Perspectives thérapeutiques?

Traitements neuroprotecteurs

Médecine personnalisée?

REVIEW

Targeted Therapies for Parkinson's Disease: From Genetics to the Clinic

S. Pablo Sardi, PharmD, PhD,[1*] Jesse M. Cedarbaum, MD,[2] and Patrik Brundin, MD, PhD[3]

Review

Progress towards therapies for disease modification in Parkinson's disease

Nirosen Vijiaratnam, Tanya Simuni, Oliver Bandmann, Huw R Morris, Thomas Foltynie

The development of interventions to slow or halt the progression of Parkinson's disease remains a priority for patients and researchers alike. To date, no agents have been shown to have unequivocal evidence of disease-modifying effects in Parkinson's disease. The absence of disease-modifying treatments might relate not only to inadequate approaches for the selection of therapeutic candidates but also to insufficient attention to detail in clinical trial design. Better understanding of Parkinson's disease pathogenesis associated with advances in laboratory models, the use of objective biomarkers of disease progression and target engagement, and a focus on agents known to be safe for human use, alongside the use of precision medicine approaches, should together greatly increase the likelihood for successful identification of disease-modifying treatments for Parkinson's disease.

Lancet Neurol 2021; 20: 559–72

Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK (N Vijiaratnam FRACP, Prof H R Morris PhD, Prof T Foltynie PhD); The National Hospital for Neurology and Neurosurgery,

Nombreux échecs antérieurs:

- Effet symptomatique/neuromodulateur
- Passage de la BHE
- Une ou plusieurs maladies de Parkinson?

cibles du traitement

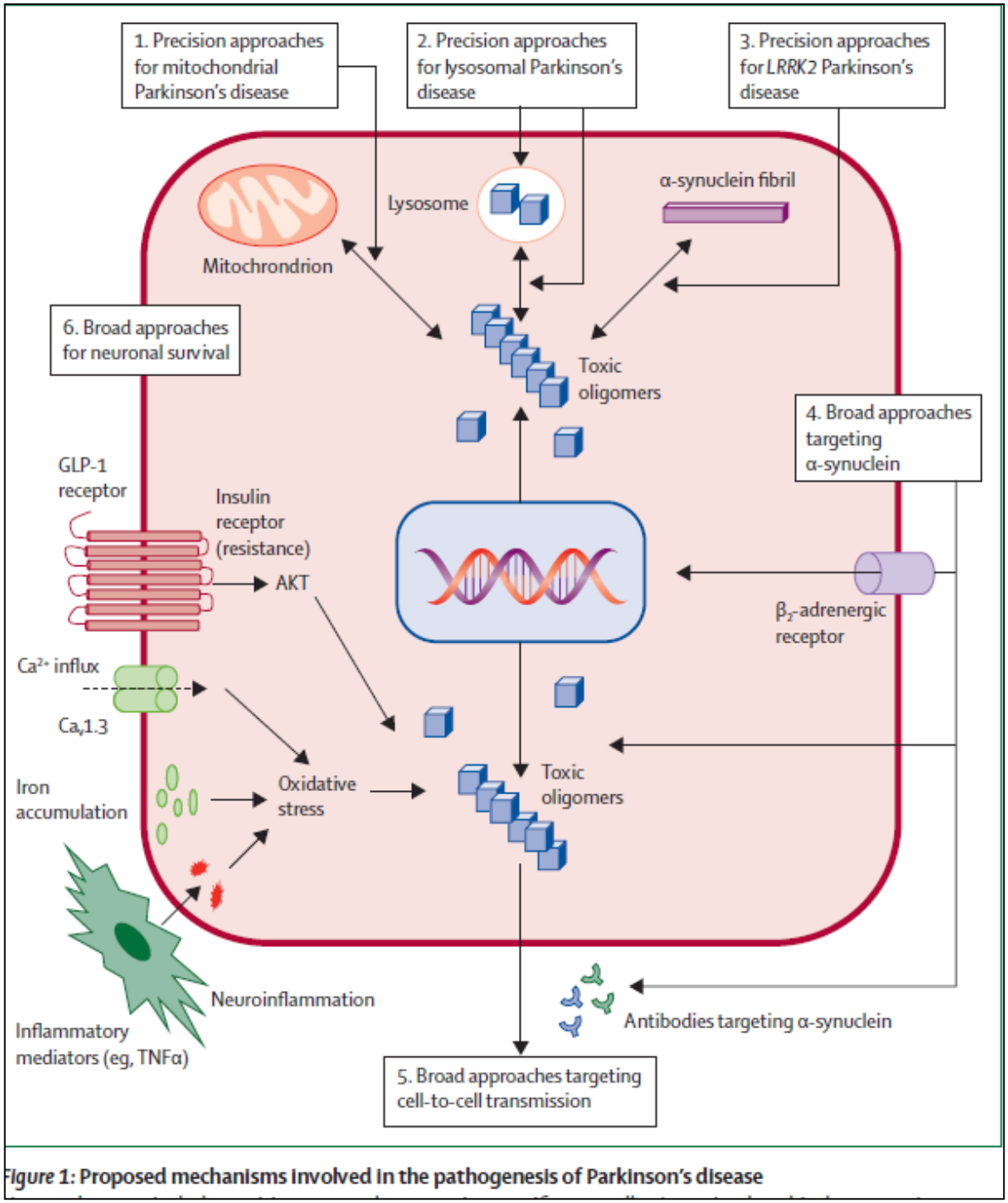


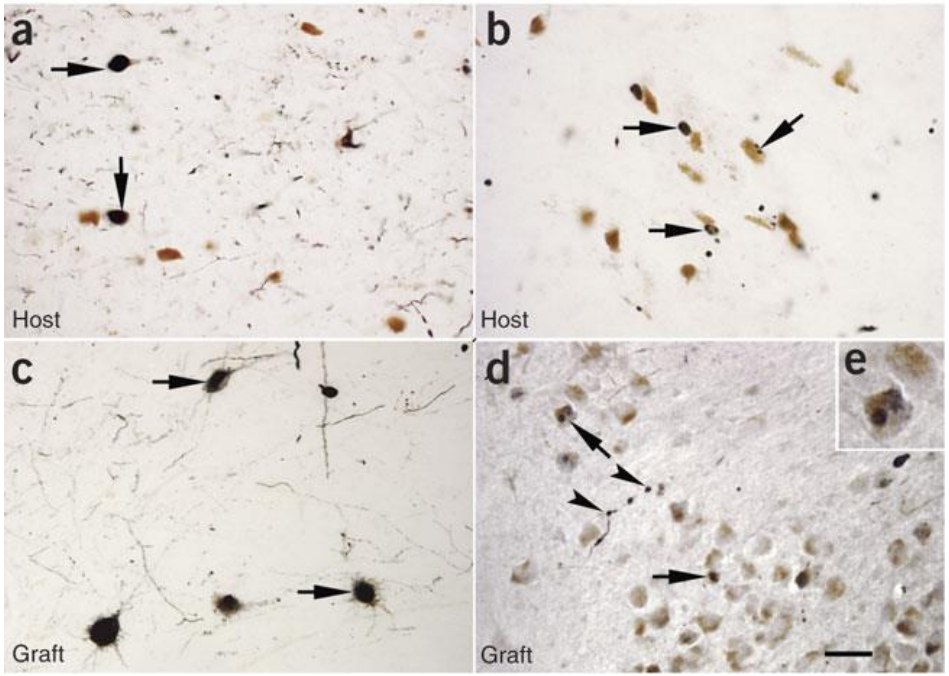
Figure 1: Proposed mechanisms involved in the pathogenesis of Parkinson's disease

Lancet Neurol 2021; 20: 559–72

Is parkinson's disease a prion disorder?

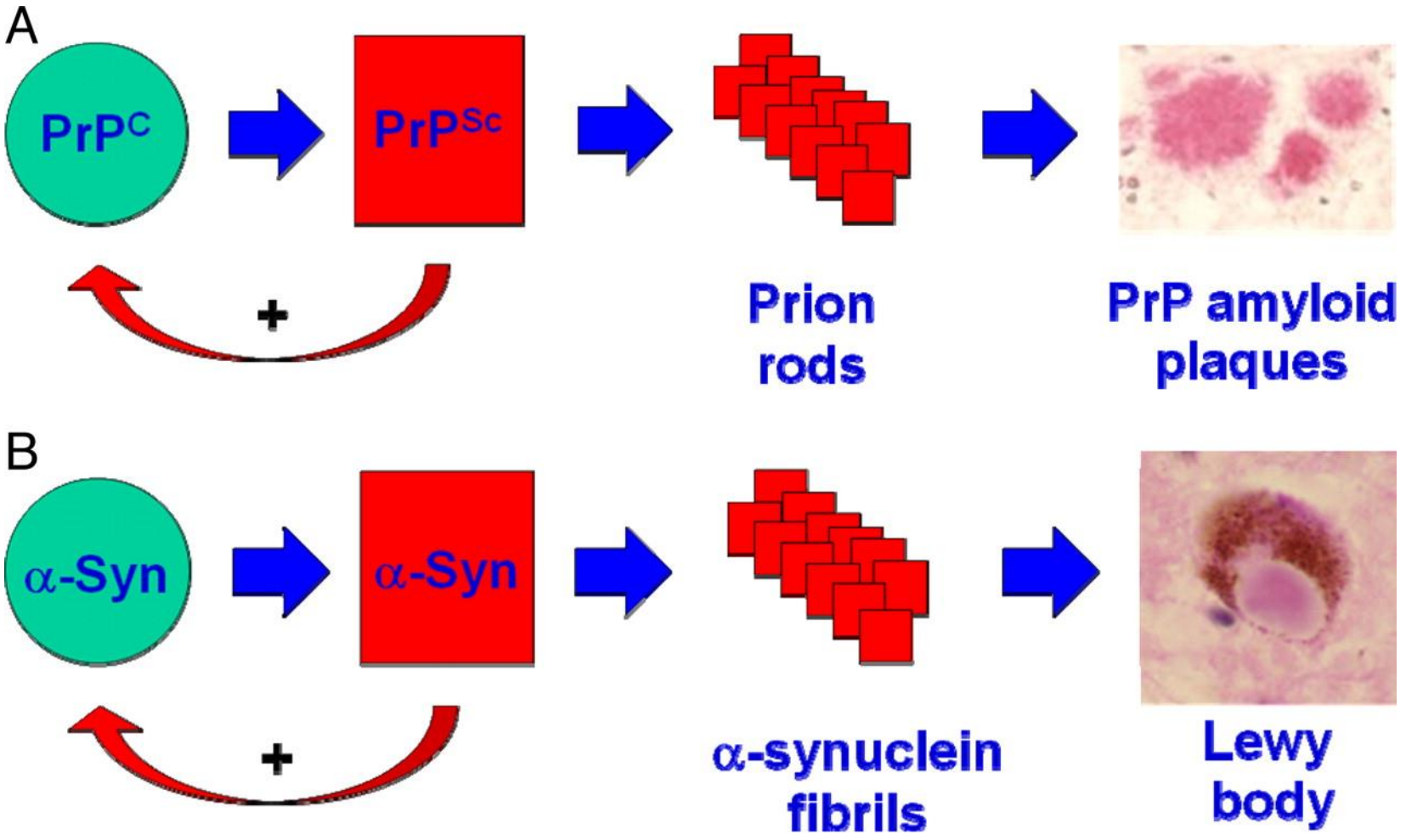
Olanow et prusiner, PNAS 2009

Présence d'inclusions de type « corps de lewy » marquées par l'alpha synucléine dans les neurones greffés 14 ans plus tôt à un patient atteint de maladie de Parkinson



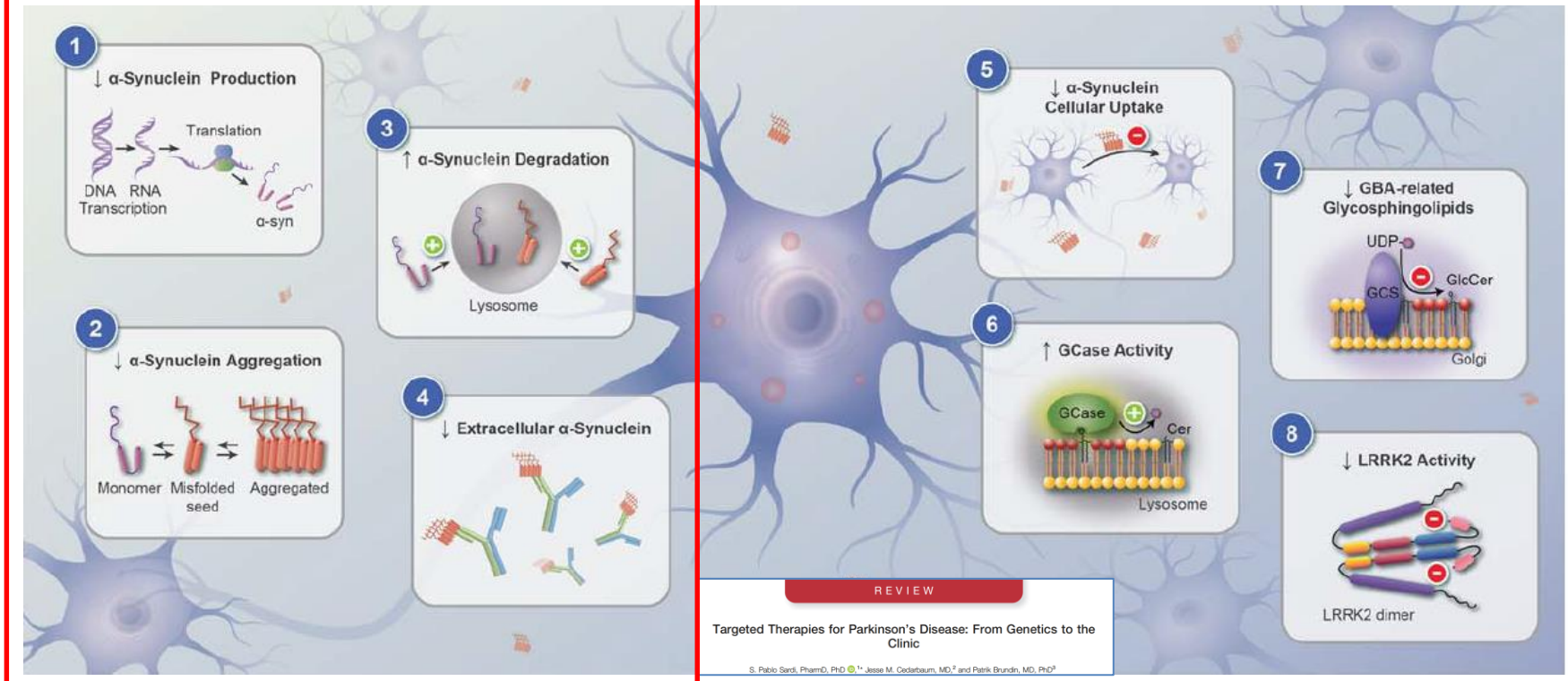
Khordower et al, 2008

Schematic illustration demonstrating similarities in the relationships between the PrPC protein and prion diseases, and the α-synuclein protein and Parkinson's disease



Olanow C W, Prusiner S B PNAS 2009;106:12571-12572

Action sur l'alpha synucléine



Diminution agrégation de l'alpha synucléine
Anticorps anti alpha synucléine
Diminution production alpha synucléine (oligonucléotides anti sens)
Diminution expression gène SCNA

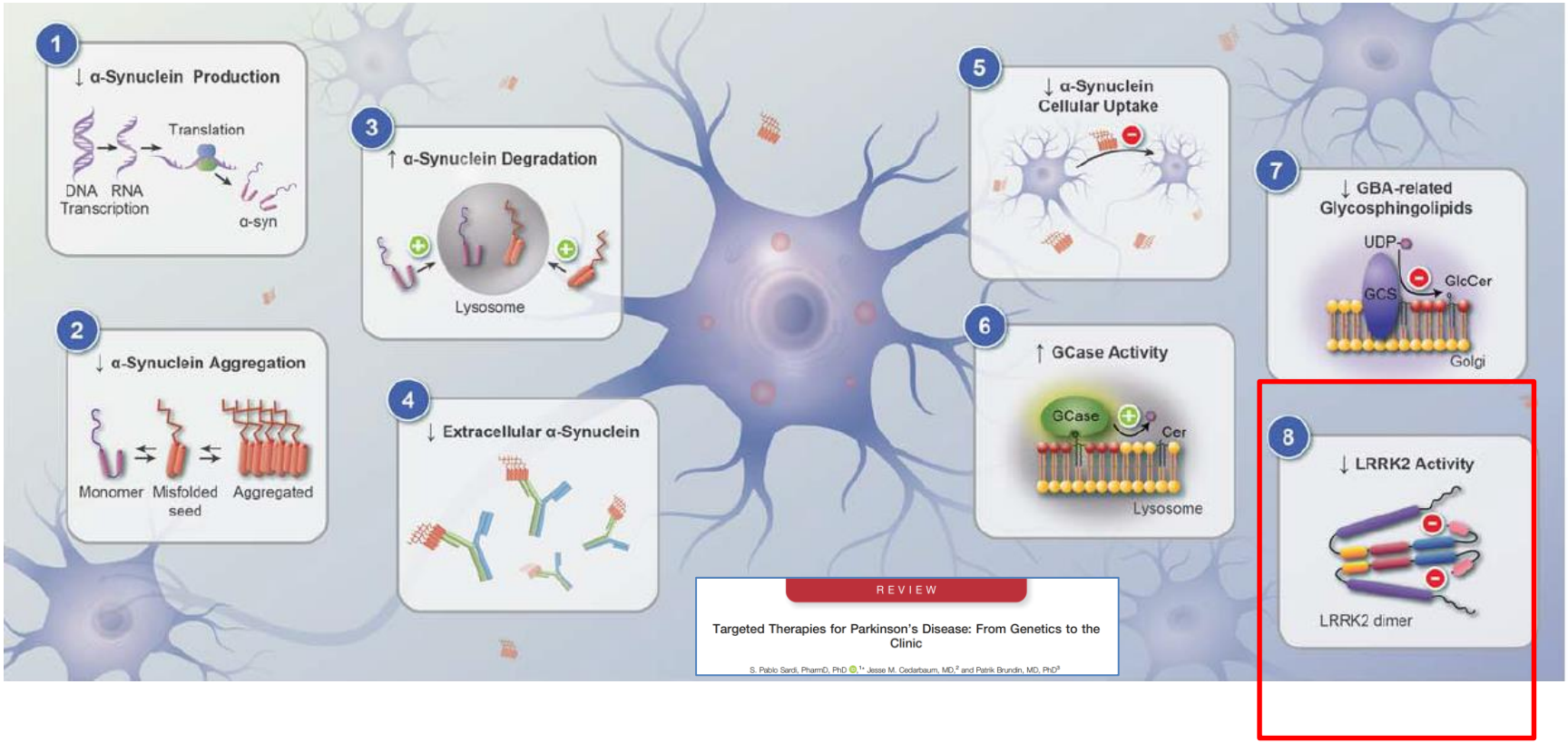
	Efficacy in preclinical models	Evidence supporting target engagement in patients	Recruitment selection strategy or primary outcomes	Status
α-Synuclein*				
Inhibition of α-synuclein aggregation (stabilising small molecule blockers)				
anle138b	Efficacy in α-synuclein transgenic mice	NA	NA; safety and tolerability	Ongoing phase 1 trial (NCT04208152)
NPT200-11	Efficacy in α-synuclein transgenic mice	NA	NA; safety and tolerability	Phase 1 trial completed (NCT02606682)
Squalamine	Efficacy in cell lines, *Caenorhabditis elegans*	Does not access CNS	NA	No longer being considered for Parkinson's disease disease modification
Inhibition of α-synuclein aggregation (autophagy-ABL1 inhibitors)				
Nilotinib	Efficacy in α-synuclein transgenic mice	Amounts of α-synuclein; dopamine metabolites in CSF; nilotinib concentrations and dopamine metabolites in CSF	Patients with Parkinson's disease on stable dopaminergic treatment; safety and tolerability	Phase 2 trial completed (NCT02954978); cohort 1 of phase 2 trial completed concluding poor CSF penetration (NCT03205488)
K-0706	NA	CSF penetrant	Patients with Parkinson's disease not receiving dopaminergic therapy; MDS-UPDRS parts 2 and 3	Ongoing phase 2 trial (NCT03655236)
ikt-148009	Efficacy in α-synuclein transgenic mice	NA	Idiopathic Parkinson's disease; modified Hoehn and Yahr stage ≤2; previous use of dopaminergic therapy for ≥30 days; safety, tolerability, and pharmacokinetic profile	Phase 1 trial in development (NCT04350177)
Anti-α-synuclein antibodies				
PRX002	Efficacy in α-synuclein transgenic mice	CSF antibody concentrations, lowering of free α-synuclein in CSF	Patients with early Parkinson's disease who are untreated or treated with monoamine oxidase B inhibitors since baseline; MDS-UPDRS sum of parts 1, 2, and 3	Phase 2 trial completed, did not meet primary outcome although some secondary outcomes positive (NCT03100149)
BIIB054	Efficacy in α-synuclein transgenic mice	DATSCAN imaging; neuromelanin imaging; CSF concentration of BIIB054 antibody, α-synuclein, neurodegenerative biomarkers	Patients with Parkinson's disease not on medication for at least 12 weeks before and not expected to require treatment for at least 6 months; MDS-UPDRS sum of parts 1, 2, and 3	Phase 2 trial completed, formal results awaited although press release suggests did not meet primary outcome (NCT03318523)
PD01A active α-synuclein immunisation	Efficacy in α-synuclein transgenic mice	CSF PD01A specific antibody production, CSF α-synuclein concentrations	NA	Phase 2 trial in development
Reducing α-synuclein production				
Antisense oligonucleotides	Efficacy in α-synuclein transgenic mice	NA	NA	NA
Small interfering RNAs	Efficacy in α-synuclein transgenic rats and mice, toxin-treated rats, wild-type non-human primates	NA	NA	NA
Reducing *SNCA* expression				
β2 agonists	Efficacy in β2-adrenergic receptor-deficient mice	NA	NA	NA

(Table 1 continues on next page)

Résultats décevants

- Mode d'administration?
- Quantité au niveau SNC?
- Autres?

Action sur les gènes impliqués dans certaines formes génétiques



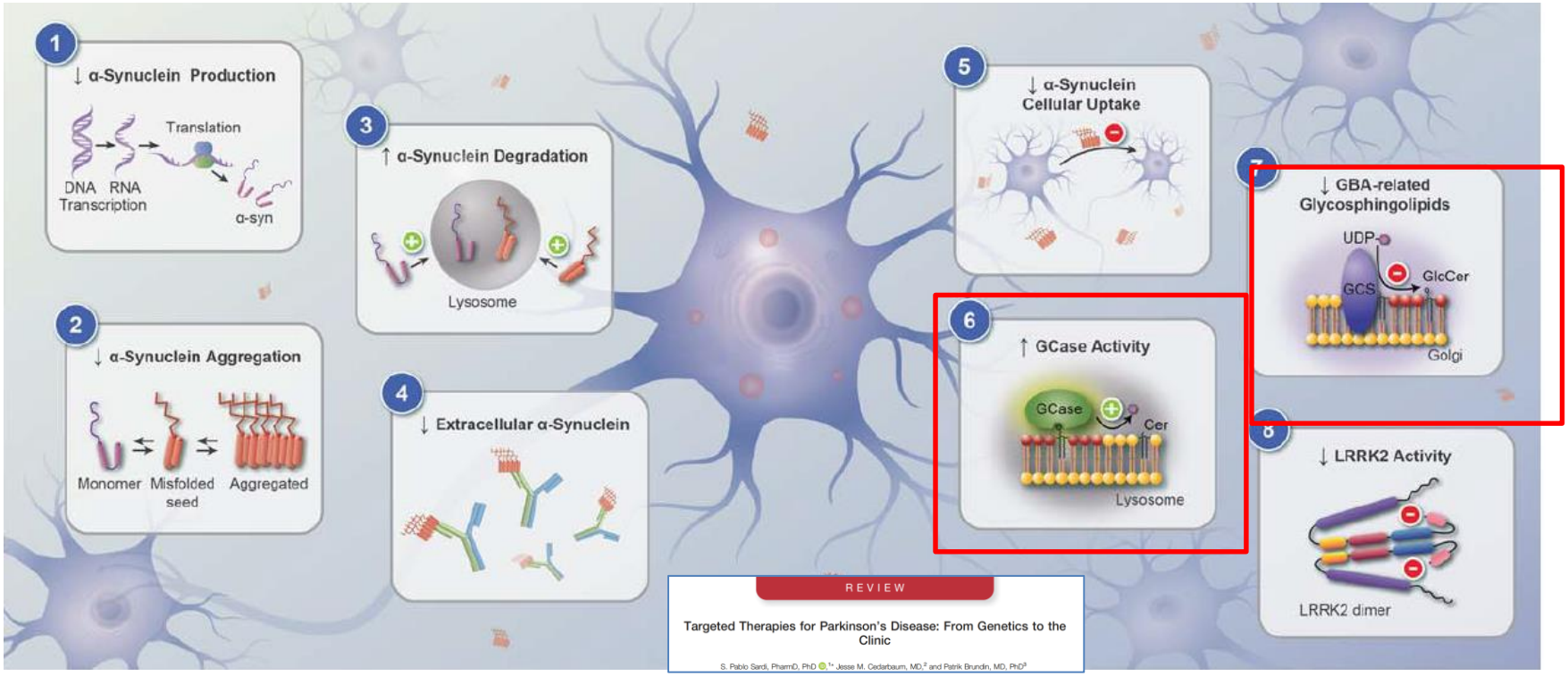
formes AD de mutation LRRK2:
gain de fonction toxique qui favoriserait la propagation de l'alpha synucléine

Action sur LRRK2

- Objectif:
  - diminuer l'activité LRRK2
  - Car dans les formes AD, gain de fonction toxique qui favoriserait la propagation de l'alpha synucléine

	Efficacy in preclinical models	Evidence supporting target engagement in patients	Recruitment selection strategy or primary outcomes	Status
(Continued from previous page)				
***LRRK2*†**				
LRRK2 inhibitors (promoting autophagy)				
DNL201 and DNL151	Efficacy in animal models of lrrk2	CSF concentrations of drug, LRRK2 pS935 in peripheral blood	NA; safety and tolerability	Completed phase 1 trial (NCT03710707); ongoing phase 1 trial (NCT04056689)
Antisense oligonucleotide for LRRK2 inhibition				
BIIB094 (intrathecal)	Efficacy in α-synuclein transgenic mice	Pharmacokinetic study	Patients with Parkinson's disease with or without *LRRK2* mutation; safety and tolerability	Ongoing phase 1 trial (NCT03976349)

Action sur l'activité de la glucocérébrosidase



Gène GBA (Glucocérébrosidase)

- Mutations homozygotes responsables de maladie de Gaucher (AR)
- Mutation hétérozygote:
  - Facteur de risque génétique le plus important de la MPI
  - Pénétrance 10 à 30%
  - Présent chez 5 à 15% des parkinsoniens caucasiens (*versus* 1% population normale)
  - Diminution de l'activité de la Beta glucocérébrosidase

ARTICLE OPEN ACCESS

Association of GBA Genotype With Motor and Functional Decline in Patients With Newly Diagnosed Parkinson Disease

Jodi Maple-Grødem, PhD, Ingvild Dalen, PhD, Ole-Bjørn Tysnes, MD, PhD, Angus D. Macleod, MRCP, PhD, Lars Forsgren, MD, PhD, Carl E. Counsell, MRCP, MD, and Guido Alves, MD, PhD

Correspondence
Dr. Maple-Grødem
jodi.maple@uis.no

Neurology® 2021;96:e1036-e1044. doi:10.1212/WNL.0000000000011411

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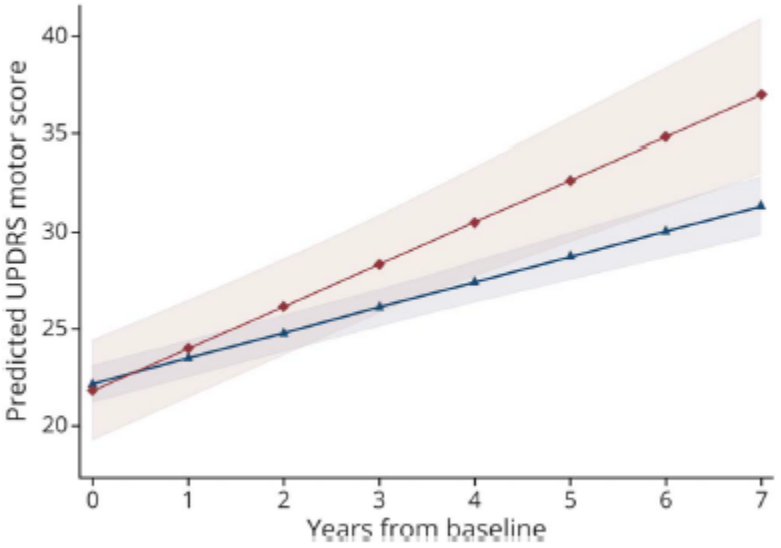
Neurology® 2021;96:e1036-e1044. doi:10.1212/WNL.0000000000011411

Figure 2 Prediction of Unified Parkinson's Disease Rating Scale (UPDRS) Motor Score Over Time



Average predicted UPDRS motor scores with confidence bands for the first 7 years after diagnosis of PD for carriers of *GBA* variants (red, diamonds) and noncarriers (blue, triangles).

Aggravation plus rapide du score moteur dans les formes GBA+

Action sur l'activité de la glucocérébrosidase

β-Glucocerebrosidase (lysosomal function)‡				
Modulator of β-glucocerebrosidase activity				
Ambroxol§	Efficacy in α-synuclein transgenic mice	CSF concentrations, β-glucocerebrosidase activity	Patients with Parkinson's disease with GBA (positive and negative); Alzheimer's Disease Assessment Scale-cognitive subscale and Clinician's Global Impression of Change; glucocerebrosidase and ambroxol concentrations in blood and CSF	Ongoing phase 2 trial (NCT02914366); completed phase 2 trial (NCT02941822)
LTI-291	NA	CSF concentrations of drug and glycosphingolipids; ^{18}F-fluorodeoxyglucose PET; functional MRI	NA	Ongoing phase 1 trial (EudraCT2017-004086-27)
Substrate reduction				
Venglustat	Efficacy in α-synuclein pathological models of Parkinson's disease (with and without *GBA* mutations)	CSF concentrations of drug and glucosylceramide	*GBA*-associated Parkinson's disease; MDS-UPDRS part 2 and 3 scores	Phase 2 trial completed (NCT02906020)
β-Glucocerebrosidase gene therapy				
PR001 (intra-cisternal injection)	Efficacy in α-synuclein transgenic mice and murine models of synucleinopathy	CSF and serum concentrations of β-glucocerebrosidase and glycosphingolipids	Moderate to severe Parkinson's disease with at least one pathogenic *GBA1* mutation; safety and tolerability; change in immunogenicity of AAV9 and β-glucocerebrosidase in blood and CSF	Ongoing phase 1 trial (NCT04127578)

Research

JAMA Neurol.
Published online January 13, 2020.

JAMA Neurology | Original Investigation

Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations

A Nonrandomized, Noncontrolled Trial

Stephen Mullin, PhD, MRCP; Laura Smith, MSc; Katherine Lee, MRes; Gayle D'Souza, MSc; Philip Woodgate, PhD; Josh Elflein, MSc; Jenny Hällqvist, BSc; Marco Toffoli, MD; Adam Streeter, PhD; Joanne Hosking, PhD; Wendy E. Heywood, PhD; Rajeshree Khengar, PhD; Philip Campbell, MRCP; Jason Hehir, BSc; Sarah Cable, BSc; Kevin Mills, PhD; Henrik Zetterberg, PhD, MD; Patricia Limousin, PhD, MD; Vincenzo Libri, MD, FRCP; Tom Foltynie, PhD, MRCP; Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci

Ambroxol

Sirop anti toux

Protéine chaperonne inhibitrice

In vivo* et *in vitro

Augmente l'activité de la glucocérébrosidase

Diminue l'alpha synucléine

Résultats:

L 'ambroxol passe la BHE et module l'activité de la glucocérébrosidase chez les patients atteints de MPI

L'ambroxol est bien toléré (doses 10x supérieures à celles habituellement utilisées)

Efficacité? Études complémentaires nécessaires

Autres cibles

cibles du traitement

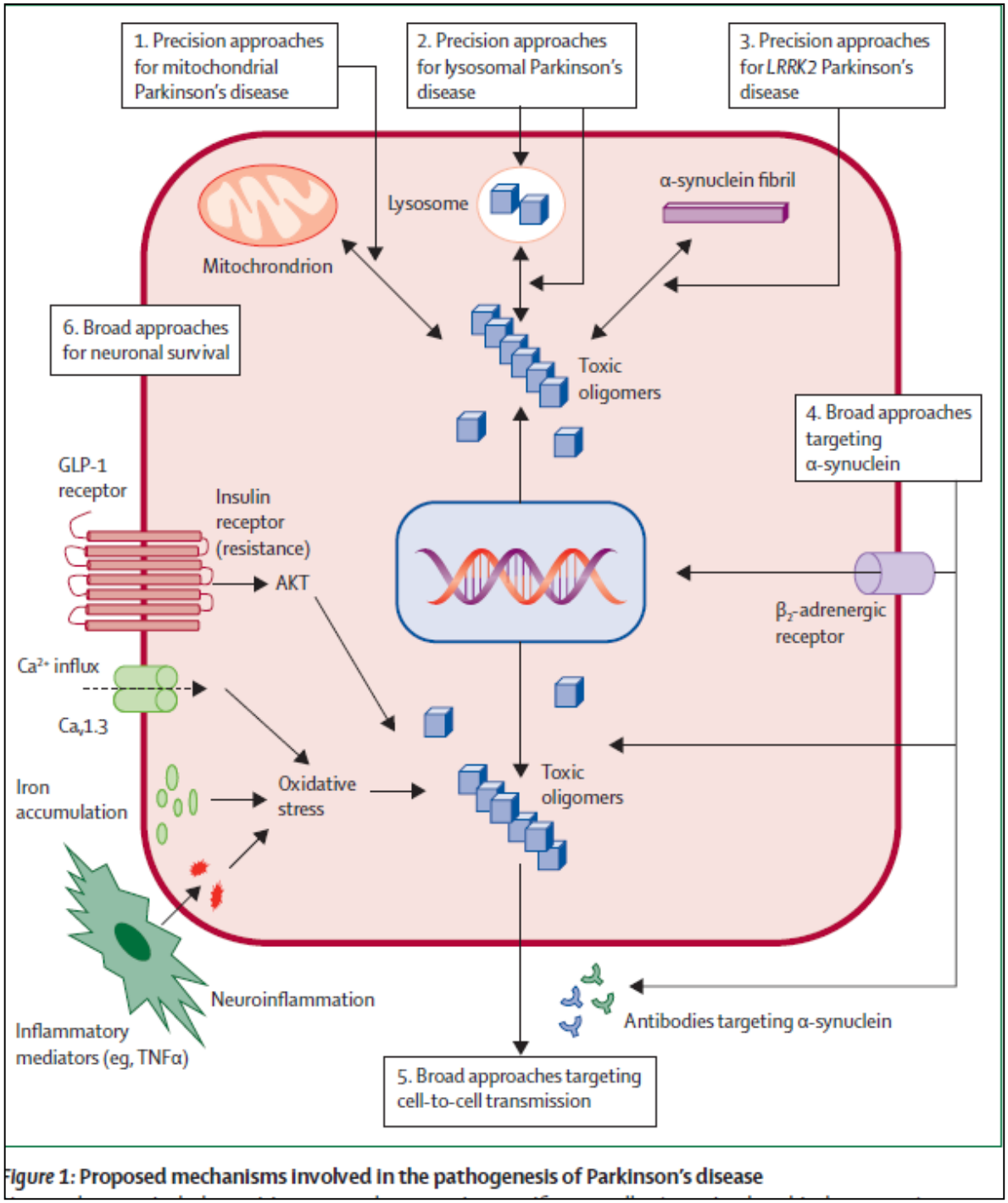


Figure 1: Proposed mechanisms involved in the pathogenesis of Parkinson's disease

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	Drugs	Efficacy in preclinical models	Evidence supporting target engagement in patients	Recruitment selection strategy or primary outcomes	Status
Neuroinflammation					
Inhibition of microglial activation	Minocycline	Efficacy in MPTP mouse model	Clinical measures only	Patients with Parkinson's disease on stable dopaminergic treatment; time to initiation of symptomatic pharmaceutical treatment	Negative phase 2 trial (NCT00063193)
Altered T-cell lineage	Sargramostim	Efficacy in MPTP mouse model	Improved regulatory T-cell function	Parkinson's disease symptoms of at least 3 years; safety and tolerability	Completed and ongoing phase 1 trials (NCT01882010; NCT03790670)
Enzyme myeloperoxidase inhibition	AZD3241	Efficacy in MPTP mouse model and α-synuclein multiple system atrophy model	Microglial PET imaging	Untreated Parkinson's disease; safety and tolerability; pharmacokinetics; PET binding (^{11}C-PBR28 to TSPO)	Ongoing phase 2 trials (NCT01603069; NCT01457807; NCT01527695)
NLRP3 inflammasome inhibition	Inzomelid	Efficacy in MPTP mouse model	Measurement of blood NLRP3 inhibition (results pending)	Healthy volunteers; safety and tolerability; pharmacokinetics and pharmacodynamics	Completed (results pending) phase 1 trial (NCT04015076)
HMG-CoA inhibition	Simvastatin	Efficacy in MPTP mouse model	Clinical measures only	Parkinson's disease, Hoehn and Yahr stage ≤3·0 in the ON medication state or MDS-UPDRS part 3 (OFF)	Ongoing phase 2 trial (NCT02787590)
Inhibition of nucleic acid synthesis, reduced lymphocyte proliferation	Azathioprine	None in Parkinson's disease models	Microglial PET imaging; CSF neuroinflammatory profile	Early Parkinson's disease predicted to progress rapidly; MDS-UPDRS part 3 (OFF)	Phase 2 trial recruiting (EudraCT 2018-003089-14)
Mitochondrial function*					
Improved mitochondrial biogenesis	Pioglitazone	Efficacy in *Cox10* or DAT-cre mice and MPTP non-human primates	Clinical measures, blood and urine biomarkers	Early Parkinson's disease on a stable regimen; MDS-UPDRS sum of parts 1, 2, and 3	Negative phase 2 trial (NCT01280123)
Increased urate (antioxidant)	Inosine	Efficacy in MPTP and 6-hydroxydopamine mouse models	Measurement of serum urate	Idiopathic Parkinson's disease; modified Hoehn and Yahr stage ≤2·5; MDS-UPDRS sum of parts 1, 2, and 3; safety and tolerability	Negative phase 3 trial (NCT02642393; NCT00833690)
Improved mitochondrial function	Ursodeoxycholic acid	Efficacy on mitochondrial function in parkin and LRRK2 cells	ATP concentrations using ^{31}P MR spectroscopy	Idiopathic Parkinson's disease, Hoehn and Yahr stage ≤2·5; safety and tolerability; 7 Tesla MR spectroscopy (ATP concentration)	Ongoing phase 2 trials (NCT03840005; NCT02967250)
Calcium†					
L-type calcium channel blocker	Isradipine	Efficacy in MPTP and 6-hydroxydopamine mouse models	Clinical measures only	Untreated Parkinson's disease Hoehn and Yahr stage ≤2·0; MDS-UPDRS sum of parts 1, 2, and 3	Negative phase 3 trial (NCT02168842)
Iron					
Iron chelation	Deferiprone	Efficacy in α-synuclein transgenic mice	Reduced iron concentrations in substantia nigra on MRI	Untreated patients with Parkinson's disease; MDS-UPDRS part 3	Ongoing phase 2 trials (NCT02655315; NCT02728843)
Insulin resistance					
GLP-1 receptor agonists‡	Exenatide, NLY01	Protective in dopaminergic toxin and α-synuclein based models	Measures of insulin resistance in serum, CSF, and neuronal derived exosomes, DATSCAN uptake	Parkinson's disease, Hoehn and Yahr stage ≤2·5; MDS-UPDRS parts 2 and 3	Ongoing phase 3 trials (NCT04232969); ongoing phase 2 (NCT04154072)
GLP-1 receptor agonist‡	Liraglutide	Efficacy in MPTP mouse model	Measurement of insulin resistance	Parkinson's disease at least 2 years; MDS-UPDRS part 3, Non-Motor Symptoms Scale, and Montgomery Asberg Depression Rating Scale-2	Ongoing phase 2 trial (NCT02953665)
GLP-1 receptor agonist‡	Lixisenatide	Efficacy in MPTP mouse model	Clinical measures only	Parkinson's disease Hoehn and Yahr stage ≤3·0; MDS-UPDRS part 3	Ongoing phase 2 trial (NCT03439943)
GLP-1 receptor agonist‡	Semaglutide	Efficacy in MPTP mouse model	DATSCAN uptake	Early Parkinson's disease; MDS-UPDRS part 3 (OFF)	Ongoing phase 2 trial (NCT03659682)

Thérapie cellulaire personnalisée

The NEW ENGLAND JOURNAL of MEDICINE

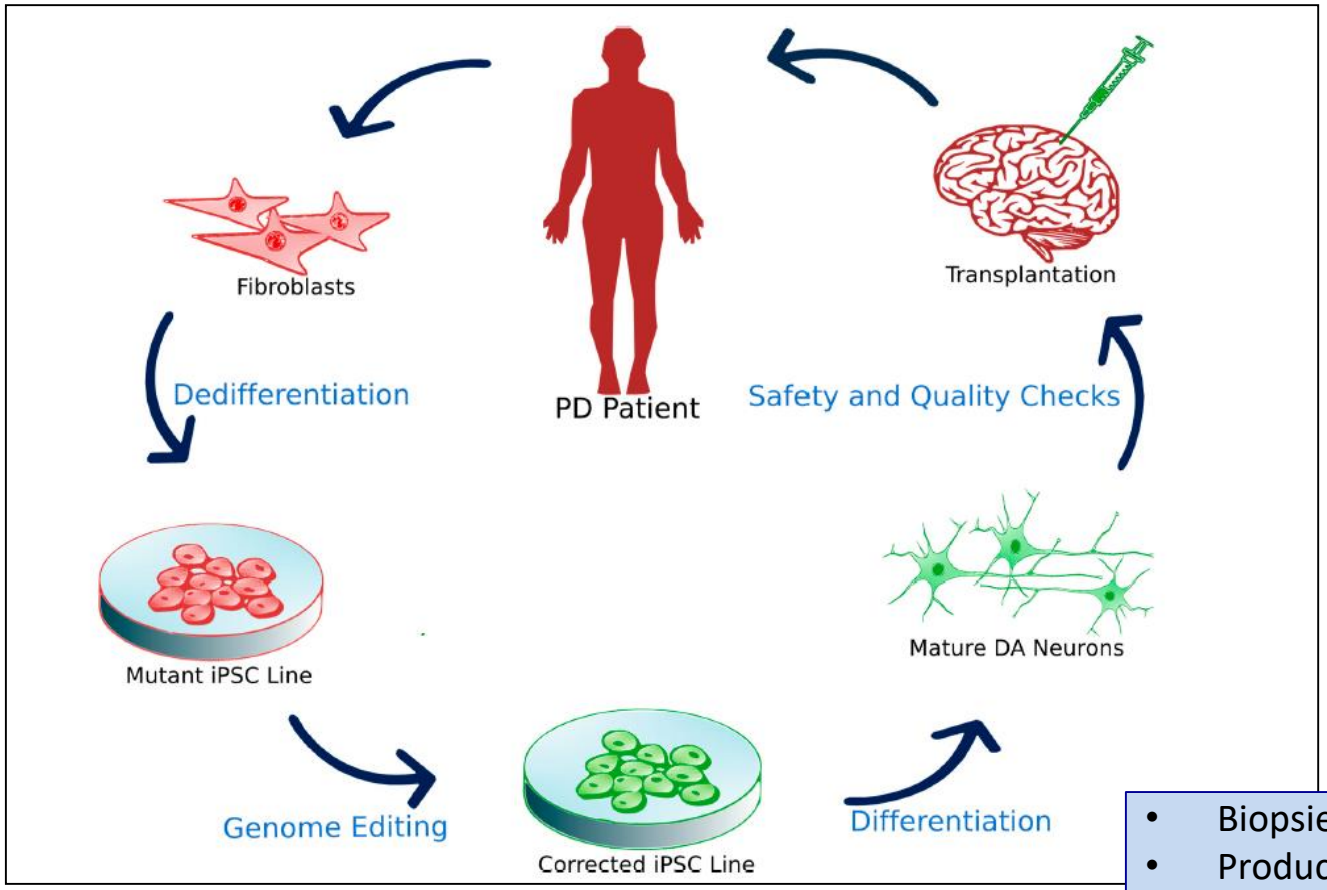
1 patient

BRIEF REPORT

Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease

Jeffrey S. Schweitzer, M.D., Ph.D., Bin Song, M.D., Ph.D., Todd M. Herrington, M.D., Ph.D., Tae-Yoon Park, Ph.D., Nayeon Lee, Ph.D., Sanghyeok Ko, Ph.D., Jeha Jeon, Ph.D., Young Cha, Ph.D., Kyungsang Kim, Ph.D., Quanzheng Li, Ph.D., Claire Henchcliffe, M.D., D.Phil., Michael Kaplitt, M.D., Ph.D., Carolyn Neff, M.D., Otto Rapalino, M.D., Hyemyung Seo, Ph.D., In-Hee Lee, Ph.D., Jisun Kim, Ph.D., Taewoo Kim, Ph.D., Gregory A. Petsko, D.Phil., Jerome Ritz, M.D., Bruce M. Cohen, M.D., Ph.D., Sek-Won Kong, M.D., Pierre Leblanc, Ph.D., Bob S. Carter, M.D., Ph.D., and Kwang-Soo Kim, Ph.D.

Greffes de cellules dopaminergiques dérivées de cellules pluripotentes autologues générées à partir de fibroblastes

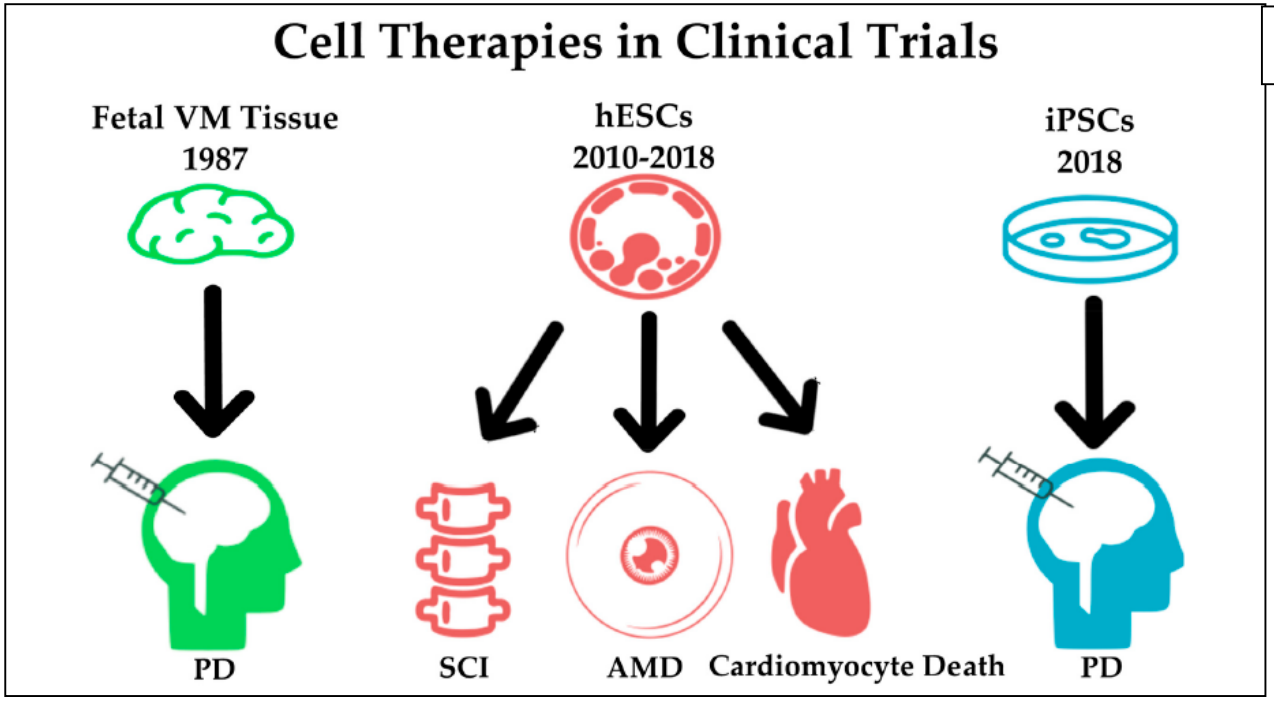


Cells **2019**, *8*, 26; doi:10.3390/cells8010026

- Biopsie de **fibroblaste**s
- Production de plusieurs **lignées de cellules souches pluripotentes**,
- Sélection d'un clone pour **production de mDAPS** (derived midbrain dopaminergic progenitor cells)
- Vérification des propriétés DA sur modèle animal et in vitro..

Efficacité en cours d'évaluation chez quelques patients

Évolution des techniques de thérapie cellulaire/ avantages de cette technique



Cells **2019**, *8*, 26; doi:10.3390/cells8010026

hESC human embryonic stem cells
iPSCs induced pluripotent stem cells

- **<u>Intérêt des cellules souches pluripotentes, guidées vers une différenciation dopaminergique mésencéphalique</u>**
  - Pas de Pb éthique
  - Production pure
  - Si production autologue, épargne des immunosuppresseurs

Évaluation en cours….

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-21022-9 OPEN

Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia

Carmen Gasca-Salas[1,2], Beatriz Fernández-Rodríguez[1,8], José A. Pineda-Pardo[1,2,8], Rafael Rodríguez-Rojas[1,2], Ignacio Obeso[1,2], Frida Hernández-Fernández[1,3], Marta del Álamo[1,2], Da Pasqualina Guida[1,2], Carlos Ordás-Bandera[4], J. Ignacio Montero-Roblas[5], Raúl Martínez-Fernández[1] Guglielmo Foffani[1,2,6], Itay Rachmilevitch[7] & José A. Obeso[1,2]✉

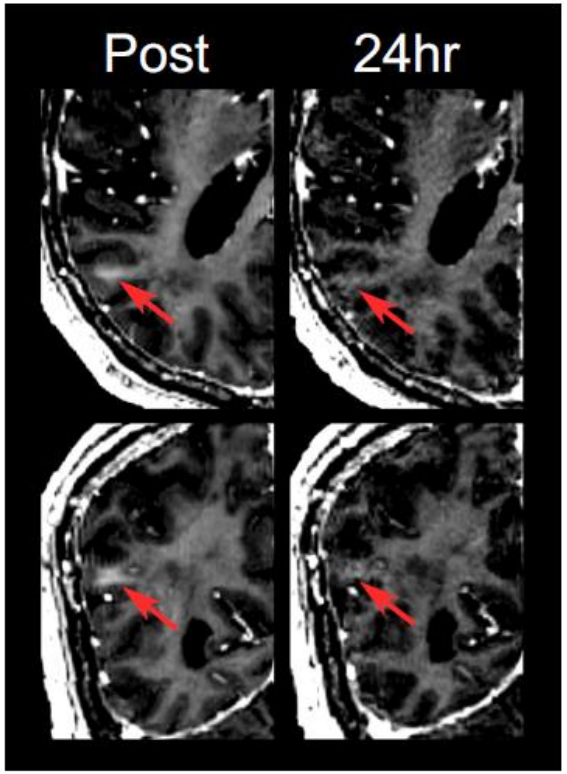


Fig. 2 Gadolinium-enhanced T1-weighted images: blood-brain barrier opening. Post: Blood–brain barrier opening of patient 2 in the targeted area immediately after sonication. 24 h: Same targeted area of patient 2, 24 h after treatment, without recognizable BBB opening. Top and bottom panels, respectively, show axial and coronal views of the parieto-occipito-temporal region.

Etude pilote
5 patients
En ouvert

Cortex parieto occipito temporal

Protocoles en cours à Strasbourg

Traitements symptomatiques

- TEMPO

- le **Tavapadon** (PF-06649751, CVL-751) est un agoniste partiel des récepteurs dopaminergiques de la famille D1 (D1R) présentant un haut degré de spécificité pour les sous-types de récepteurs D1 et D5 (D1/D5).
- En ciblant le sous-type D1R, le tavapadon vise à améliorer les symptômes du contrôle moteur tout **en minimisant les événements indésirables (EI)** susceptibles d'être liés mécaniquement aux agonistes du récepteur dopaminergique D2/D3 (notamment, l'hypotension limitant la dose, les troubles du contrôle des impulsions, les troubles du sommeil et, potentiellement, certaines formes d'hallucinations).
- Cette étude a pour objectif de mieux définir et confirmer l'ampleur de l'efficacité et le profil risques/bénéfices du tavapadon sur une plage posologique cible de 5 à 15 mg une fois par jour (1x/j)

Traitements neuro-protecteurs

- PADOVA
  - **Prasinezumab**
  - Anticorps humanisé dirigé contre l'alpha syncucléine agrégée

- ORCHESTRA
  - L'UCB0599 est un inhibiteur du repliement anormal de l'alpha-synucléine (ASYN) et de son agrégation en aval, administrable par voie orale