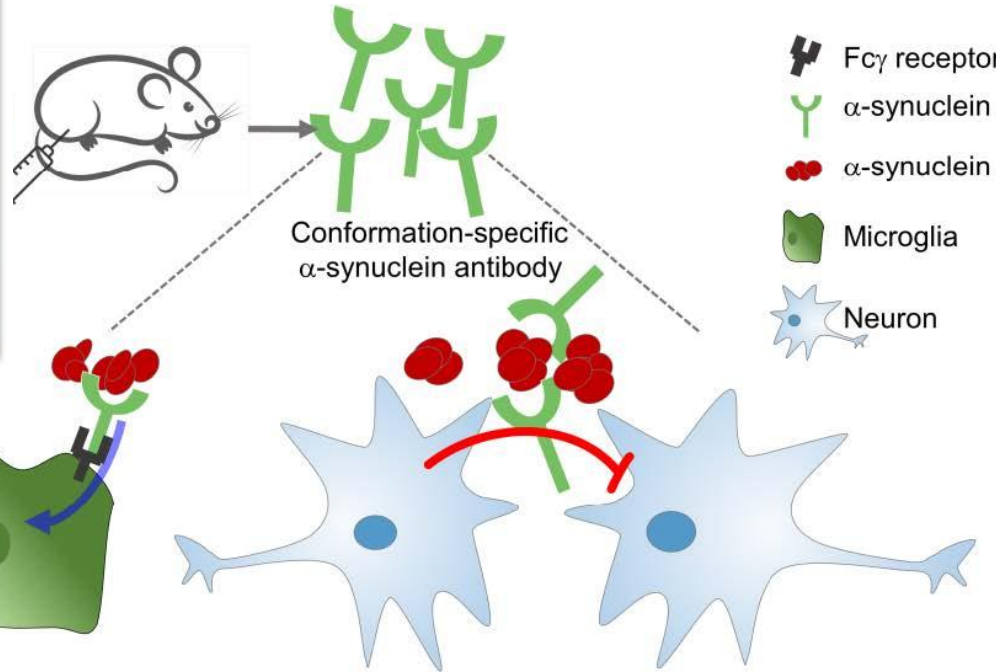


Targeting alpha-synuclein

- Antibodies: Akin to the new Alzheimer's therapies
  - Infusion of drug is antibodies to Lewy Bodies
- Vaccine: injection of a protein like A-syn which induces body to make antibodies to Lewy Bodies
- Small molecules blocking A-syn aggregation



Antibody Effect



Immune Therapies

Early Phase trials

- Vaccines
  - Not clearly beneficial yet
  - Not certain the antibodies can get INSIDE neurons where the Lewy Bodies are
- Prasinezumab/antibodies
  - Slower progression
  - Digital motor scoring with apple watch-like devices

- Need to leave physiologically active normal A-syn alone

Tetanus Vaccine?

- Comparing people who got Tetanus vaccine vs not
- Risk reduction for developing PD for the next 5 years (0.17 risk compared to non-tetanus shot patients)
- Slower disease progression

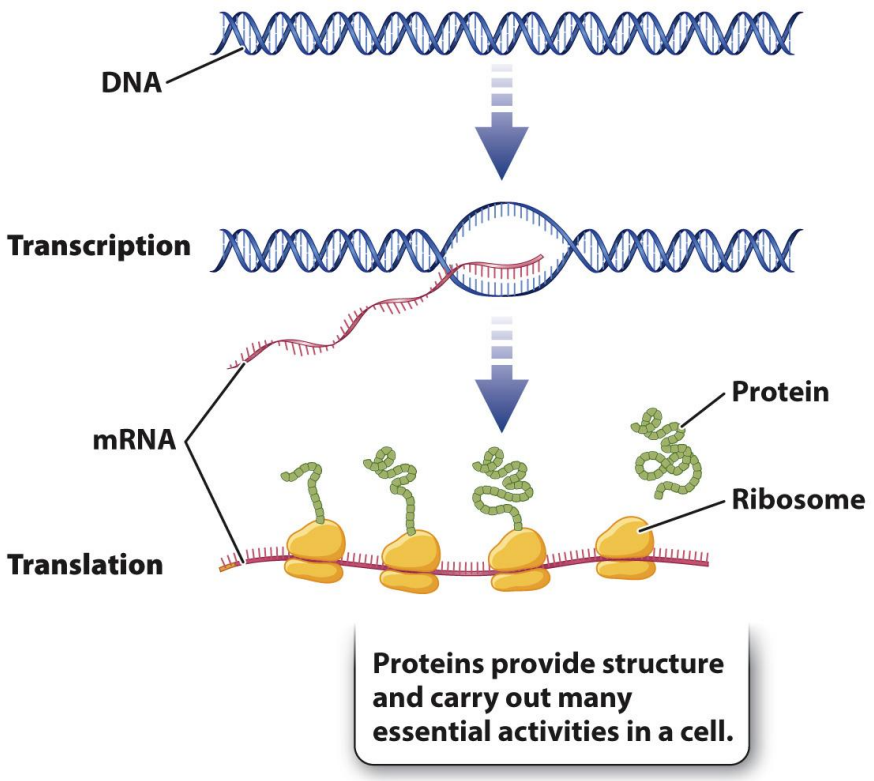
Why?

- Vaccine given when you get a dirty wound, which you get when you are more active?

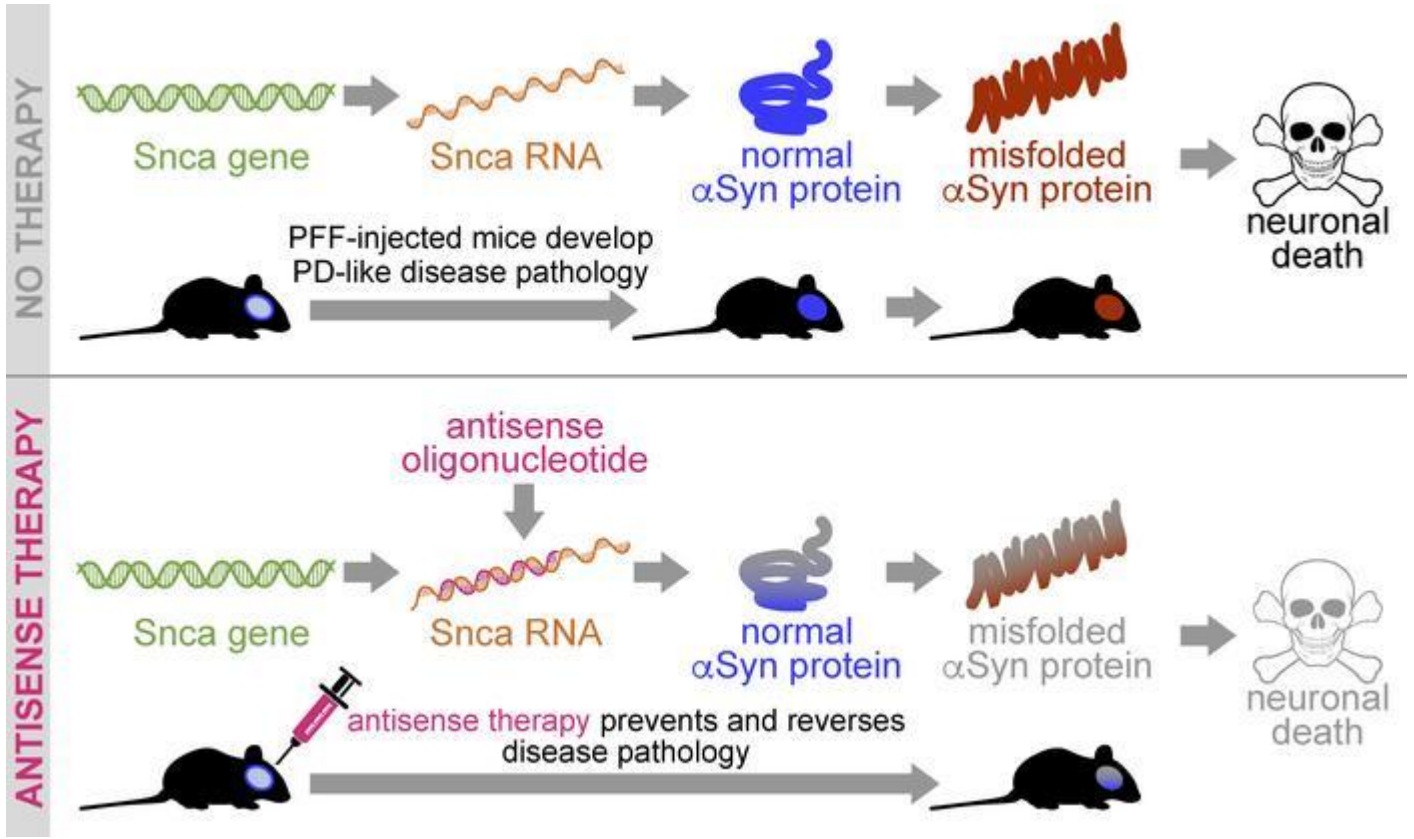
Genetics

- Antisense Oligonucleotides
  - Block alpha-synuclein expression

DOGMA of BIOLOGY



ASO


NO THERAPY
Snca gene
Snca RNA
normal αSyn protein
misfolded αSyn protein
neuronal death
PFF-injected mice develop PD-like disease pathology
ANTISENSE THERAPY
antisense oligonucleotide
Snca gene
Snca RNA
normal αSyn protein
misfolded αSyn protein
neuronal death
antisense therapy prevents and reverses disease pathology

Is A-synuclein actually the problem?

YES

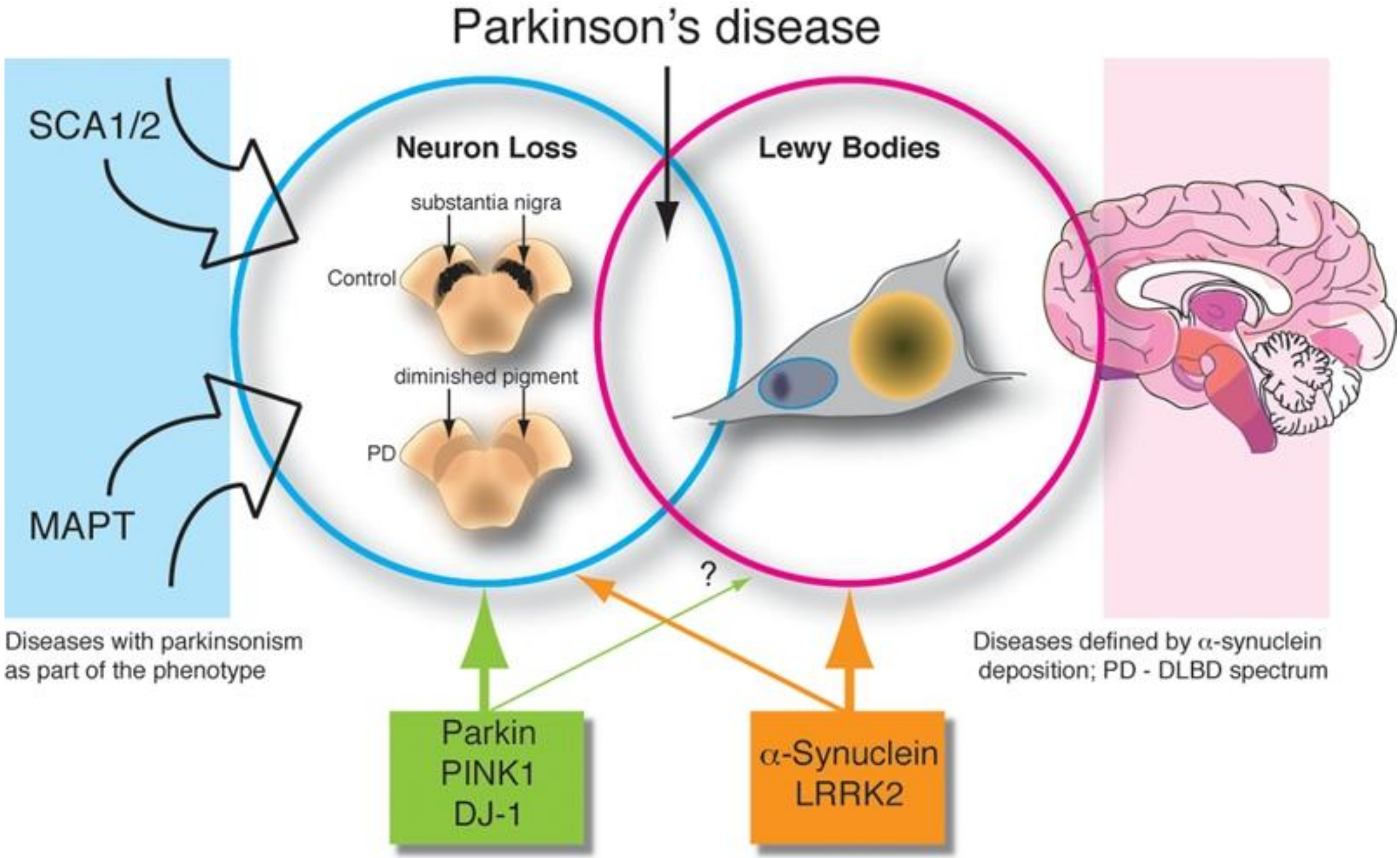
- Present in all PD and PD+
- Genetic causes of PD have some relation to A-syn
- Injecting into mice can cause more to form and develop something like PD

NO

- Inflammation starts BEFORE A-syn in disease models
- Cells that are **alive** have A-syn in them
- Important for neurotransmitter control
- There are A-syn inclusions in people *without* disease
- Concentrations don't correlate with disease severity

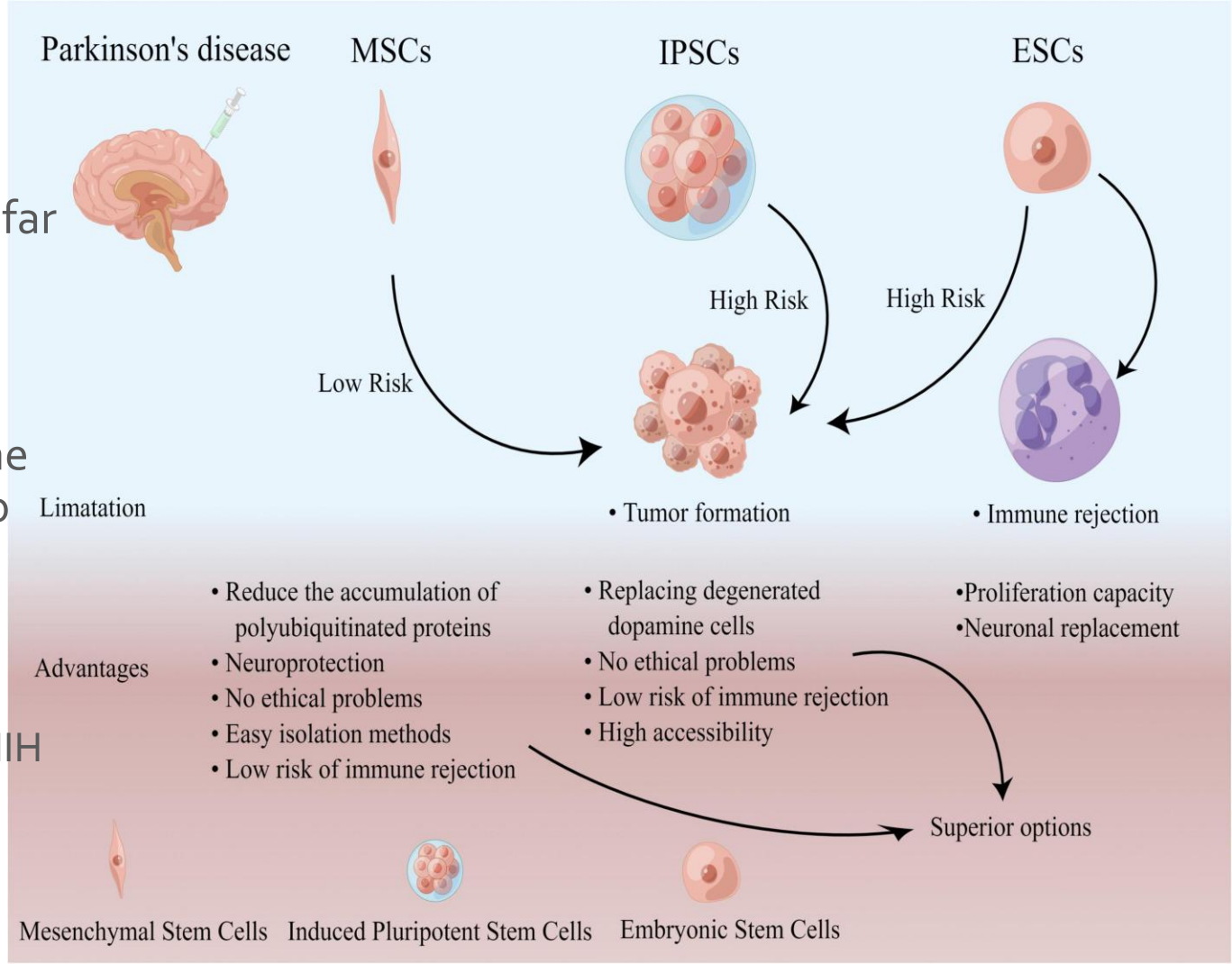
A-syn in Dopamine Neurons

- Helps maintain pacemaker characteristics
- Nigral cells are VERY fast and active
- They “burn out” easier

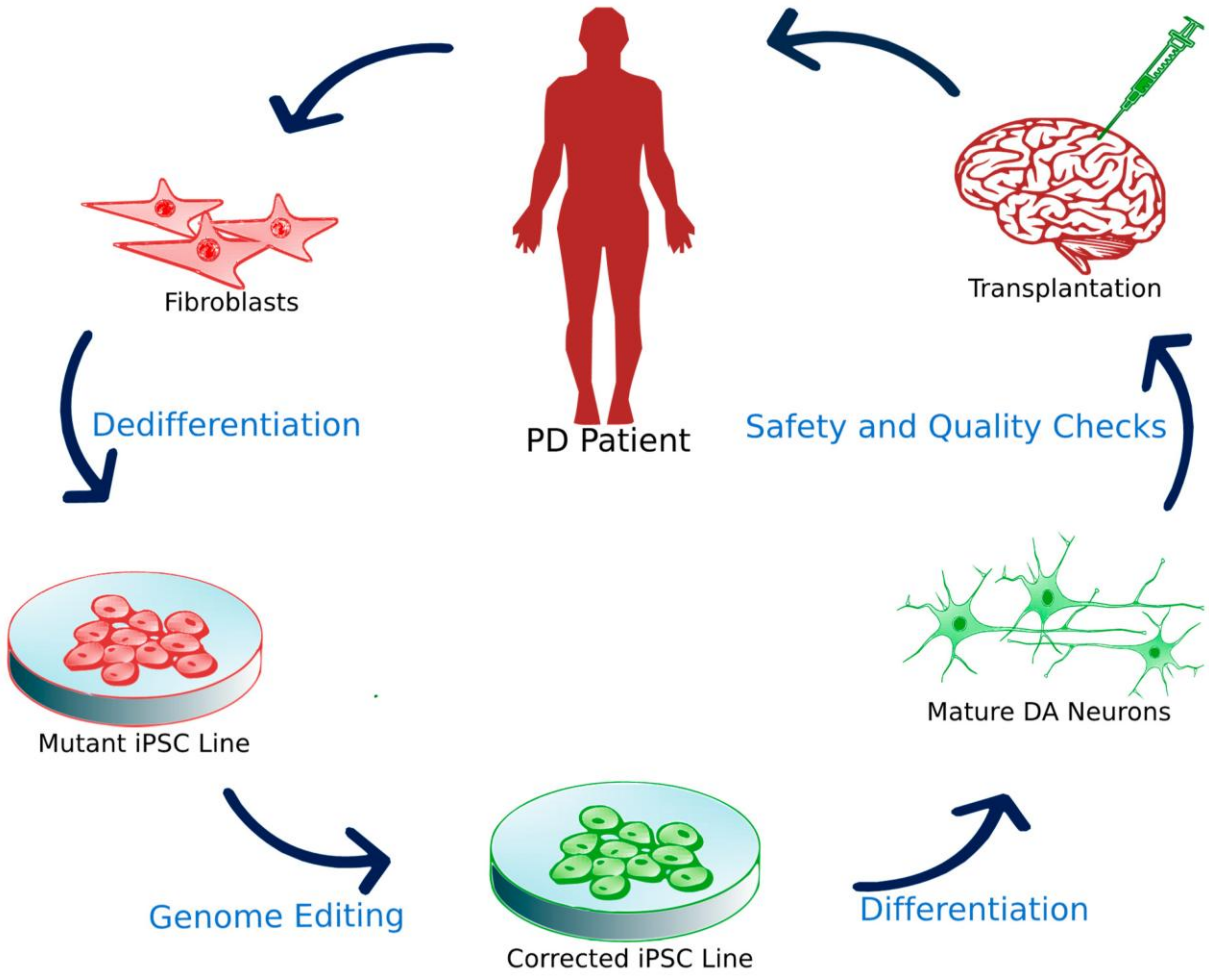

Parkinson's disease
SCA1/2
MAPT
Neuron Loss
substantia nigra
Control
diminished pigment
PD
Lewy Bodies
?
Parkin
PINK1
DJ-1
α-Synuclein
LRRK2
Diseases with parkinsonism as part of the phenotype
Diseases defined by α-synuclein deposition; PD - DLBD spectrum

Stem Cells

- Tried many times without success so far
- They type you can buy are not able to become any cell, especially dopamine and cannot get into the brain
- Clinical trials on clinicaltrials.gov
  - Not vetted by NIH



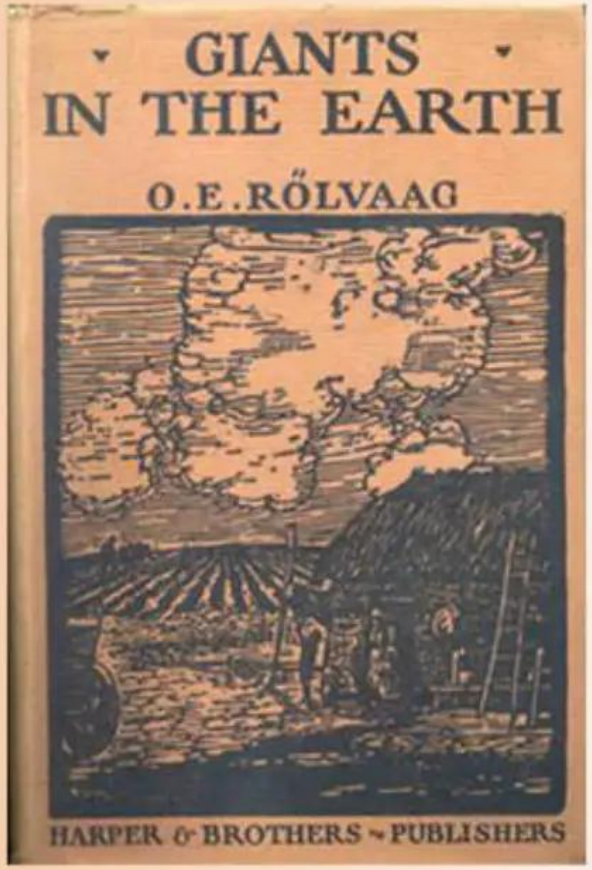
Stem Cells


Fibroblasts
Dedifferentiation
PD Patient
Transplantation
Safety and Quality Checks
Mature DA Neurons
Mutant iPSC Line
Genome Editing
Corrected iPSC Line
Differentiation

SDSO

SOUTH DAKOTA SYMPHONY ORCHESTRA

DELTA DAVID GIER, MUSIC DIRECTOR

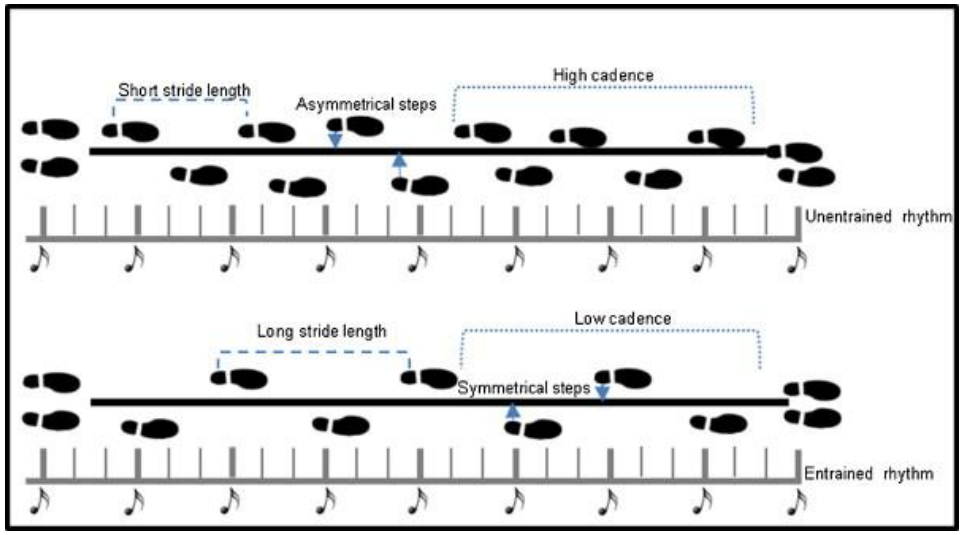


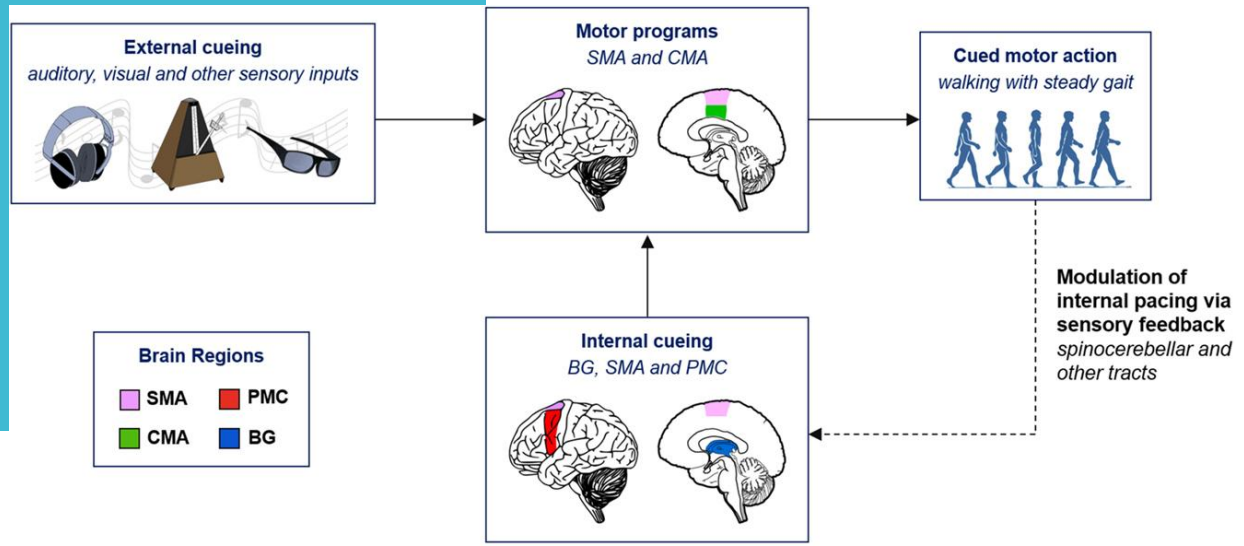
- Never recorded opera about Norwegian immigrants settling east of Sioux Falls
- Pulitzer prize in 1951
- Tonight at 7:30 and Sunday at 2:30 at the Washington Pavilion!

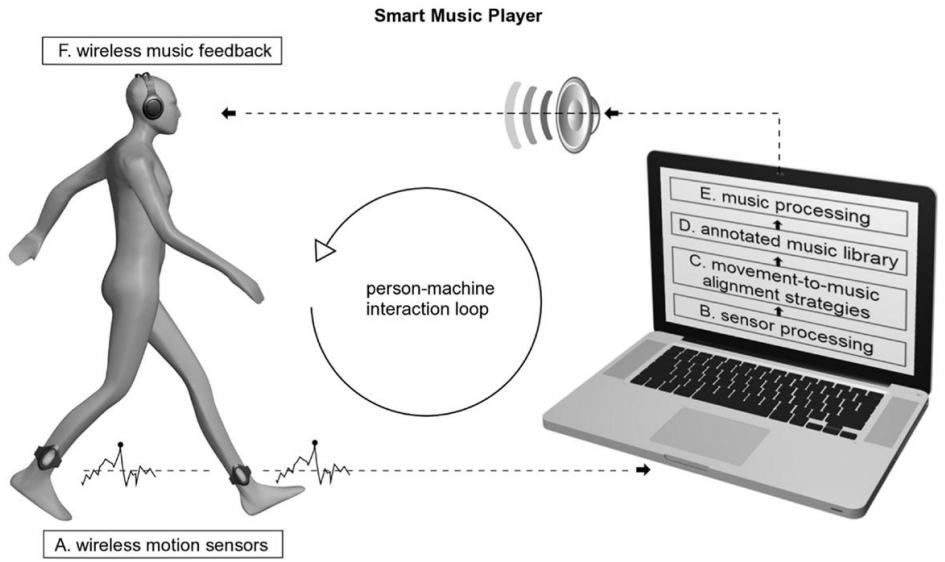
Acoustic therapies

Rhythmic auditory Stimulation

- Walk to the beat
- Music Therapy
- Singing helps too!



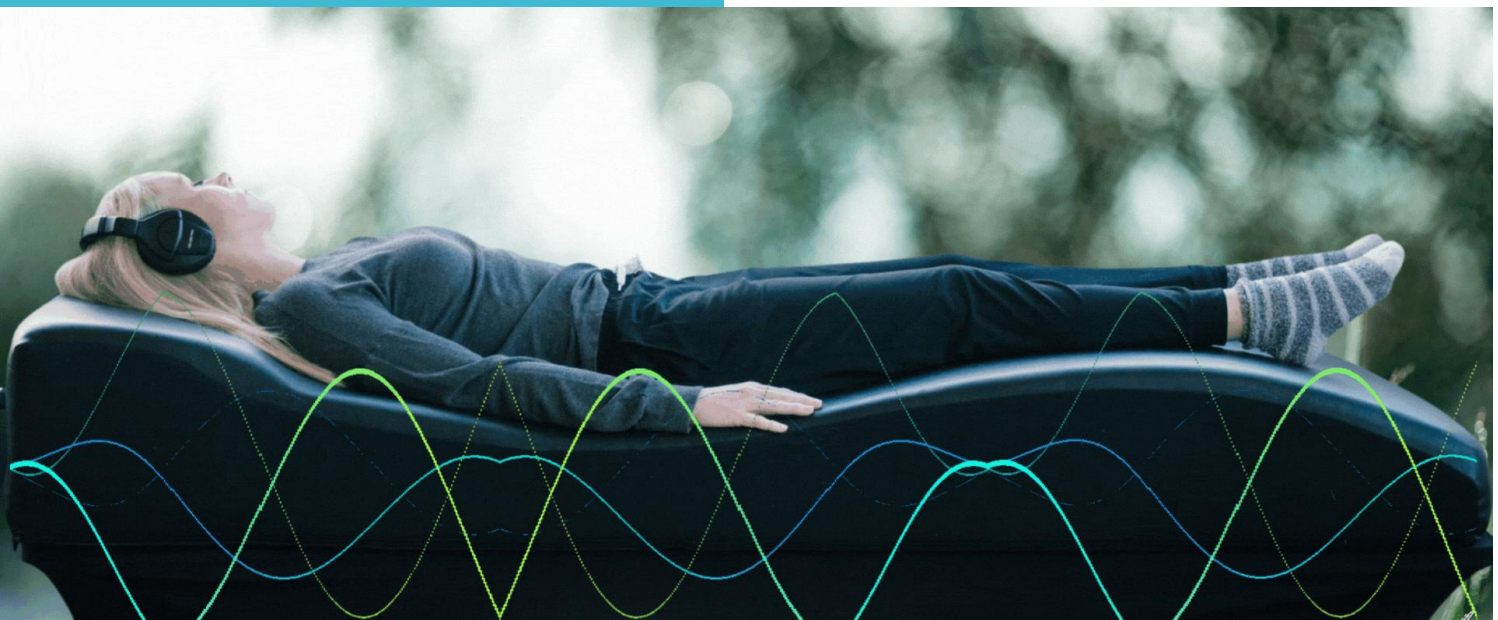




Vibroacoustic Therapy

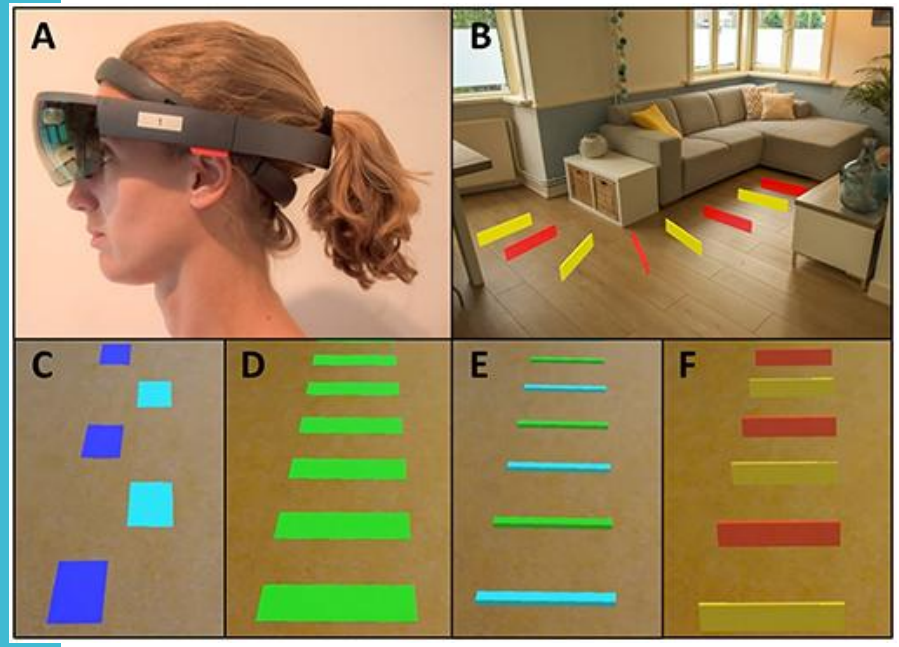
Subsonic vibrations

- May help tremors

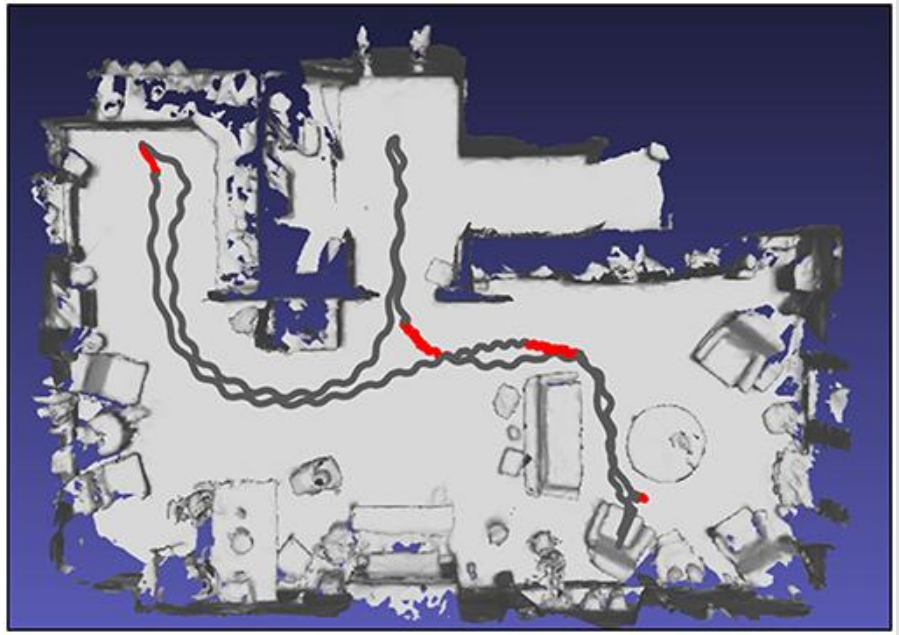


VR Visual cuing

Cuing steps



Mapping walking and freezing



With the display turned on, **56% of the patients improved either their walking speed**, or their stride length, or both, by over 20%. After device removal, and waiting for 15 minutes, the patients were instructed to walk again: 68% of the patients showed over 20% improvement in either walking speed or stride length or both. One week after participating in the first test, 36% of the patients showed over 20% improvement in baseline performance with respect to the previous test. Some of the **patients reported that they still walked on the tiles in their minds.**

Overview

Available

- L-dopa infusions
- L-dopa extended formats
- Apomorphine infusions

Future Directions

- Anti-Alphasynuclein immune therapy
- Anti-Alphasynuclein Genetic therapy
- Stem Cells
- Assistive devices

And one more for the road