

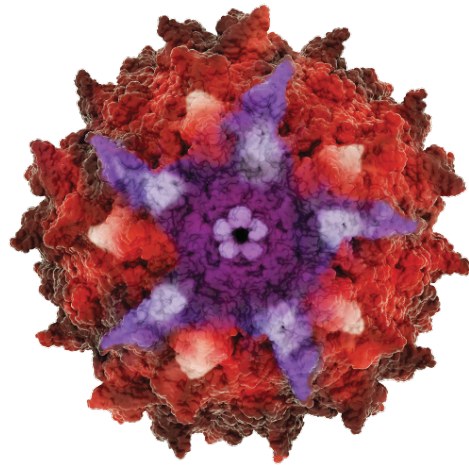


LIVING WELL

PARKINSON'S DISEASE CONFERENCE



Gene Therapy Approaches for Parkinson's Disease



AskBio™

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VP Clinical Development, CNS Gene Therapy

10 April 2022



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Topics for discussion

Who is AskBio?

What gene therapy *isn't*

What gene therapy *is*

Why gene therapy for PD?

How do you do gene therapy in the brain?

How to participate in clinical trials?

FIRST



to clone AAV for
therapeutic purposes



to deliver
AAV intrathecally



to treat DMD and
Pompe patients



to deliver AAV
to the brain

RICH, DIVERSIFIED DEVELOPMENT PIPELINE OF THERAPEUTICS

*Select programs
shown*



Pompe Disease, LGMD2i,



Congestive
Heart Failure



Huntington's, Parkinson's,
Multiple Systems Atrophy

BEST-IN-CLASS GENE THERAPY TOOLBOX



Tissue-specific
targeting (capsids)



Alternative delivery methods,
including crossing BBB



Precise cell targeting
(promoters)



Enhanced gene editing



Re-dosing / better
immunogenicity



Scaled, integrated manufacturing
(Pro10™ and plasmid alternative)

STATE-OF-THE-ART MANUFACTURING CAPABILITIES



3 facilities with
>350,000 sq ft capacity



Addresses internal manufacturing needs and
generates revenues through Viralgen CDMO

- **Asklepios BioPharmaceutical (AskBio)**, is a gene therapy company headquartered in Research Triangle Park, North Carolina, with research and development facilities in Columbus, Ohio; Edinburgh, Scotland; Paris, France; & San Sebastián, Spain.
- Founded in 2001 by **Jude Samulski**, a pioneer of gene therapy. Our clinical pipeline covers a broad range of genetic diseases targeting central nervous system, muscle, respiratory, and heart tissues.
- Our technology and **adeno-associated virus (AAV)** therapeutic assets have been acquired or licensed by leading biopharmaceutical companies such as Pfizer, Takeda, and Novartis.
- **AskBio is a leader in next-generation AAV gene therapy** and a pioneer in almost every element of design, application and manufacturing of AAV therapeutics and technology.
- *The gene therapies addressed in this presentation are currently investigational in nature and have not been approved by FDA or other regulatory authorities*

AskBio Is an Independent Subsidiary of Bayer AG



To meet our ambitious goals, AskBio was acquired by Bayer in December 2020 as a cornerstone of its newly formed Cell & Gene Therapy Unit within Bayer Pharmaceuticals



Bayer is strongly committed to leading the field of cell and gene therapies, an area that represents the next wave of medical innovation and **an attractive growth opportunity**



To retain our entrepreneurial culture and encourage innovation, we operate on an arm's length basis as **an independent subsidiary**

Significant Benefits to AskBio

Access to:

Financial resources | Experienced clinical translation expertise | Pricing and reimbursement know-how
Worldwide commercialization channels

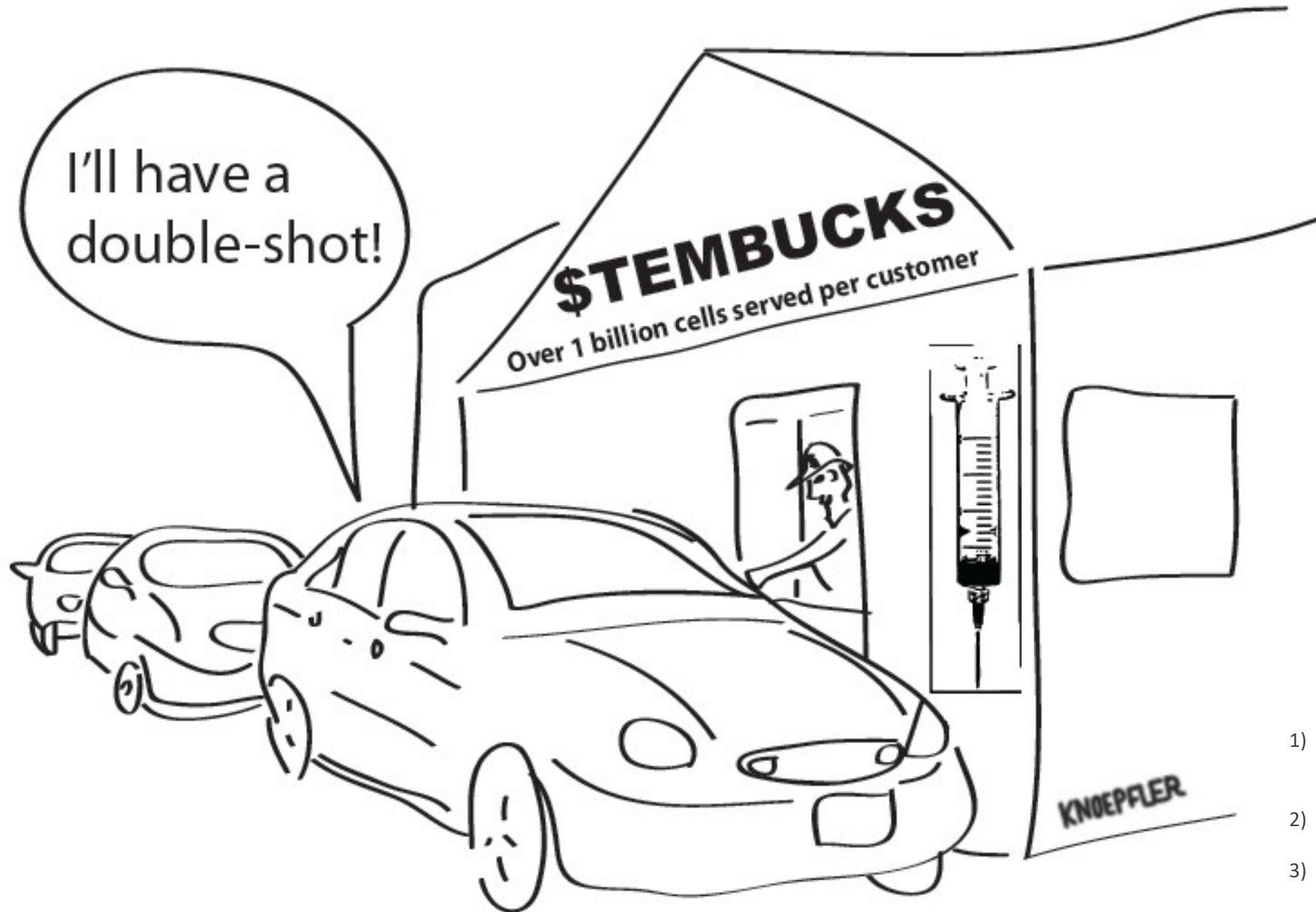
Continue to focus on discovery and development of genetic medicines

Have a greater impact on patient's lives than we would as AskBio alone

What *isn't* gene therapy?
What *is* gene therapy?



What our gene therapy Is NOT...



- 1) <https://www.timetoast.com/timelines/cloning-and-biotechnology-b15d9f4a-366b-4be0-a9cc-6816b3582e5d>
- 2) <https://upfront.scholastic.com/issues/2018-19/051319/designer-babies.html#1270L>
- 3) <https://ipscell.com/wp-content/uploads/2012/12/Stembucks.jpg>

Gene therapy 101

- Genes are the **instructions** for growth and health of our cells
 - Genes = DNA = blueprint
- Cells read genes (or “instructions”) to make new **proteins**
 - Proteins are used by cells to signal health of a cell and many other functions to keep the cell alive
- Gene therapy harnesses this natural function of cells to make a protein that acts as the medication



Genes and Gene Therapy

- Genes are the **instructions** for growth and health of our cells
- Gene therapy has potential benefit in several diseases:
 - 1) **Correct** abnormal/mutated gene = **RESTORE** function
 - 2) **Inhibit** or turn off “bad” genes = **INACTIVATE** function
 - 3) **Add** genes to enhance function = **MODIFY** function

A 3D white figure is shown from the back, running towards the right. The figure is carrying a blue bag over its left shoulder and holding a large yellow envelope in its right hand. The background is a solid dark gray.

How do you deliver genes to
brain cells?

What *is* Gene Therapy?

- Gene therapy uses a copy of **DNA (gene)** as a new way to treat diseases
- The healthy gene is packaged for delivery in an **empty “viral vector”** that helps the healthy gene enter cells impacted by disease
- Adeno-associated virus or **AAV**, is the vector used by AskBio and many others
 - AAV is modified and does not cause infection

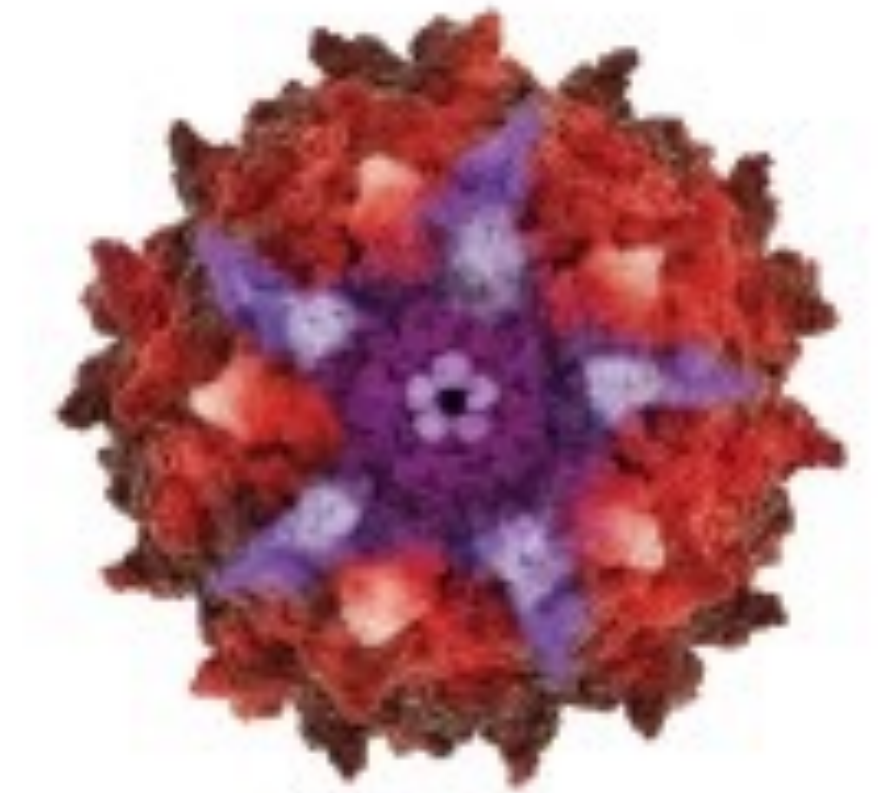


What is AAV?

- Adeno-associated viral vector
 - Envelope or packaging for genes
 - AAV₂ most common for brain



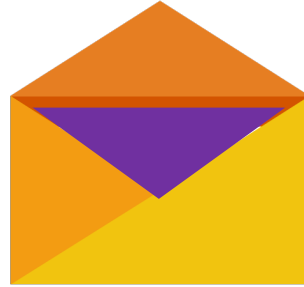
- **Effective** for passing genes into brain cells
- **Safely** used in many neurological gene therapy trials
- **Durable** effect in the brain



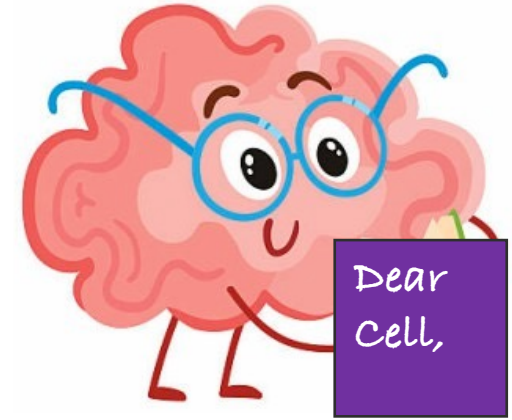
AskBio

Dear Cell,
Please read
this DNA
(Gene).
Thank you,
Management

+



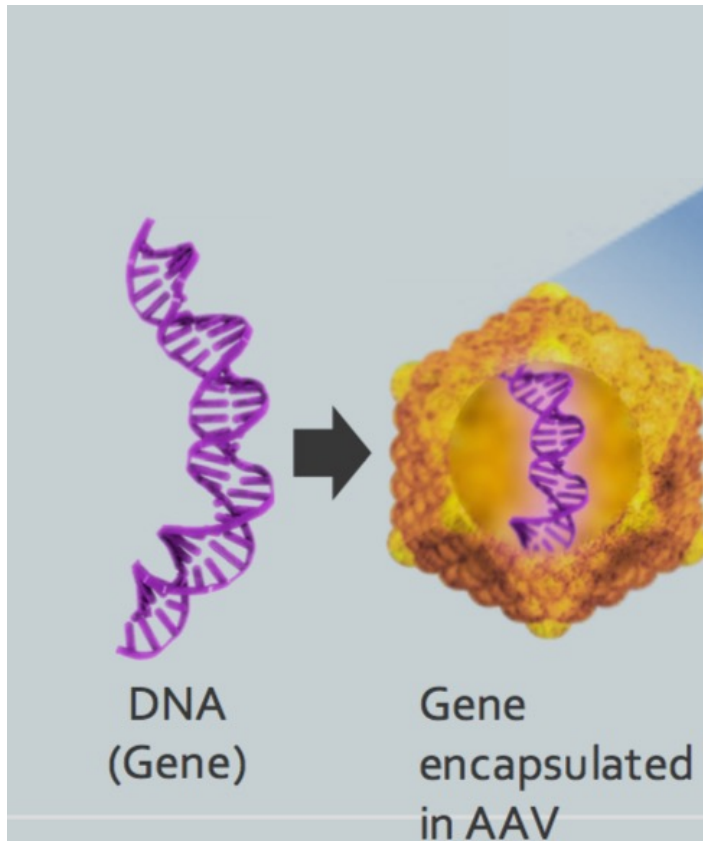
Surgery=
Mail truck

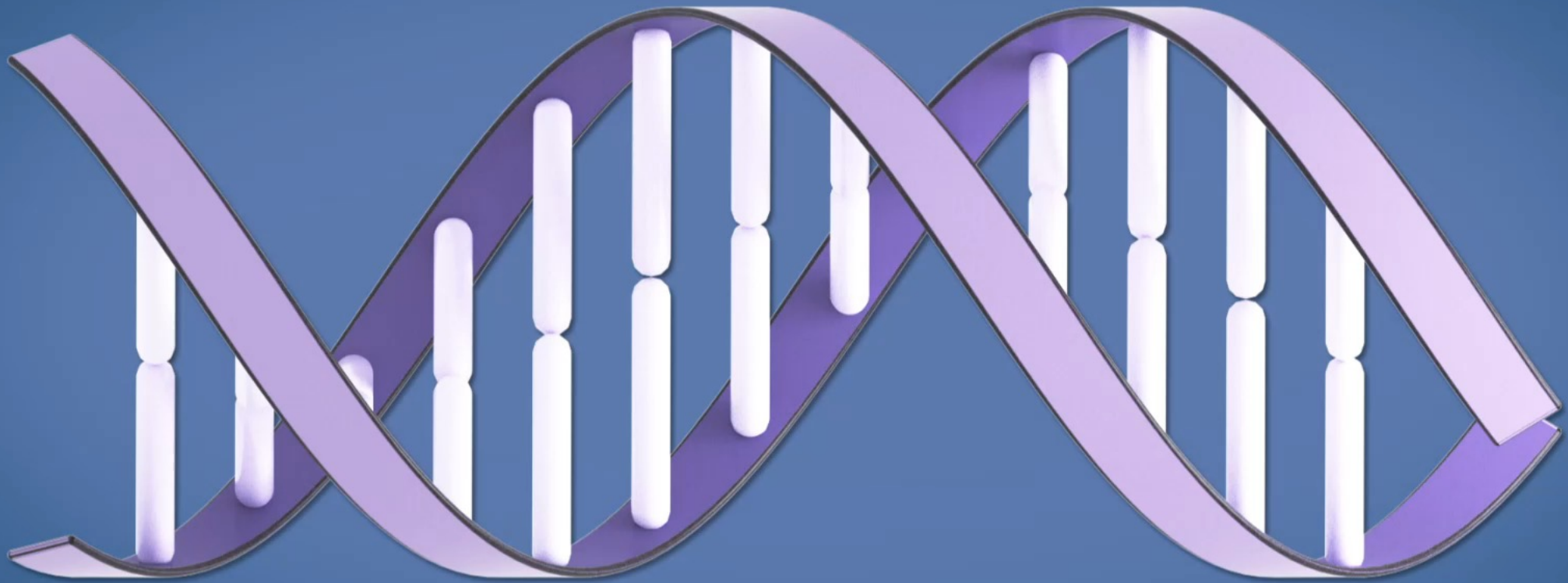


Brain cells = **Reader**

DNA (Gene) = **Letter**

Vector = **Envelope**





Gene

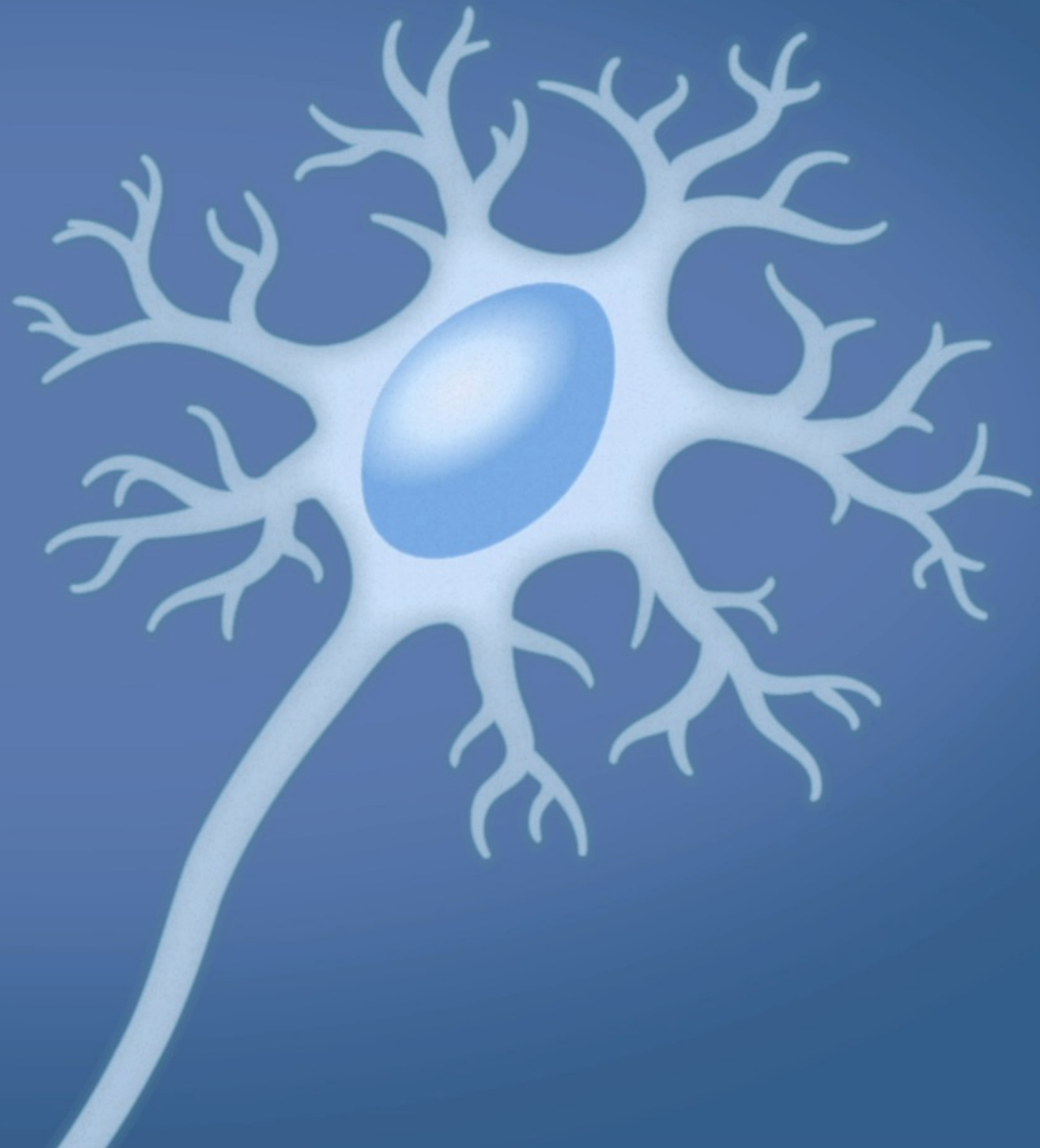
AAV Vector
“Package”





GDNF

(Glial Cell Line-Derived Neurotrophic Factor)



Why gene therapy for PD?


Gene therapy is NOT just for “genetic” diseases

- One-time treatment that is expected to be long-lasting
- Gene therapy for PD has focused primarily on:
 - A. Increasing dopamine levels
 - B. Slowing disease progression




PD Gene Therapy Trials

As of March 2022, there are 2 gene therapy studies recruiting for PD:

- **1) AAV-GBA** 

Correct mutation

- Only recruiting for known GBA1 mutation and PD
 - Infuse into spinal fluid
 - Immune suppression
- **2) AAV-GDNF** 

Neurorestoration

- Not recruiting advanced PD
 - Infuse directly into the brain

*Note: No currently active gene therapy studies to enhance dopamine levels

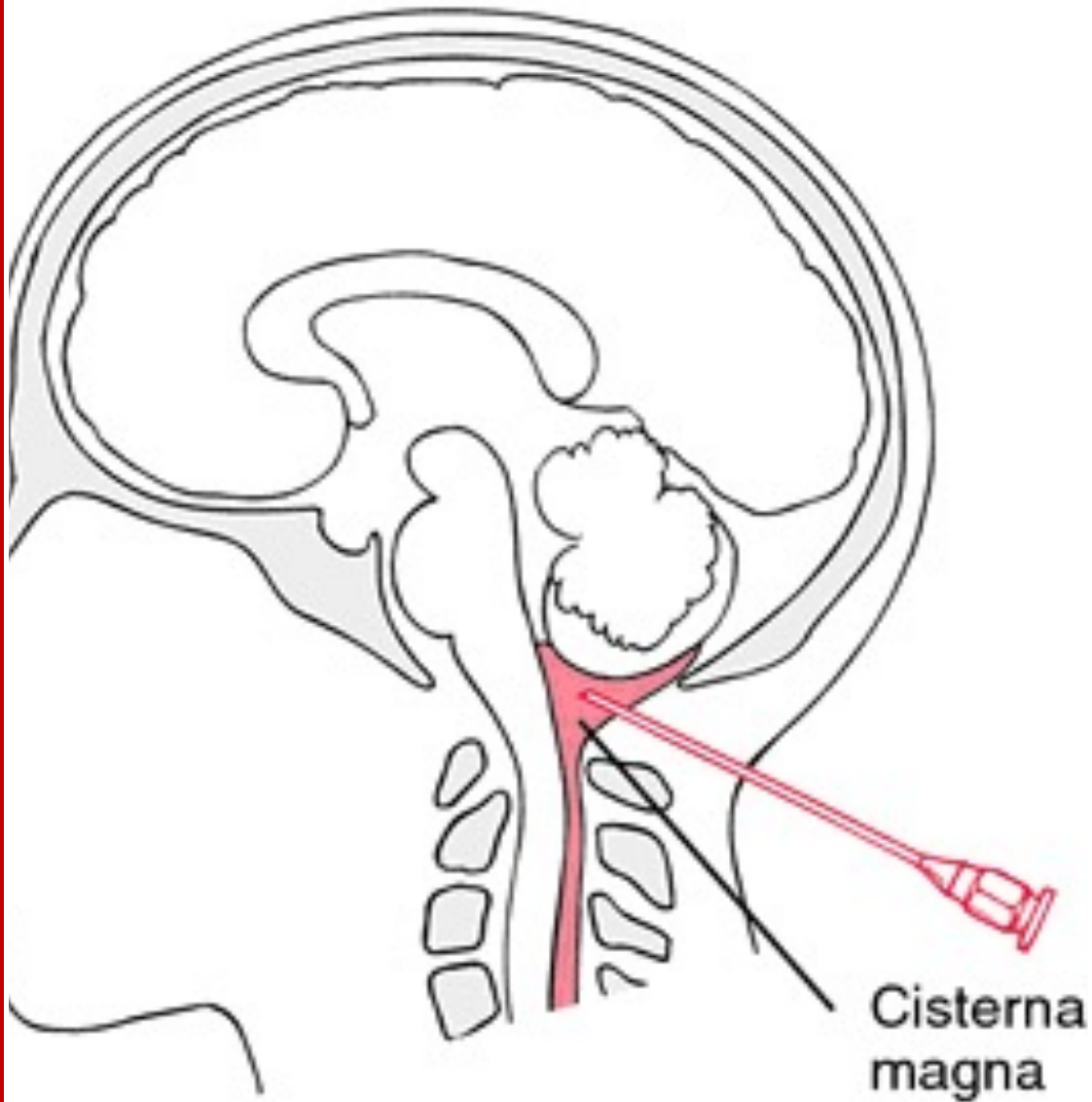
AAV9-GBA1

Short title: PROPEL

Sponsor: Prevail Therapeutics

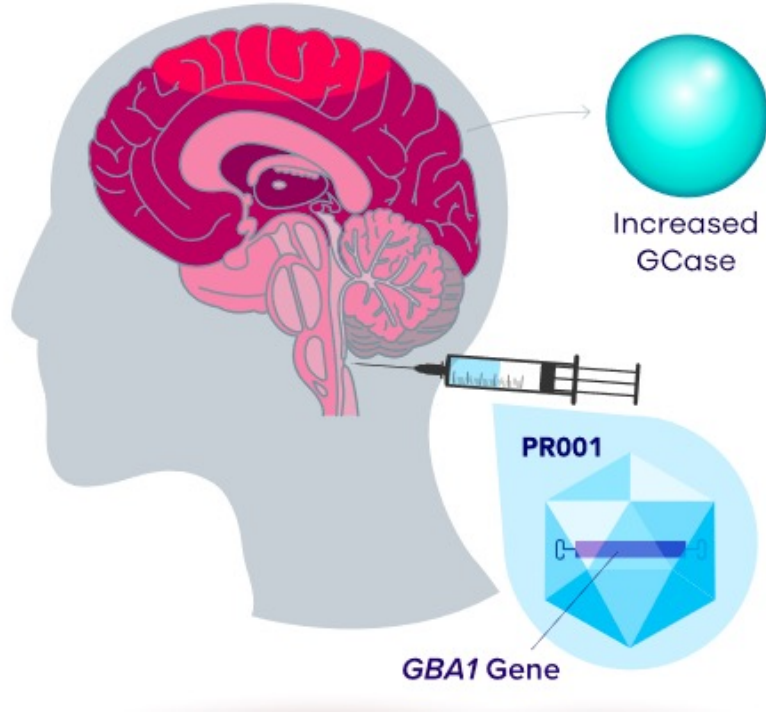
Trial status: Phase 1/2a, Now recruiting (US and Israel)

Who?: 12 PD participants with known GBA1 mutation



Parkinson's Disease

WITH GBA1 MUTATION



Substrate Decreases
(GluCer, GluSph)

Product Increases

Secondary Lipids
Normalize

Neurodegeneration
Slowed or Stopped

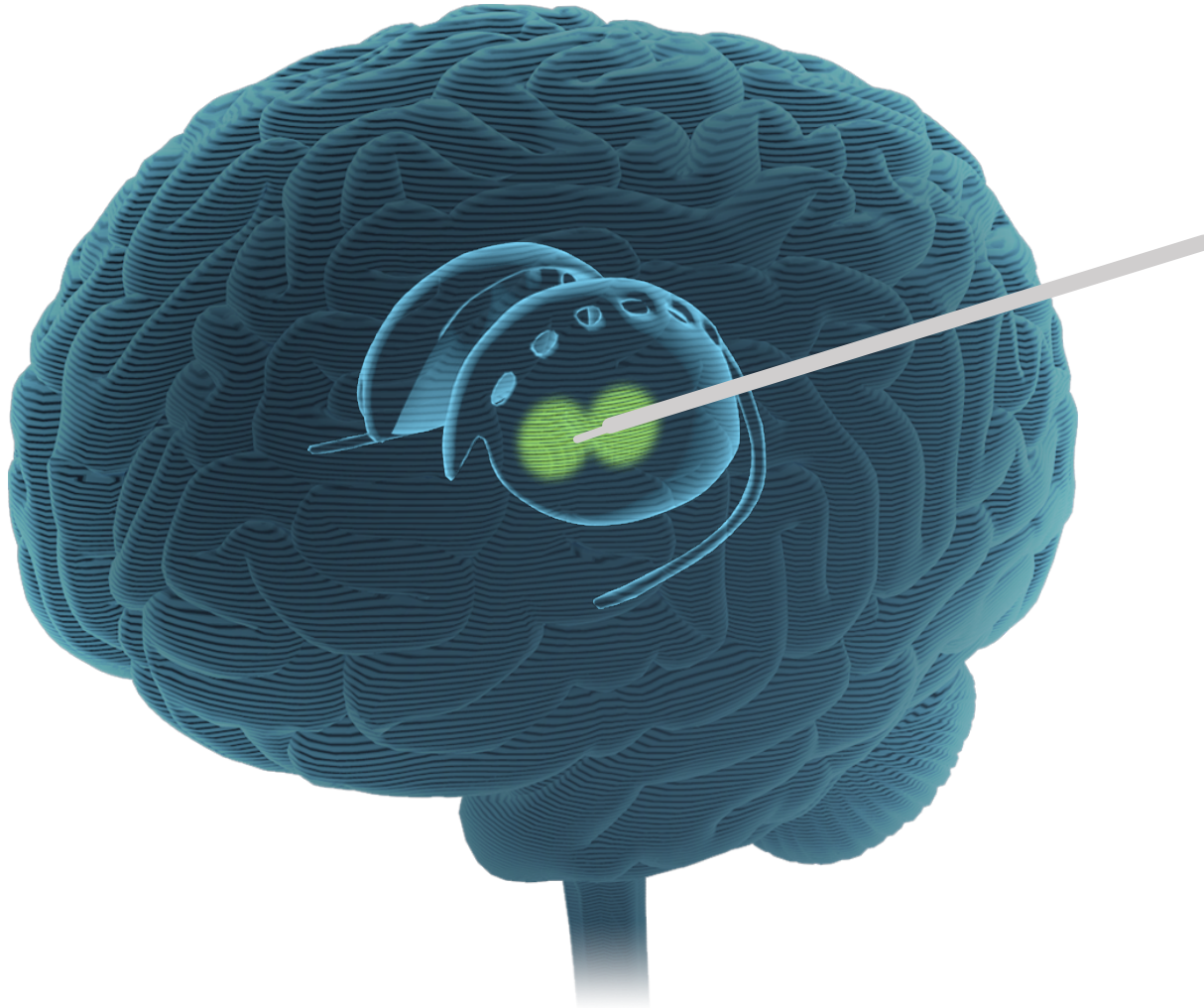
Inflammation
Reduced

Protein Aggregation
Reduced

PR001
Treated

- GCase needed for proper disposal and recycling in cells
- AAV9-GBA1 provides a healthy copy of GBA1 that can increase GCase levels

Putamen



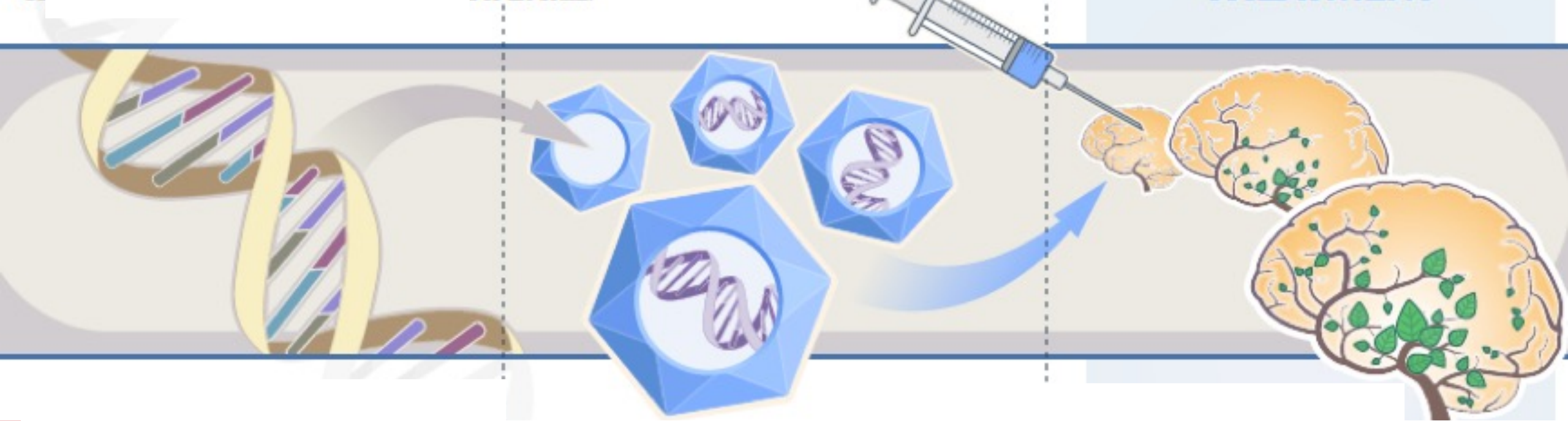
AAV₂-GDNF

Short title: GDNF-102

Sponsor: AskBio & Brain
Neurotherapy Bio

Trial status: Phase 1b ongoing,
near completion (US only)

Who?: 12 PD participants with
mild to moderate symptoms



AAV₂-GDNF

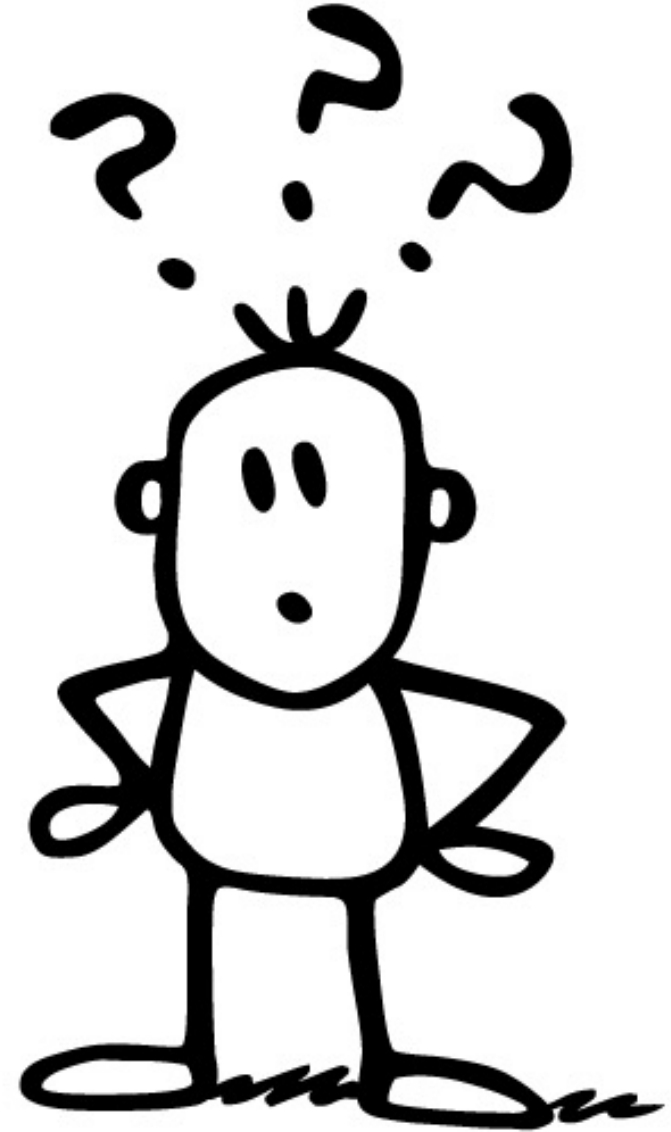
- GDNF is a growth factor that promotes healthy function of dopamine cells
- High levels in youth, lessens with age.... BUT still needed in adult brains
- Hope to demonstrate that a growth factor like GDNF will alter the course of PD, not just treat symptoms

AskBio's GDNF Program for PD

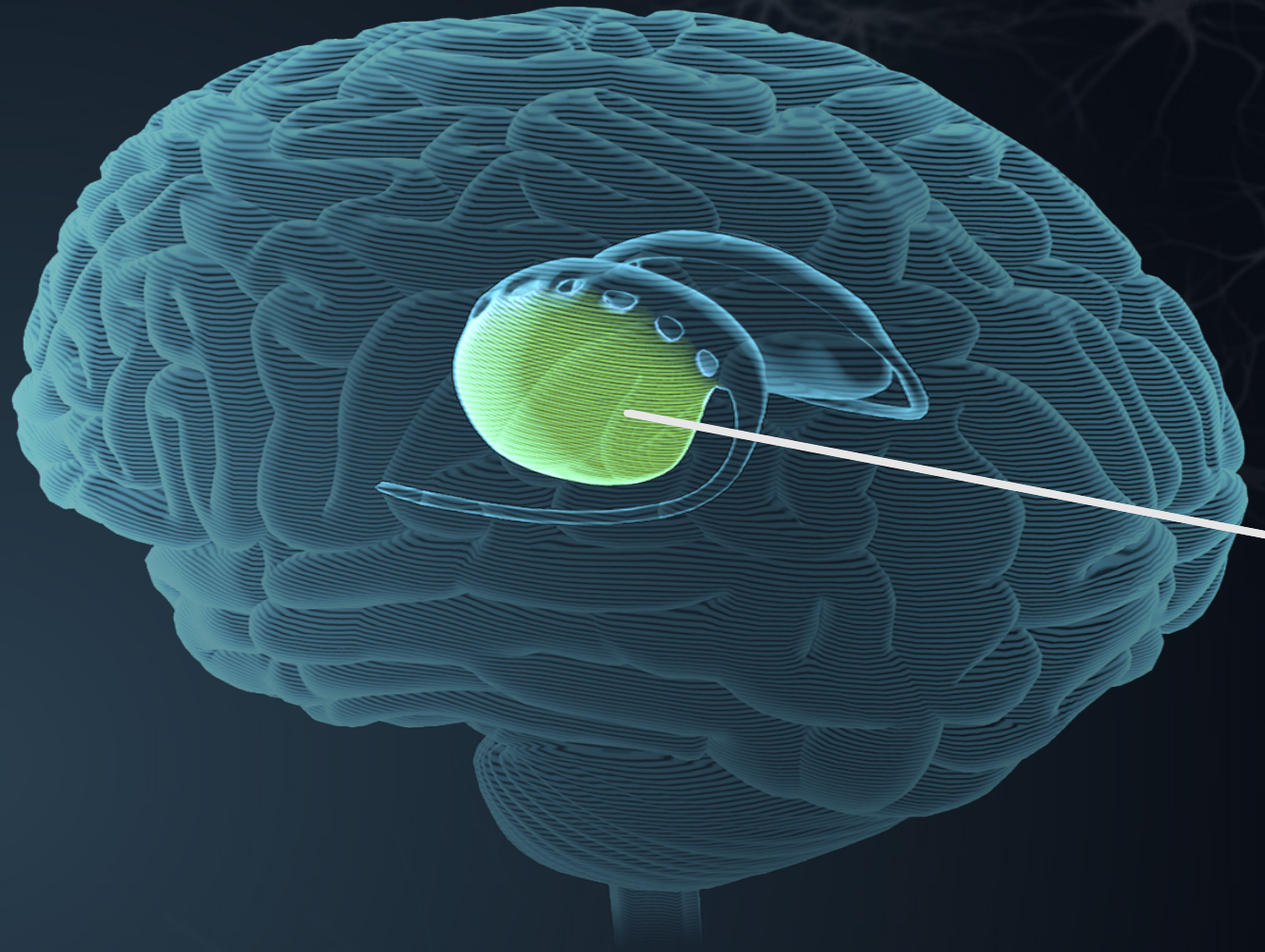
- Loss of GDNF may be a contributing factor in PD progression
- Investigational GDNF gene therapy may help remaining healthy cells not affected by PD to make GDNF
- If more GDNF is available to **restore the health of sick or dying brain cells**
 - This opens the possibility to change the course of PD and improve symptoms



But... How do you
DO gene therapy in
the brain??

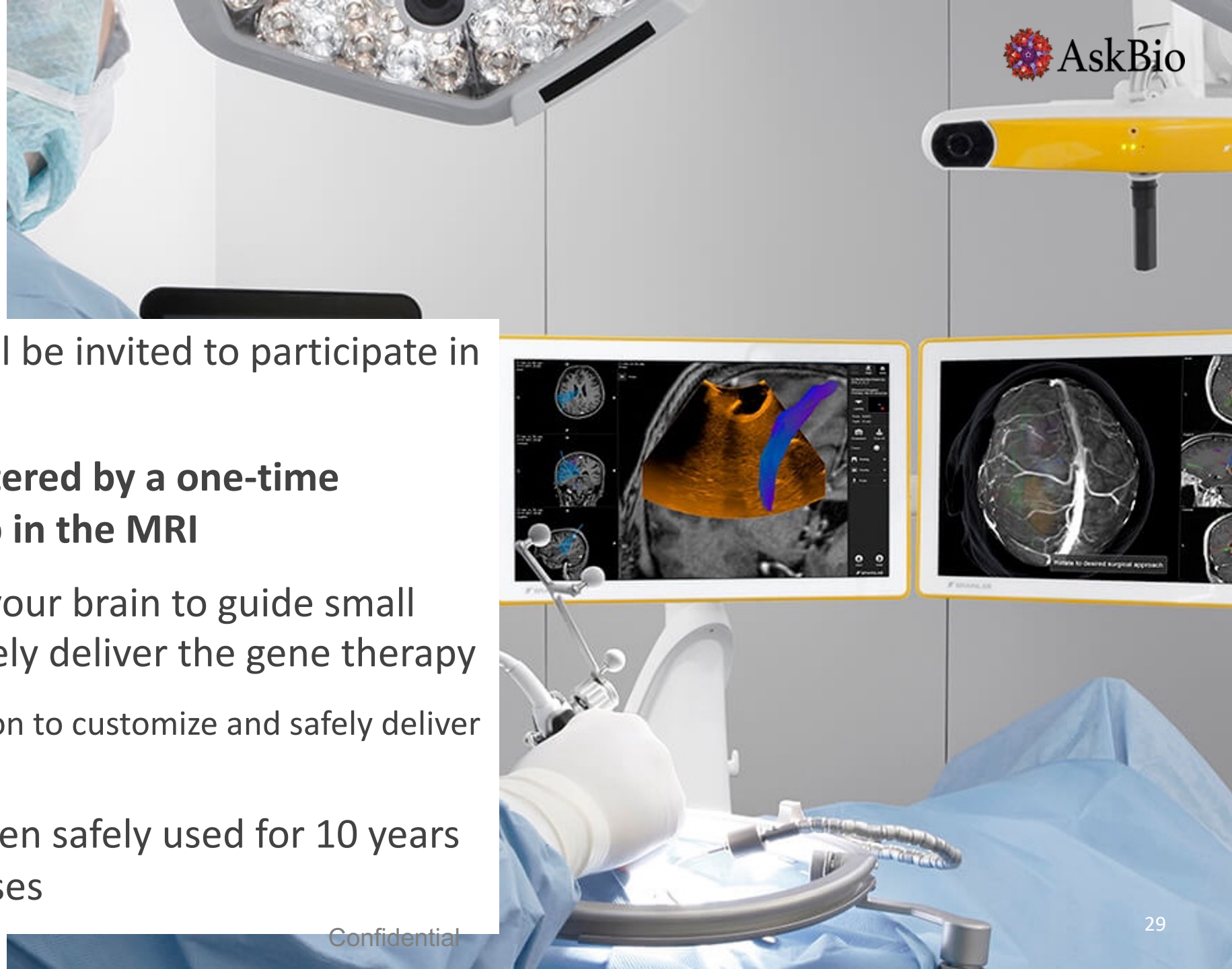


MRI- Monitored Gene Therapy Delivery

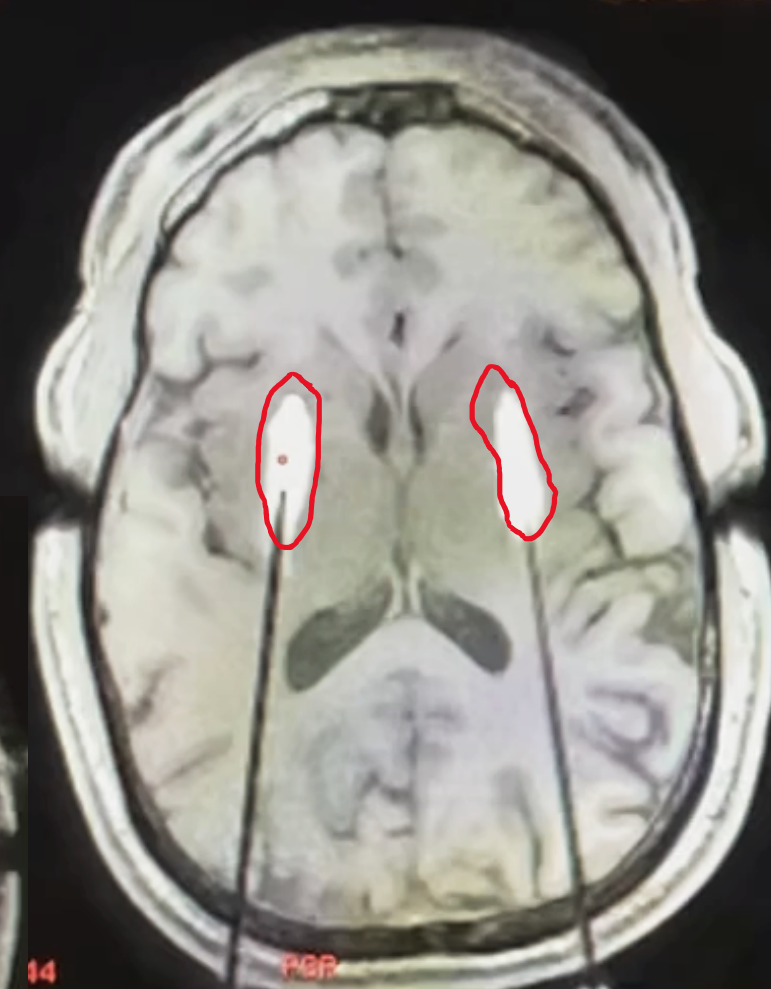


MRI-Monitored Brain Delivery

- Patients who qualify will be invited to participate in the AAV2-GDNF study
- **AAV2-GDNF is administered by a one-time procedure while asleep in the MRI**
- Using MRI imaging of your brain to guide small hollow tubes to precisely deliver the gene therapy
 - MRI allows the surgeon to customize and safely deliver AAV2-GDNF
- This technique has been safely used for 10 years in various brain diseases

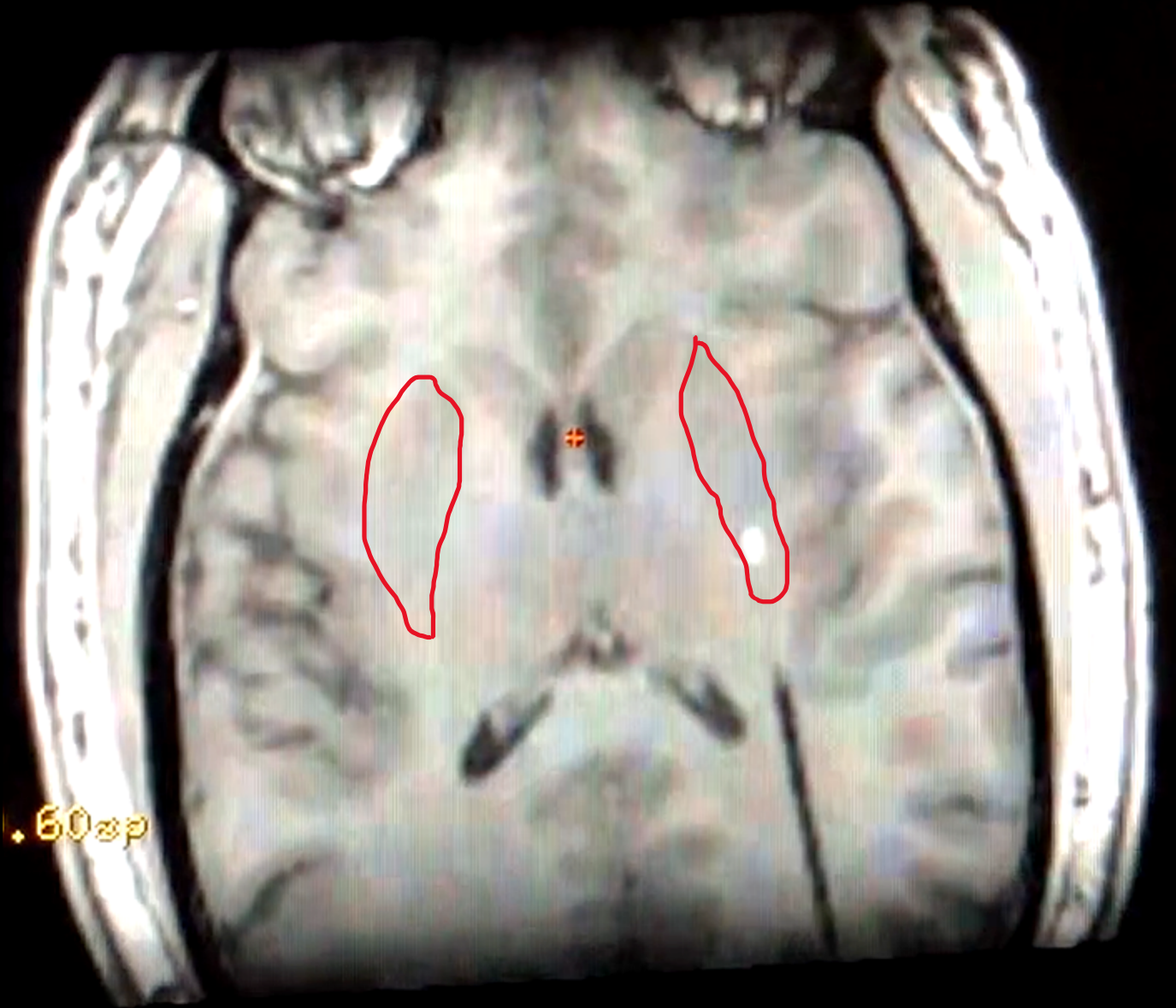


Slow, MRI-monitored infusion of gene therapy to precise brain areas



Current technique for direct gene delivery

- Single infusion in each putamen
 - “Shape Fitting”
- Reduced infusion time
- Cover >50% of each putamen



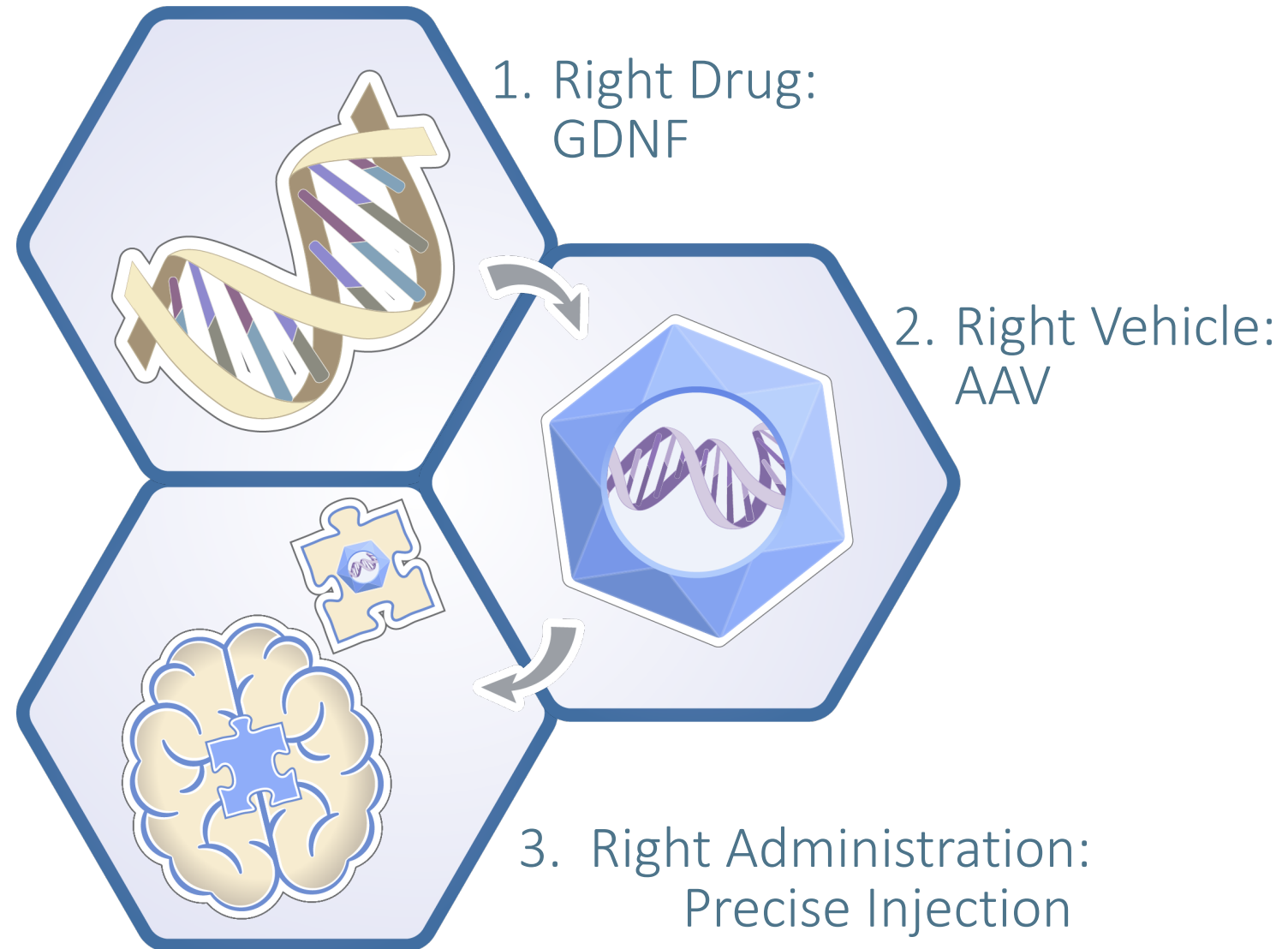
1. Rosenbluth et al., 2013, PLOS One
2. Sudhakar et al., 2020, JNS
3. Heiss et al., 2019, MDS
4. Christine et al., 2019, Ann Neurol
5. Richardson et al., 2020, JNNP

Why does tailored AAV2-GDNF delivery matter?



Gene Therapy: Convergence of three technologies

- Better delivery is needed to get the “right dose”
- Hope that this will result in better outcomes for patients with PD



Pre-Gene Therapy Natural History Study



PD/MSA Natural History Study

- **Includes both PD and early MSA**
 - MSA and PD can look identical at early stages
 - Potential to enroll into upcoming GDNF Gene Therapy study

WHO?

- Target PD study population:
 - **Early to Moderate PD:** 1-6 years from diagnosis
 - At least 6 months of levodopa therapy

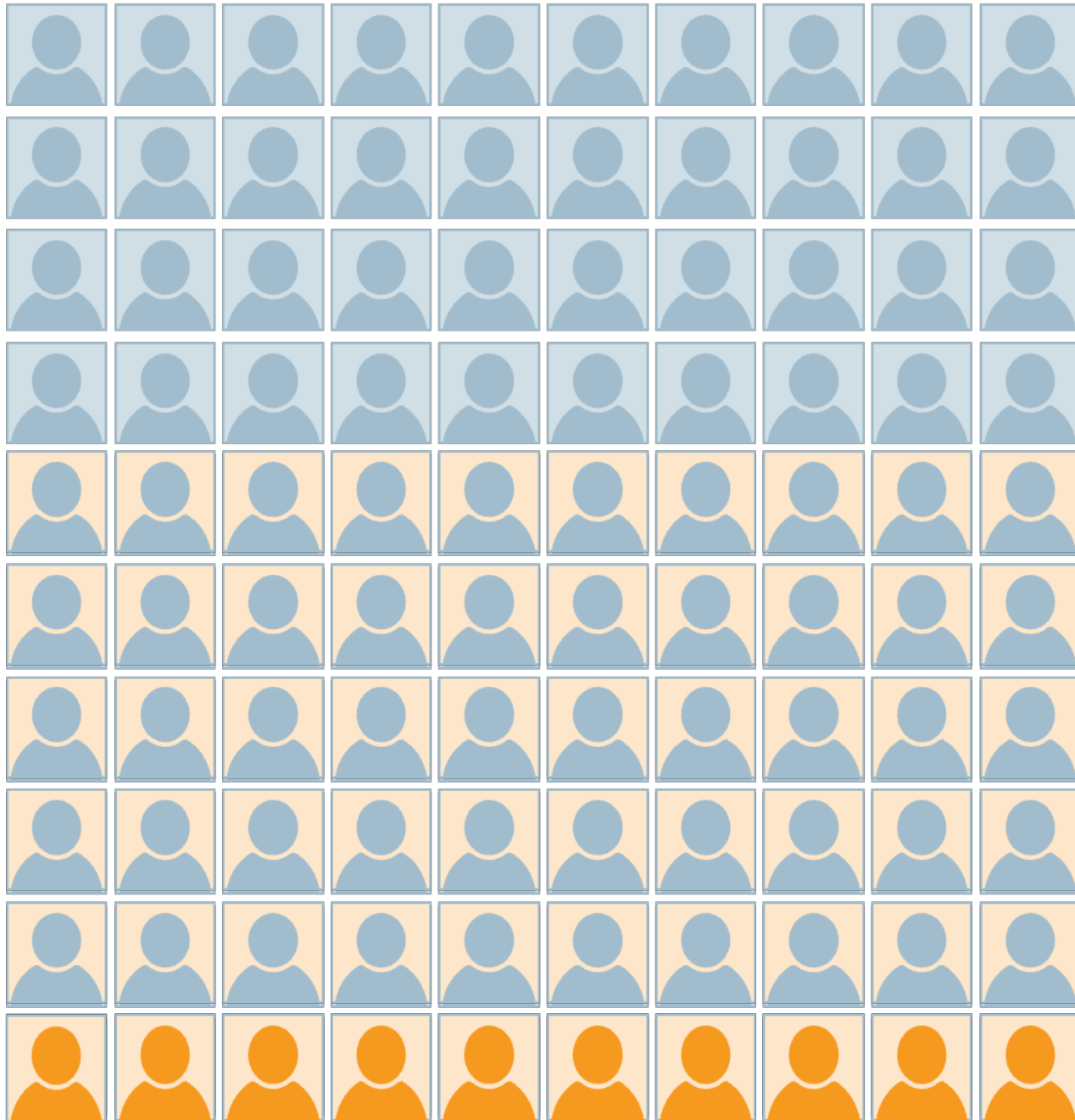
WHAT?

- Monitor changes over time of exams and other assessments
 - PD-specific clinical assessments and questionnaires
 - MRI brain
 - Blood and CSF biomarkers



Join the fight.....

Consider participating in a clinical trial!



Though **60%** of people with Parkinson's say they would be willing to participate in a trial

Only **10%** of patients with PD will sign up for clinical trials

How to learn more



www.clinicaltrials.gov

How to learn more



www.foxtrialfinder.michaeljfox.org

For more information:



- Talk to your neurologist
- Find us here at the Expo!



Tricia Kovacs

Assoc. Director, Clinical Operations

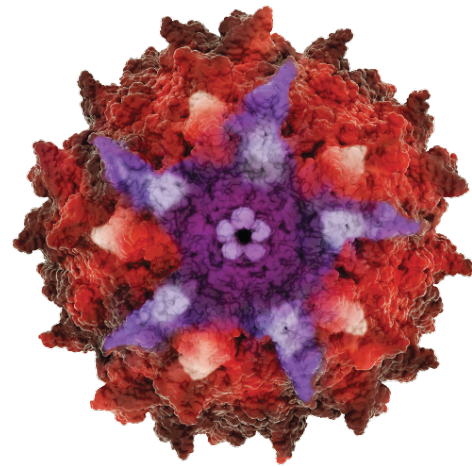


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