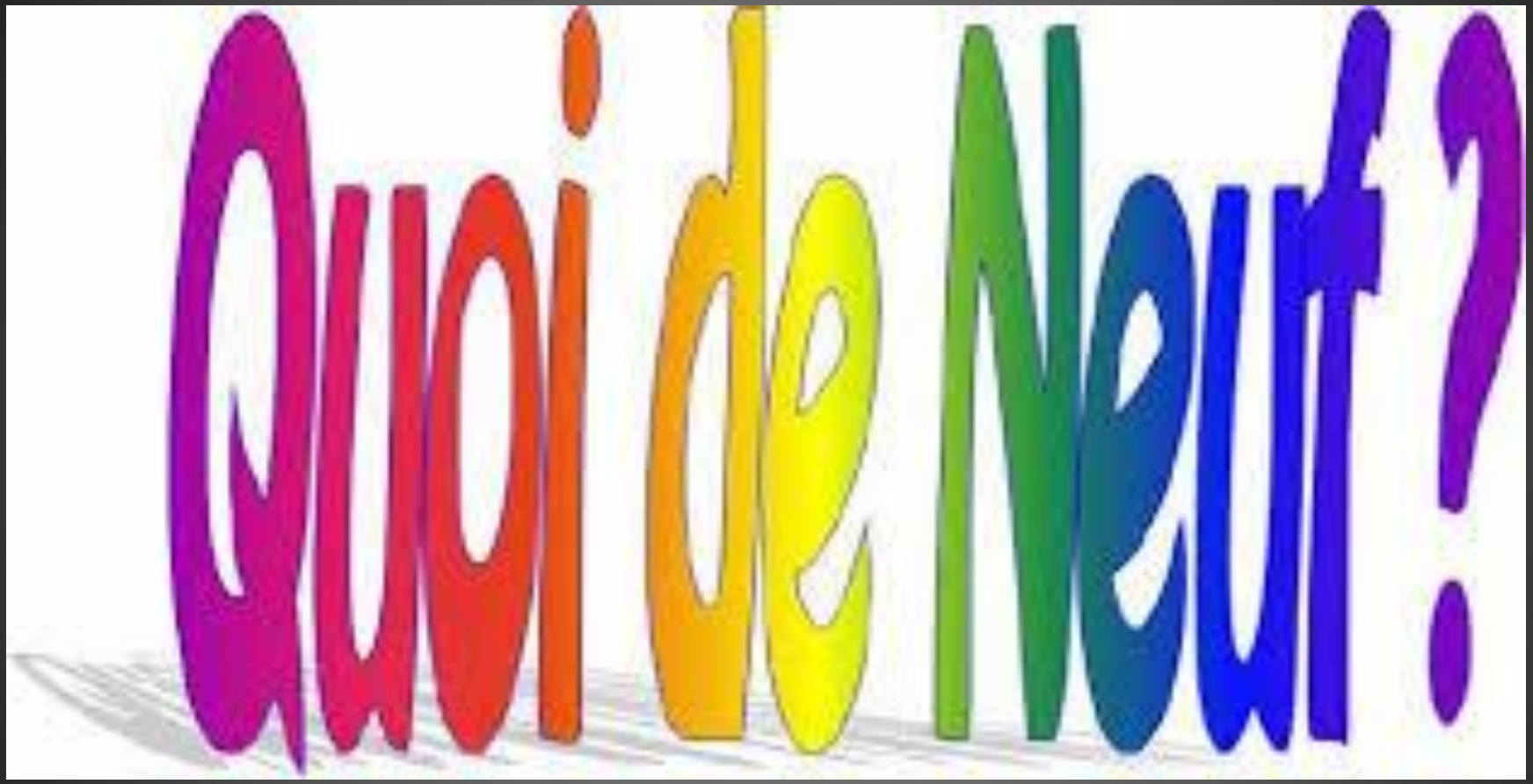
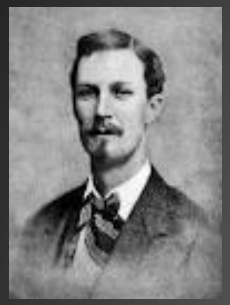
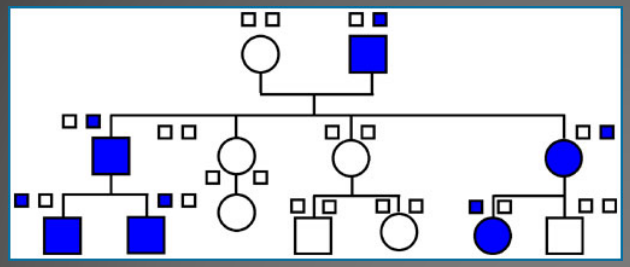
Maladie de HUNTINGTON: Quoi de neuf?
Recherche et Essais thérapeutiques

Docteur Lamia GUETTAT
Neurologue
Convention Huntington Namur
Enroll-HD site Beauvallon


Quoi de Neuf ?

Rappel





… 1872 1911 1983 1993 1996 2006

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

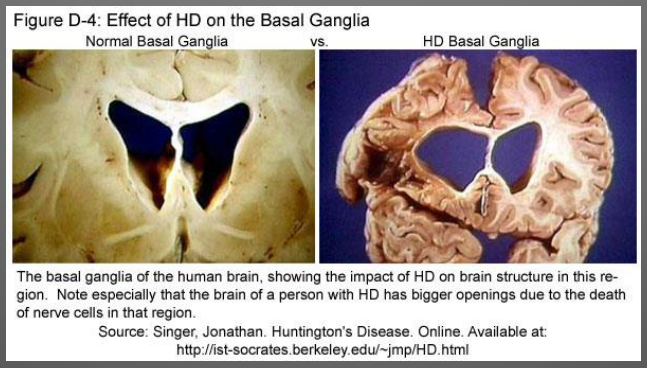
By George Huntington, M. D.,

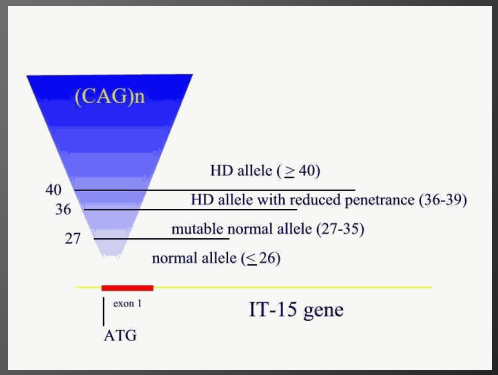
Of Pomeroy, Ohio.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-





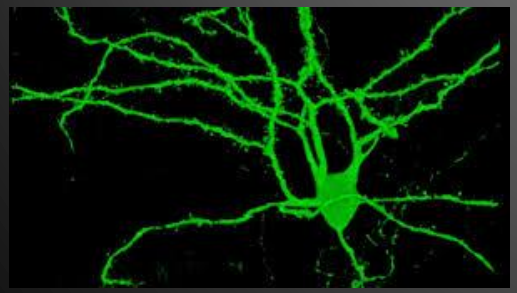
On le sait dèjà…

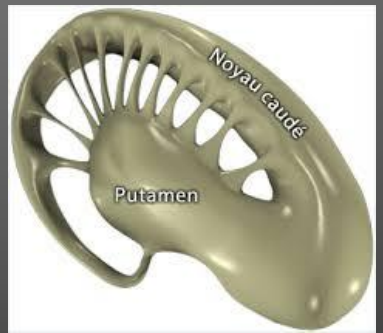
- Maladie neurodégénérative héréditaire qui touche environ 1000 personnes en Belgique (Prévalence en Europe: 5-10/100 000 - > 50 000 patients-)
- Elle est causée par une expansion hétérozygote anormalement longue de répétitions trinucléotides CAG (codant pour la Glutamine) dans le gène de la Huntingtine
- Le mode de transmission est autosomique dominant: risque de transmission à la descendance de 50%
- L'âge de début est (en partie) déterminé par le nombre de répétitions

On le sait déjà…

La dégénérescence s'observe au niveau du SNC

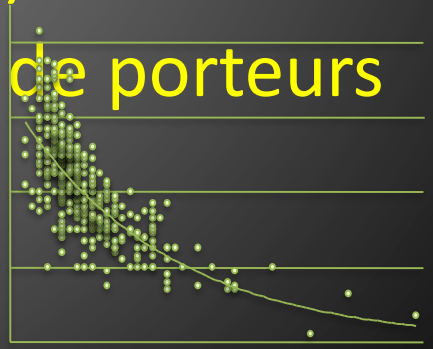
L'atteinte neuronale prédomine du striatum: elle y touche les neurones épineux moyens (impliqués dans la voie indirecte du contrôle du mouvement). Ceci explique le caractère hyperkinétique (chorée) de l'atteinte motrice précoce dans la MH





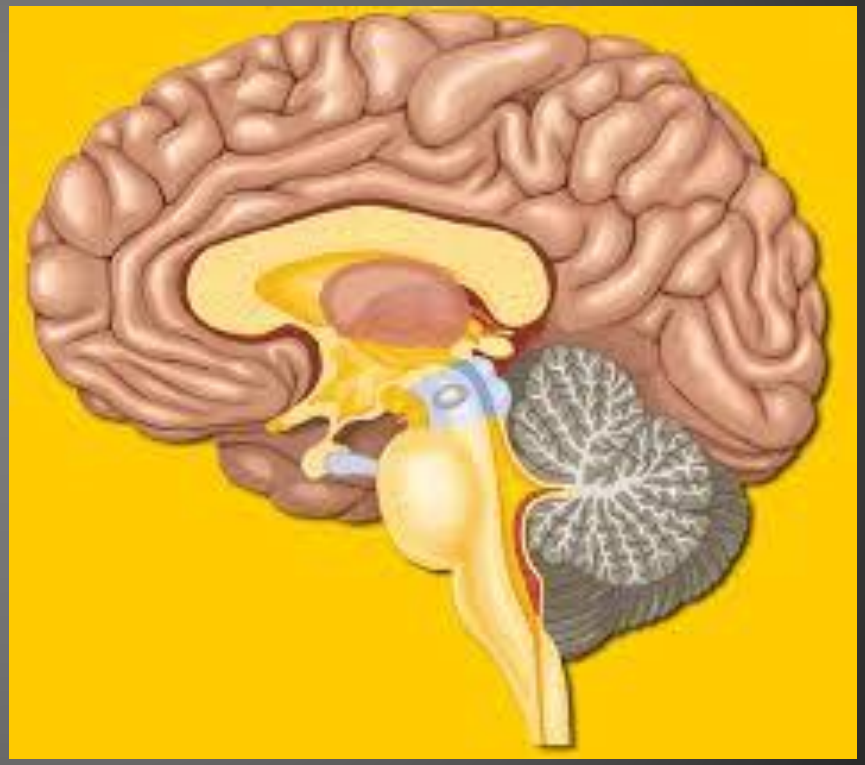
On le sait déjà…

- De 36 à 39 répétitions: la pénétrance est complète et la maladie ne se déclare pas systématiquement
- 40 répétitions et plus: certitude de développer des symptômes en général à l'âge adulte
- La forme juvénile se retrouve chez les porteurs de 60 triplets. Ces patients ont hérité l'allèle muté de leur père (phénomène d'anticipation)
- Mutations de Novo: chez les enfants de porteurs masculins de 27 à 35 répétitions



On le sait déjà…

- ✓ ***Troubles moteurs***: chorée, impersistance motrice, dystonie, incoordination des mouvements, rigidité, dysarthrie,…
- ✓ ***Déficits cognitifs***: dysfonctionnement exécutif précoce
- ✓ ***Troubles du comportement*****: apathie, irritabilité, agitation**, désinhibition, euphorie, dépression, **TOC**, psychose
- ✓ ***Signes associés*****:** troubles sphinctériens, Crises comitiales, troubles végétatifs, amaigrissement



On le sait déjà…

- Traitements symptomatiques
- Absence de traitement « causal », curatif, « préventif » qui empêche l'apparition des symptômes cliniques clinique ou qui retarde l'évolution

L’Espoir …

«Les batailles de la vie ne sont pas gagnées par les plus forts, ni par les plus rapides, mais par ceux qui n’abandonnent jamais»

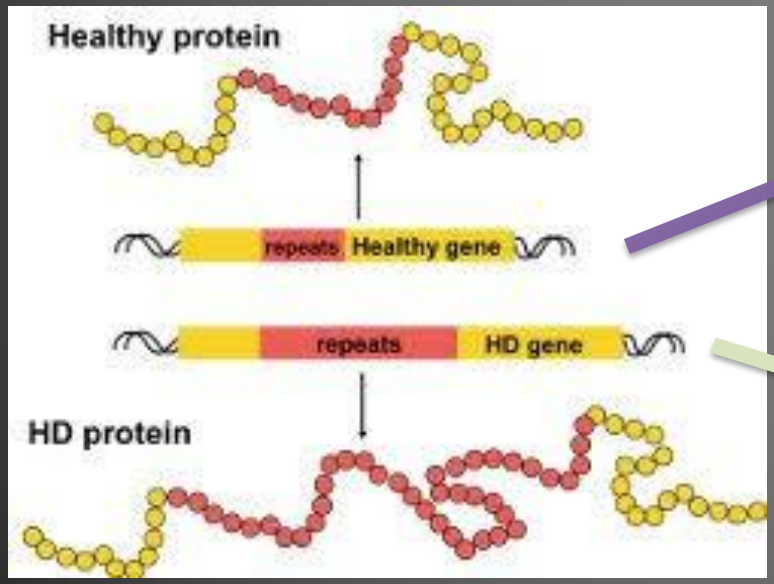
La Huntingtine

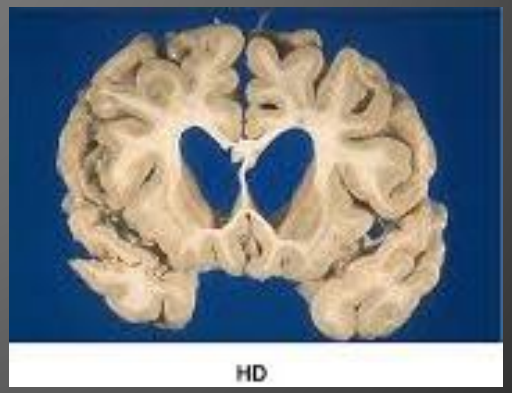
- On sait maintenant que:

La Huntingtine par ses nombreuses et interactions avec diverses protéines dans différents organites du neurone va provoquer de nombreux bouleversements à l'échelle moléculaire et cellulaire.

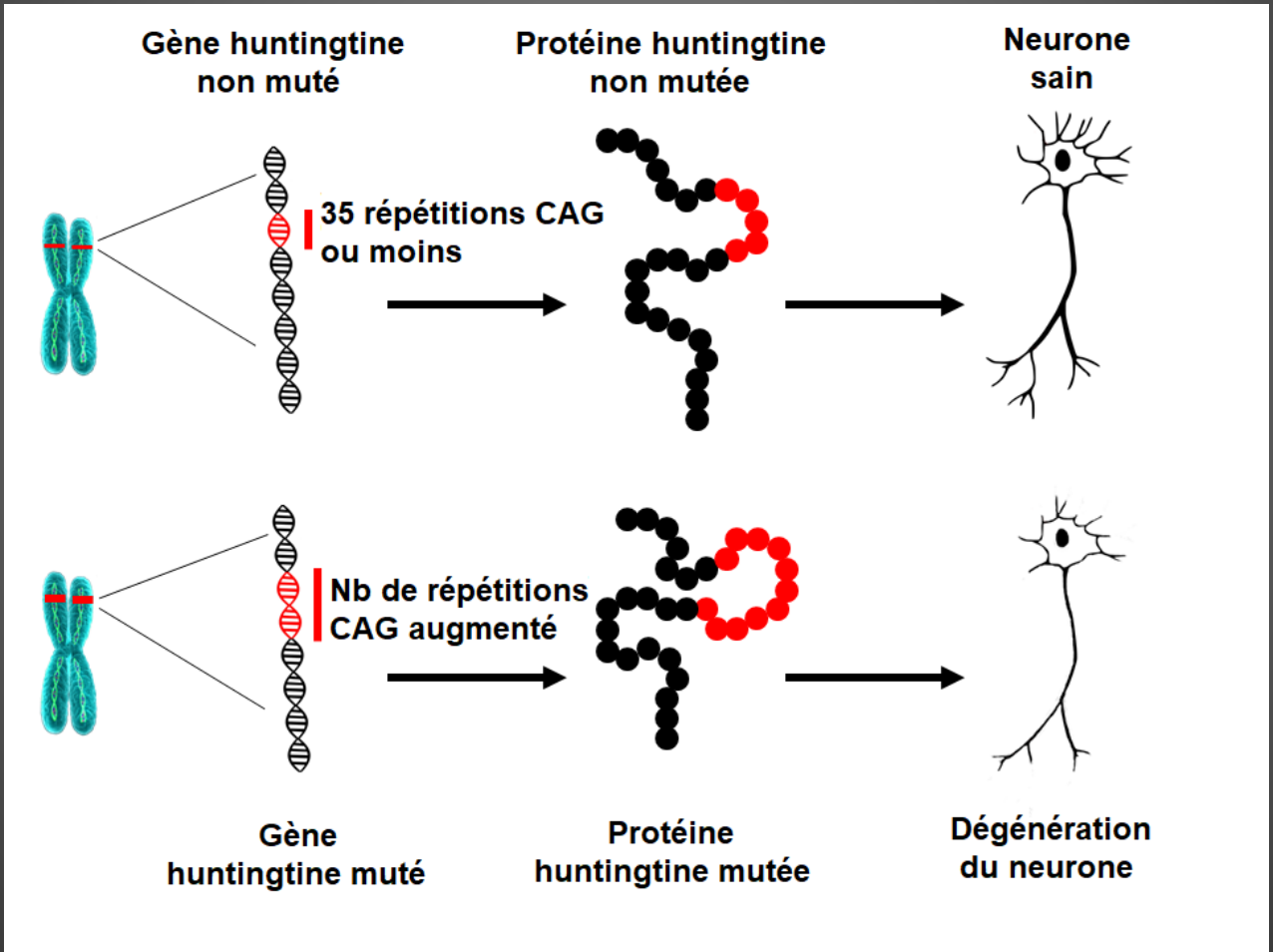
les gains de fonctions toxiques de la huntingtine mutée et les pertes de fonctions de la huntingtine sauvage

HUNTINGTINE



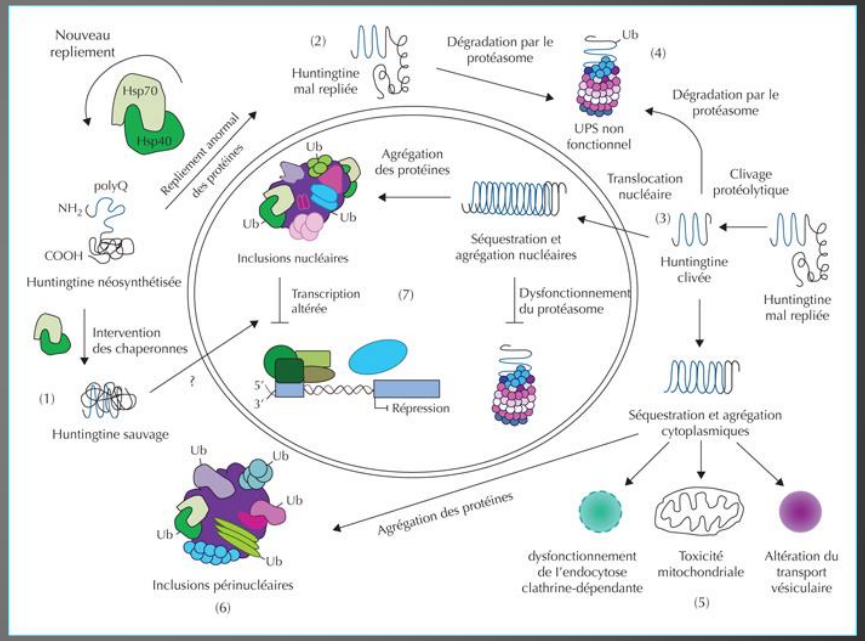


Huntingtine

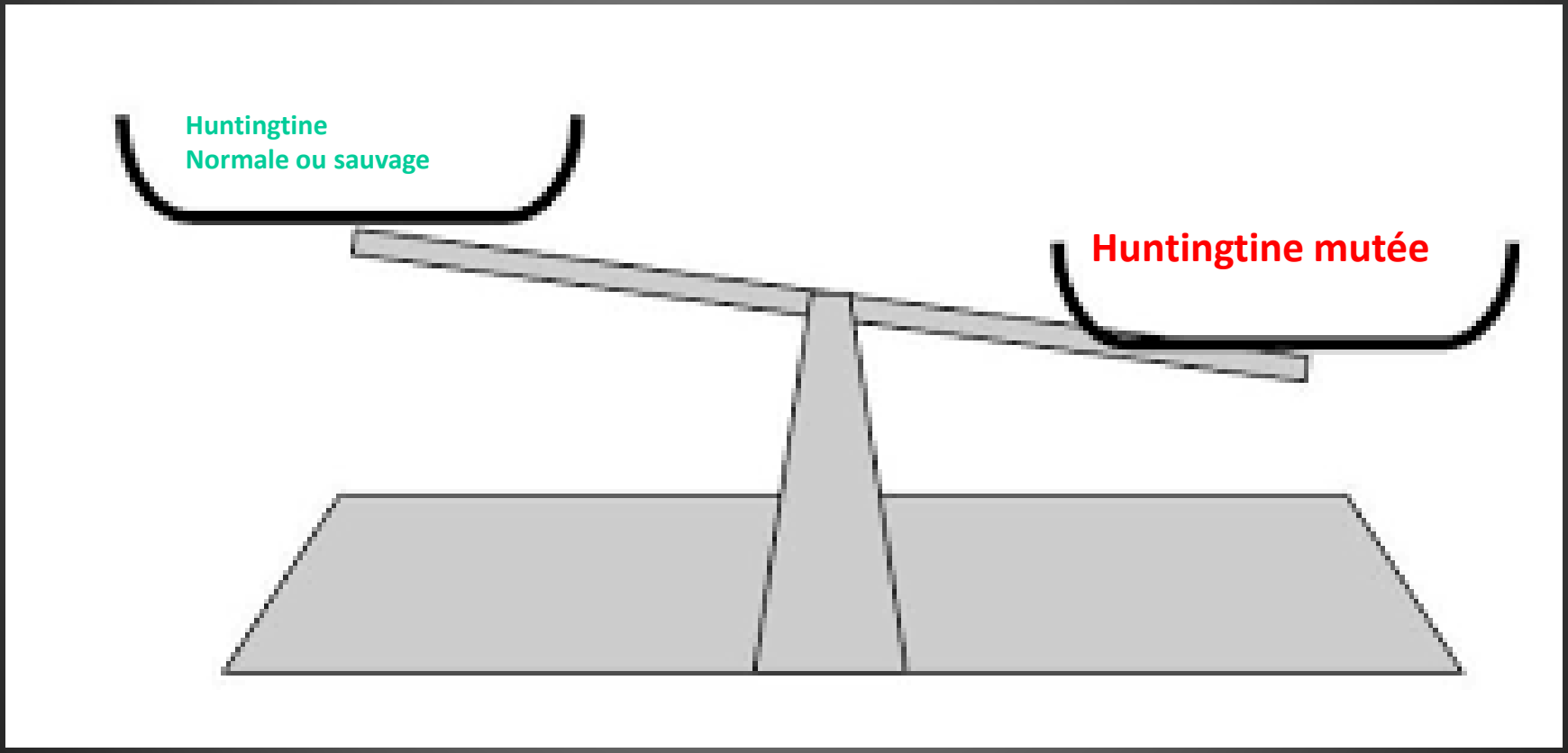


Mécanismes d'action de la Huntingtine muté: gain de la fonction toxique

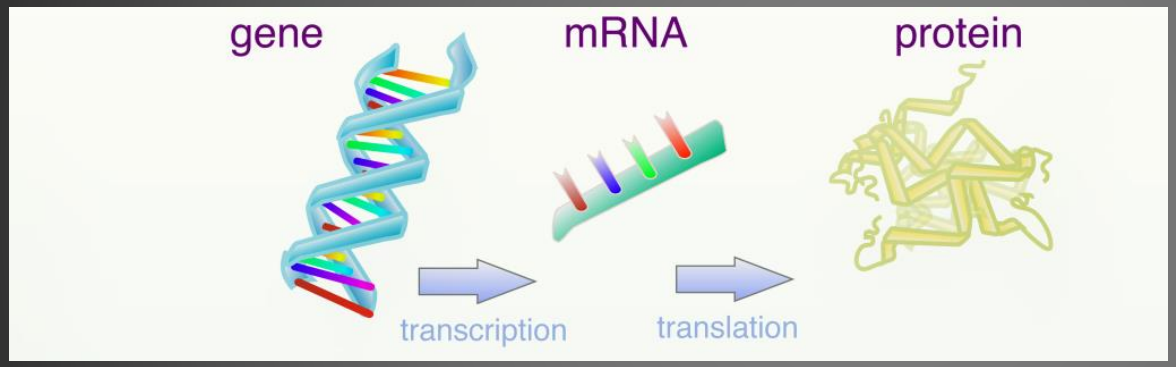
- Perturbation de l'homéostase protéique
- Dérégulation transcriptionnelle
- Dysfonction mitochondriale
- Altération du transport axonal
- Altération de la synapse et des circuits neuronaux
- Altération de l'Autophagie

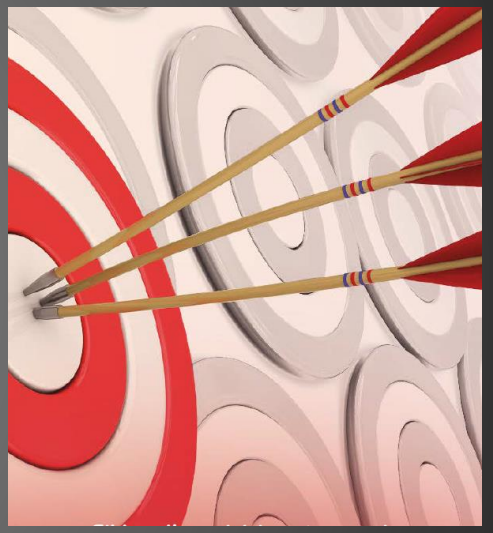


HUNTINGTINE



Cibles potentielles pour les agents modificateurs de la maladie





https://i1.wp.com/web.stanford.edu

Fonctions de la Huntingtine Normale

Protéine ubiquitaire

Région	Niveau d'Expression
Cerveau	
Cervelet	+++
Cortex	+++
Substantia Nigra Pars Compacta	++
Putamen	+
Noyau caudé	+
Thalamus	
Tissus Périphériques	
Testicules	+++
Colon	+
Foie	+
Pancréas	+

La Huntingtine est une molécule clé pendant le développement

- Rôle dans le développement embryonnaire
- Réduction de l'apoptose des Neurones
- Signal transduction
- Endocytose
- Structure du cytosquelette, division cellulaire
- Transport de vésicules (BDNF)
- Métabolisme énergétique/Mitochondrie
- Régulation de la transcription

Huningtin Knock out: lethal
Knock out at time of birth: mild neurologic deficits.

IOS Press

Research Report

Fifteen Years of Clinical Trials in Huntington's Disease: A Very Low Clinical Drug Development Success Rate

André M. Travessa[a], Filipe B. Rodrigues[a,b,c], Tiago A. Mestre[d] and Joaquim J. Ferreira[a,b,e,*]
[a]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal*
[b]*Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal*
[c]*Huntington's Disease Centre, Institute of Neurology, University College London, United Kingdom*
[d]*Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada*
[e]*CNS – Campus Neurológico Sénior, Torres Vedras, Portugal*

Abstract.
Background: Drug development in Huntington's disease (HD) is particularly challenging, and only two compounds are approved by the FDA. It is therefore essential to appraise drug development programs in order to understand the reasons for their failure during the early stages of development.
Objectives: To describe the landscape of HD therapeutic development and critically explore the causes of compound attrition in the different stages of drug development, from phase 1 to phase 4.
Methods: All HD clinical trials registered in the WHO International Clinical Trials Search Portal, from inception to May 2017, were analyzed. Two independent authors selected and extracted data. Success rate in a trial phase was calculated as the number of compounds that progressed to the next trial phase divided by the number of compounds in that phase. The overall success rate was calculated as the ratio between the number of compounds that receive regulatory approval and the total number of compounds.
Results: Ninety-nine trials assessing 41 compounds and eleven non-pharmacological interventions (devices and cell therapies) were identified. Twenty-four (24.2%) were phase 1 trials, 46 (46.5%) phase 2, 20 (20.2%) phase 3, and two (2.0%) phase 4. Sixty trials (60.6%) received industry sponsorship. The most frequently studied compounds were creatine, latrepirdine and pridopidine. The mean number of participants enrolled was 92.0 and the length of treatment was 262.9 days, and both increased from phase 1 to phase 3 trials. The success rate was 25.0% from phase 1 to phase 2, 19.4% from phase 2 to phase 3, and 14.3% from phase 3 to approval. The overall success rate was 3.5%.
Conclusions: Although HD is a rare condition, 99 HD trials were identified in a comprehensive clinical trial registry. We found a low success rate at earlier phases of drug-development and a very low trial success rate at later phases. There is a significant gap between drug discovery and development success rates that warrants careful appraisal and improvement.

Keywords: Clinical development, clinical trials, Huntington disease, medicines

*Correspondence to: Joaquim J. Ferreira, MD, PhD, Labo-

Table 1
Distribution of HD trials by clinical phase and year of registration

Year of registration	Phase 1	Phase 2	Phase 3	Phase 4	Unknown phase	Total
1999–2004	1	6	0	0	0	7
2005–2009	13	17	14	0	0	44
2010–2017	10	23	6	2	7	48
Total	24	46	20	2	7	99

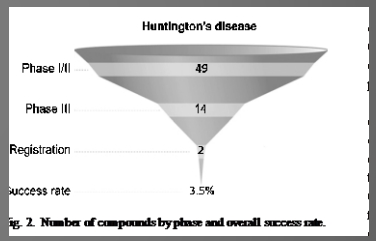


Fig. 2. Number of compounds by phase and overall success rate.

Table 2
Ongoing clinical trials (May 22, 2017)

	Phase 1	Phase 2	Phase 3	Phase 4	Unknown	Total
Drugs	1	9	5	2	3	20
Devices and radiation therapy	1	1	0	0	4	6
Cell transplantation	1	0	0	0	0	1
Total	3	10	5	2	7	27

Dernières nouvelles

Journal of Huntington's Disease 7 (2018) 89–98
DOI 10.3233/JHD-189001
IOS Press

Huntington's Disease Clinical Trials Corner: February 2018

Filipe B. Rodrigues[a,b,c] and Edward J. Wild[a,*]
[a]*Huntington's Disease Centre, University College London, UK*
[b]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Portugal*
[c]*Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal*

Abstract. In the second edition of the Huntington's Disease Clinical Trials Corner we list all currently registered and ongoing clinical trials, summarise the top-line results of the recently-announced IONIS-HTT$_{RX}$ trial (NCT02519036), expand on Wave Life Sciences' PRECISION-HD1 (NCT03225833) and PRECISION-HD2 (NCT03225846), and cover one recently finished trial: the FIRST-HD deutetrabenazine trial (NCT01795859).

Keywords: Huntington disease, clinical trials

INTRODUCTION

The Huntington's Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner are listed in Table 1.

Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

Registration ID	Trial name	Intervention	Ed
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$	Se
NCT02215616	LEGATO-HD	Laquinimod	2
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	Pride-HD	Pridopidine	

In this edition, we summarise the re
announced top-line results from the phase
IONIS-HTT$_{RX}$ huntingtin-lowering an
oligonucleotide (ASO) trial (NCT0251903
highlight the new Wave Life Sciences allele-se

*Correspondence to: Edward J. Wild, UCL Huntingto
ease Centre, Russell Square 10-12, London, WC1B 5
E-mail: e.wild@ucl.ac.uk.

ASO trials, PRECISION-HD1 (NCT03225833) [2] and PRECISION-HD2 (NCT03225846) [3], and summarise the results of the FIRST-HD (NCT01795859) [4, 5] trial of deutetrabenazine.

Finally we tabulate all currently registered and ongoing clinical trials in Tables 2 to 4. For further details on the methodology used please refer to the September 2017 edition of Huntington's Disease Clinical Trials Corner [6].

If you would like to draw attention to specific

BREAKING NEWS

December 11th 2017 saw the initial announcement of top-line results from the first-in-human phase 1b/2a trial of IONIS-HTT$_{RX}$, the first ASO designed to lower huntingtin protein (HTT) to be tested in people with HD (NCT02519036) [1]. The announcement came in the form of a press release from the sponsor, Ionis Pharmaceuticals [7], and was followed by substantial media coverage [8, 9]. As we detailed in the previous Clinical Trials Corner [6], the trial had safety

Dernières nouvelles

IOS Press

Huntington's Disease Clinical Trials Corner: August 2018

Filipe B. Rodrigues[a,b,c] and Edward J. Wild[a,*]
[a]*Huntington's Disease Centre, University College London, UK*
[b]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Portugal*
[c]*Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisbon, Portugal*

Abstract. In the third edition of the Huntington's Disease Clinical Trials Corner we list all currently registered and ongoing clinical trials, expand on the SIGNAL trial (NCT02481674), and cover the recently finished CREST-E trial (NCT00712426).

Keywords: Huntington disease, clinical trials

INTRODUCTION

The Huntington's Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner are listed in Table 1.

In this edition, we highlight the SIGNAL trial (NCT02481674) [1], and summarise the results of the recently published CREST-E trial (NCT00712426) [2, 3]. Finally we tabulate all currently registered and ongoing clinical trials in Tables 2 to 4. For further details on the methodology used, please refer to the September 2017 edition of Huntington's Disease Clinical Trials Corner [4].

If you would like to draw attention to specific trials, please feel free to email us at: f.rodrigues@ucl.ac.uk and e.wild@ucl.ac.uk.

ONGOING CLINICAL TRIALS

A list of all ongoing clinical trials is given in Tables 2–4.

*Correspondence to: Edward J. Wild, UCL Huntington's Dis-

SIGNAL (NCT02481674)

Study title

VX15/2503 Treatment for Huntington's Disease (SIGNAL) [1].

Intervention

VX15/2503 (20 mg/kg), an anti-semaphorin 4D antibody [5].

Description

The SIGNAL trial, sponsored by Vaccinex (Rochester, NY, USA), aims to evaluate the safety, tolerability, pharmacokinetics and efficacy of monthly intra-venous VX15/2503 in adults (≥21 years of age) with late prodromal (i.e. a CAG-age Product superior to 200 and a Unified Huntington's Disease Rating Scale [UHDRS] Diagnostic Confidence Level of 2 or 3) and early manifest HD (i.e. a UHDRS Diagnostic Confidence Level of 4 and a UHDRS Total Functional Capacity [TFC] above or equal to 11), comparing with intra-venous placebo, for disease modification.

This trial is phase 2, multi-centre, national, randomized, placebo controlled, double-blind, parallel study. It is divided into cohort A and cohort B, and

Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

Registration ID	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$	September 2017 [4]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	Pride-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [15]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018
NCT00712426	CREST-E	Creatine	

Qu'est ce qu'un essai clinique?

- **Synonymes: étude clinique, essai thérapeutique, clinical trial, research study**
- **Un essai clinique désigne la recherche scientifique effectuée chez l'être humain et destiné à améliorer la santé. Il permet d'étudier et de s'assurer des propriétés de molécules, afin de pouvoir en faire par la suite un usage efficace, sécurisé et responsable**
- **Mettre un médicament à la disposition des patients est le fruit d'un processus long et complexe (en moyenne 14 ans)**

AFMPS

Essai Clinique

- Le médicament testé est-il sûr et efficace?
- Peut-il prévenir la maladie ciblée?
- Peut-il avoir un effet positif sur la progression de la maladie?
- Permet-il une guérison complète?
- La qualité de vie du malade est-elle améliorée?
- Quelles personnes répondront au nouveau traitement?
- Quelle dose doit être administrée et pendant combien de temps?
- Le médicament testé peut-il être associé à d'autres traitements et comment?

AFMPS

ETUDES PRE-CLINIQUES

ETUDES CLINIQUES

Phase I

Phase II

Phase III

Animal

Homme

fagg
federaal agentschap voor geneesmiddelen en gezondheidsproducten
afmps

ENREGISTREMENT

ET

TRANSPARENCE

Mise sur le Marché

Rembou

RIZIV
INAMI

Phase IV

ESSAI CLINIQUE: Les différentes phases (www.afmps.be)

- Phase 1: petit nombre de volontaires pour:

Déterminer la posologie optimale, étudier la tolérance, étudier la toxicité éventuelle

- Phase 2: centaine de patients pour:

Tester son efficacité, répertorier les effets indésirables

- Phase 3: nombre plus important de patients pour:

Confirmer la balance entre les bénéfices et les risques, effets par rapport à d'autres médicaments existants ou un placébo

- Phase 4: médicament mis sur le marché pour surveiller plus étroitement les effets indésirables.

ISIS-HTT$_{Rx}$

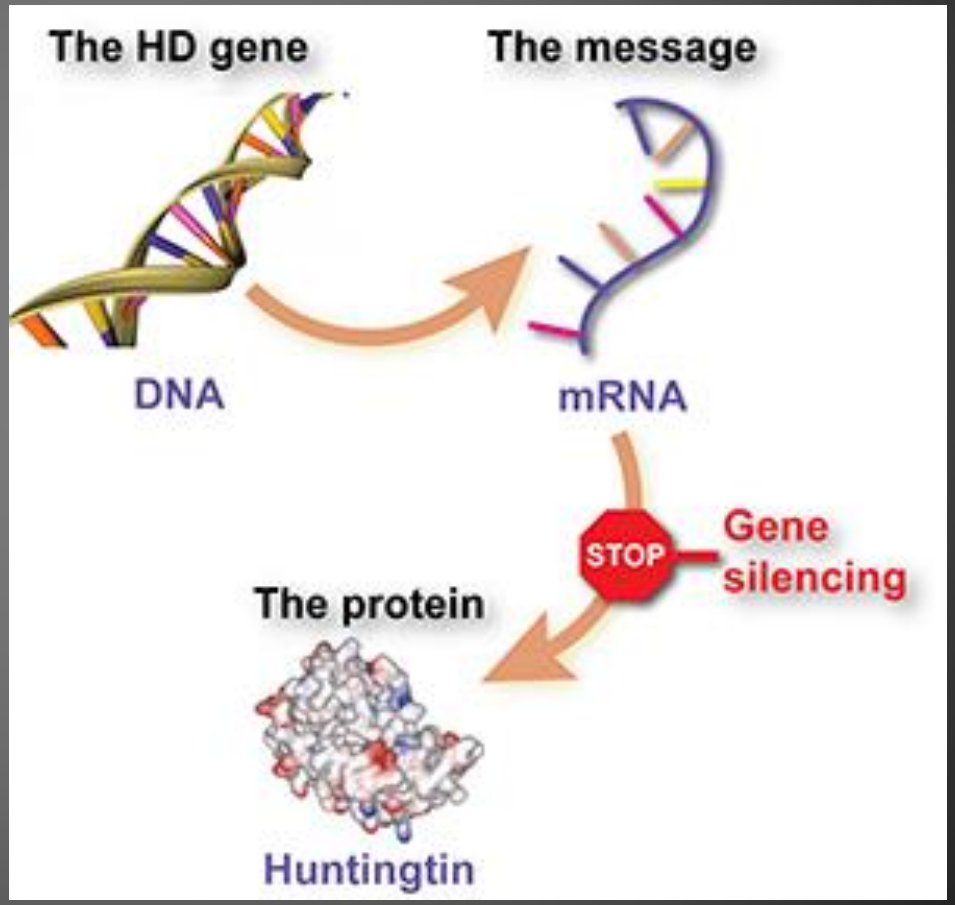
Prof TABRIZI, HD Centre UCL Institute of Neurology

IONIS PHARMACEUTICALS

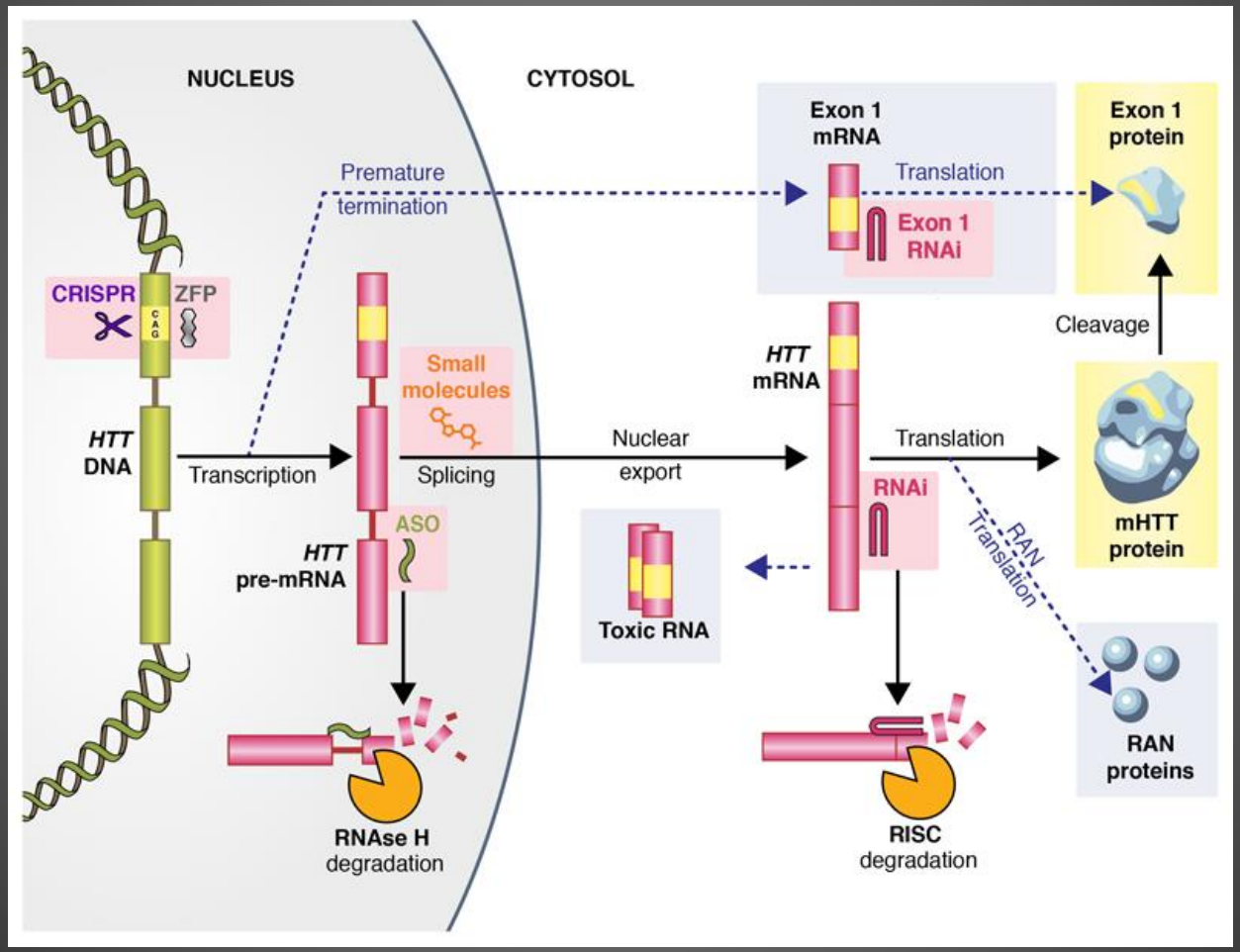
Roche

ISIS-HTT_{Rx} ou IOSIS-HTT_{Rx}

Diminution de la HUNTINGTINE
« silençage génique »



Mécanisme d'action



Wild et Tabrizi, Lancet Neurology 2017

IONIS-HTT$_{Rx}$: Histoire

2000: ASO: Antisens Oligonucleotides, médicaments révolutionnaires, protéinopathies

ISIS-394343 (Nusinersen ou *Spinarza*^{R}): Amyotrophie spinale (SMA) type I (autorisation pour usage compassionnel depuis le 13/4/2018)

2013: partenariat avec Roche pour le développement d'un ASO pour la MH

2015: Début de l'essai clinique

Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis

Holly B Kordasiewicz, Lisa M Stanek, Edward V Wancewicz, Curt Mazur, Melissa M McAlonis, ...

Neuron 74 (6), 1031-1044, 2012

The primary cause of Huntington's disease (HD) is expression of huntingtin with a polyglutamine expansion. Despite an absence of consensus on the mechanism(s) of toxicity, diminishing the synthesis of mutant huntingtin will abate toxicity if delivered to the key affected cells. With antisense oligonucleotides (ASOs) that catalyze RNase H-mediated degradation of huntingtin mRNA, we demonstrate that transient infusion into the cerebrospinal fluid of symptomatic HD mouse models not only delays disease progression but mediates a sustained …

Neurology® Journals

Discovery and early clinical development of ISIS-HTTRx, the first HTT-lowering drug to be tested in patients with Huntington's disease (PL01. 002)

Blair Leavitt, Sarah Tabrizi, Holly Kordasiewicz, Bernhard Landwehrmeyer, Scott Henry, Tom ...

Neurology 86 (16 Supplement), PL01. 002, 2016

Htt Lowering Interventions 1st generation

- Phase 1/2a:
- Essai exploratoire!
- Multicentrique: 3 sites RU, 2 sites en Allemagne et 1 site au Canada
- Traitement administré en bolus IT
- 4 doses/patient espacées de 28 jours

IOSIS-HTT$_{Rx}$ (RG6042)

Phase I/2a (juillet 2015 à novembre 2017): inclusion de 46 patients à un stade débutant

Résultats:

-Réduction de la HTT (LCR) dose administrée dépendante

-Tolérance et Innocuité

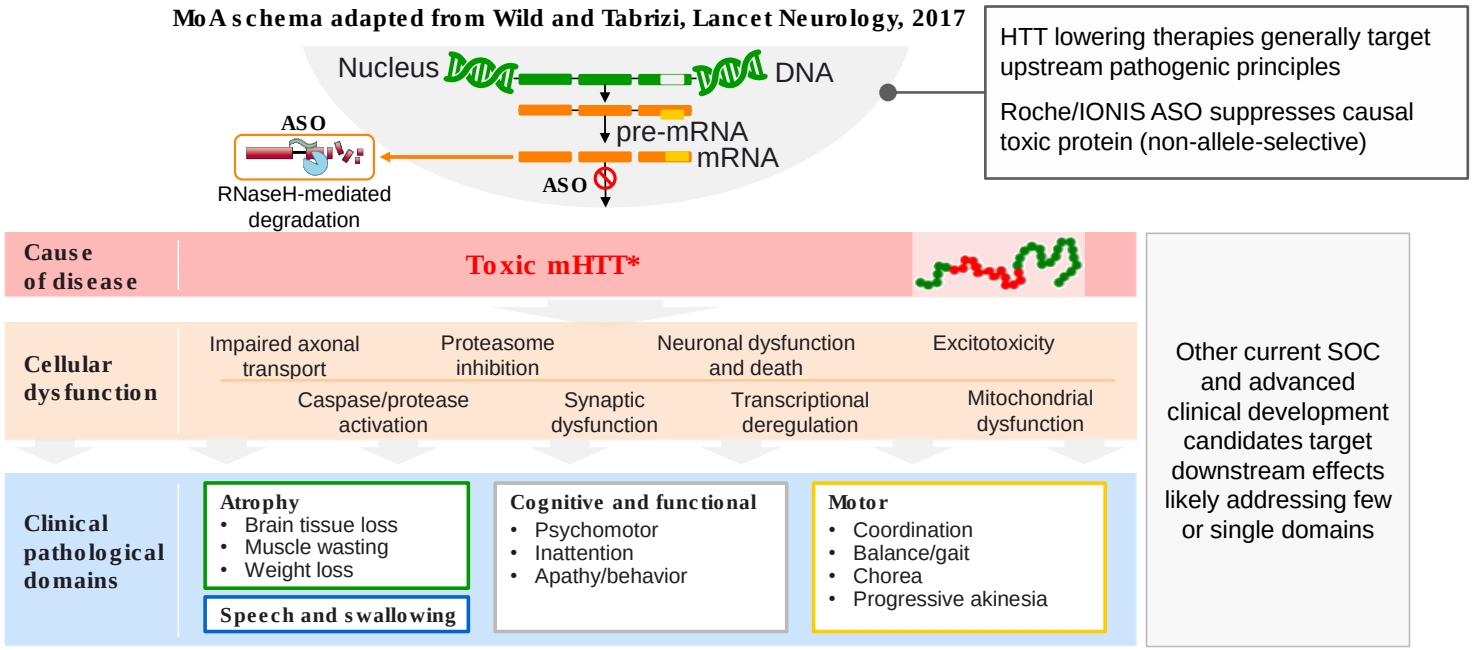
-Durée trop courte pour évaluer un effet clinique (diminution ou arrêt de progression de la maladie)

Résultats

Démonstration d'une diminution moyenne de 40% (jusque 60%) du taux de Huntingtine dans le LCR pendant 3 mois aux doses les plus élevées.

« La réduction de la protéine mutante observée est supérieure à la réduction nécessaire pour observer une modification de la maladie chez les modèles animaux » Tabrizi

HTT lowering therapies may slow or stop clinical progression



*Toxic mHTT=*HTT* 36+ CAG repeats.
ASO, antisense oligonucleotide; *HTT*, Huntingtin gene; HTT, Huntingtin protein; mHTT, mutant Huntingtin protein; MoA, mechanism of action; mRNA, messenger RNA; SOC, standard of care.
Wild EJ, Tabrizi SJ. *Lancet Neurol.* 2017; 16:837–847.

Non-allele-selective ASO selected for clinical development

Data from RG6042 to date suggest the non-allele-specific approach is well tolerated and has the broadest patient eligibility

- Non-allele-specific approach preferentially developed due to:
  - broad eligibility for all HD patients irrespective of individual SNP
  - ability to screen the entire *HTT* gene to identify a highly potent ASO with favorable safety profile

Preclinical safety	Preclinical efficacy	Pharmacology
• Lowering of total HTT in the CNS with irreversible (e.g. siRNA) or reversible (e.g. ASO) approaches appear safe in normal animals[1–3]	• Non-allele-specific ASOs have demonstrated efficacy in transgenic animal models, similar to allele selective approaches[1,2,4,5]	• RG6042 results in the dose-titratable, partial and reversible reduction of HTT • Approach appears well tolerated in Phase I/IIa and OLE • >200 doses of RG6042 have been administered in the OLE study to date

RG6042 (previously known as IONIS-HTTRx) is an investigational medicine and has not yet received regulatory approval in any country.
ASO, antisense oligonucleotide; HD, Huntington's disease; *HTT*, Huntingtin gene; HTT, Huntingtin protein; OLE, open-label extension; siRNA, small interfering RNA; SNP, single nucleotide polymorphism.
1. Kordasiewicz HB, *et al. Neuron* 2012; 74:1031–1044; 2. Drouet V, *et al. Ann Neurol.* 2009; 65:276–285; 3. Stiles DK, *et al. Exp Neurol.* 2012; 233:463–471; 4. Stanek LM, *et al. Hum Gene Ther.* 2014; 25:461–474; 5. Boudreau RL, *et al. Mol Ther.* 2009; 17:1053–1063. For further details see poster **J03**: Leavitt B, *et al.* Partial lowering of total huntingtin levels to treat adults with HD: Potential benefits and theoretical risks from human studies and animal models.

RG6042 Global Development Program

Today

Phase I/IIa study[1,2]

- First-in-human study
- Safety, tolerability, PK and PD
- Early manifest HD patients
- N=46

Open-Label Extension Study[3]

- Long-term safety, tolerability, PK and PD
- Early manifest HD patients
- 15 months follow-up
- N=46 *(participants of Phase I/IIa study)*

HD Natural History Study[4]

- Prospective, longitudinal study
- Early manifest HD patients
- 15 months
- N=100

Pivotal Phase III Study

- Long-term efficacy and safety
- Manifest HD patients
- 25 months (plus follow-up)
- N=660

HD, Huntington's disease; PD, pharmacodynamics; PK, pharmacokinetics.
1. ClinicalTrials.gov. NCT03342053; 2. Tabrizi S, *et al. Neurology*. 2018; 90(15 Suppl); Presented at AAN 2018 (Abstract CT.002); 3. ClinicalTrials.gov. NCT02519036;
4. ClinicalTrials.gov. NCT03664804.

IOSIS-HTT$_{Rx}$ (RG6042) Et la suite???

- Phase 3: Generation –HD1
- Durée de l'étude 25 mois
- 660 patients, âgés de 25 à 65 ans avec une MH symptomatique:

- 220 patients: Placebo
- 220 patients; RG6042 chaque mois
- 220 patients: RG6042, un mois sur deux et placebo un mois sur deux.

- Ensuite: Open-Label extension Study

IOSIS-HTT$_{Rx}$ (RG6042)
Et la suite???

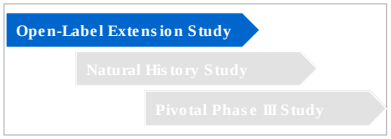
- Début 2019
- 80-90 sites à travers le monde (environ 15 pays)
- 1 journée à l'hôpital chaque mois pendant 25 mois
- Bonne tolérance de la Ponction Lombaire, des prises de sang et de l'IRM
- Monitoring des effets indésirables

IOSIS-HTT$_{Rx}$ (RG6042)
Et la suite: Phase 3 Generation HD1

- Critères d'éligibilité (patient):
- Âge: 25-65 ans
- CAP score >400
  (Nombre de répétition anormale CAG-33,66) x âge
- Echelle d'autonomie (Independance scale) ≥ 70
- … www.hdtrialfinder.org

Open-Label Extension (OLE) study of RG6042

Objective: Extend understanding of effects of anticipated therapeutic dose over longer follow-up



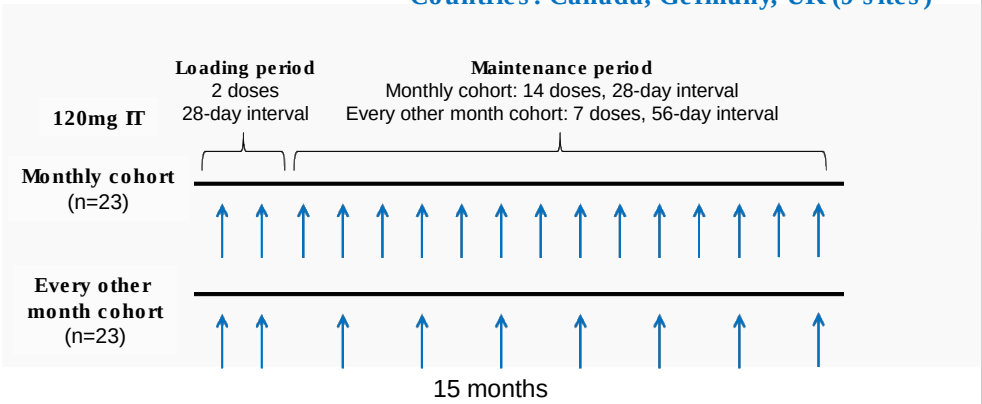
Ongoing study

Countries: Canada, Germany, UK (9 sites)

Key study features

- Early manifest HD patients (Stage I)
- Must have participated in Phase I/IIa study of RG6042
- Participants randomised to more vs. less frequent regimen (all participants to receive active drug in open-label setting)

n=46



Long-term safety, tolerability, PK and PD of RG6042 120mg in more vs. less frequent regimen

- Explore magnitude and sustainability of PD effect on CSF mHTT
- Explore effects on biomarkers and UHDRS clinical measures and linked digital clinical outcomes

CSF, cerebrospinal fluid; HD, Huntington's disease; IT, intrathecal; mHTT, mutant Huntingtin protein; PD, pharmacodynamics; PK, pharmacokinetics; UHDRS, Unified Huntington's Disease Rating Scale.
ClinicalTrials.gov. NCT03342053

IOSIS-HTT$_{Rx}$ (RG6042)
Et la suite: Phase 3 Generation HD1

- Critères d'éligibilité (patient):
- Âge: 25-65 ans
- CAP score >400
  (Nombre de répétition anormale CAG-33,66) x âge
- Echelle d'autonomie (Independance scale) ≥ 70
- … www.hdtrialfinder.org

GENERATION HD1 – RG6042 Pivotal Phase III study design

Objective: Evaluate efficacy and safety of intrathecally-administered RG6042 in adult patients with manifest HD

Study launch planned for end of 2018 with patients enrolling by early 2019

Countries: ~15 countries worldwide (80–90 sites)

Randomised, multicenter, double-blind, placebo-controlled study

Key inclusion criteria

- Clinically diagnosed manifest HD (DCL=4)
- Aged 25–65 years
- CAP >400
- Independence scale > or equal to 70
- Ambulatory, verbal

n=660

R 1:1:1

RG6042 120mg monthly (Q4W) (n=220)
(Q4W IT bolus)

RG6042 120mg bimonthly (Q8W) (n=220)
(Q4W RG6042 120mg for doses 1–2, thereafter, RG6042 120mg alternating with placebo Q4W IT bolus)

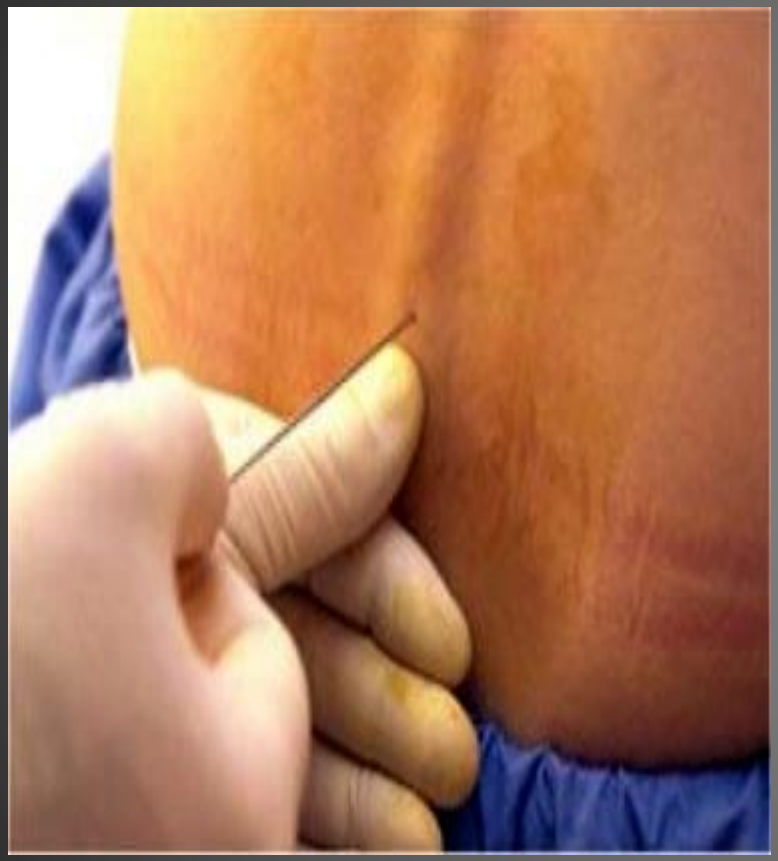
Placebo monthly (Q4W) (n=220)
(Q4W IT bolus)

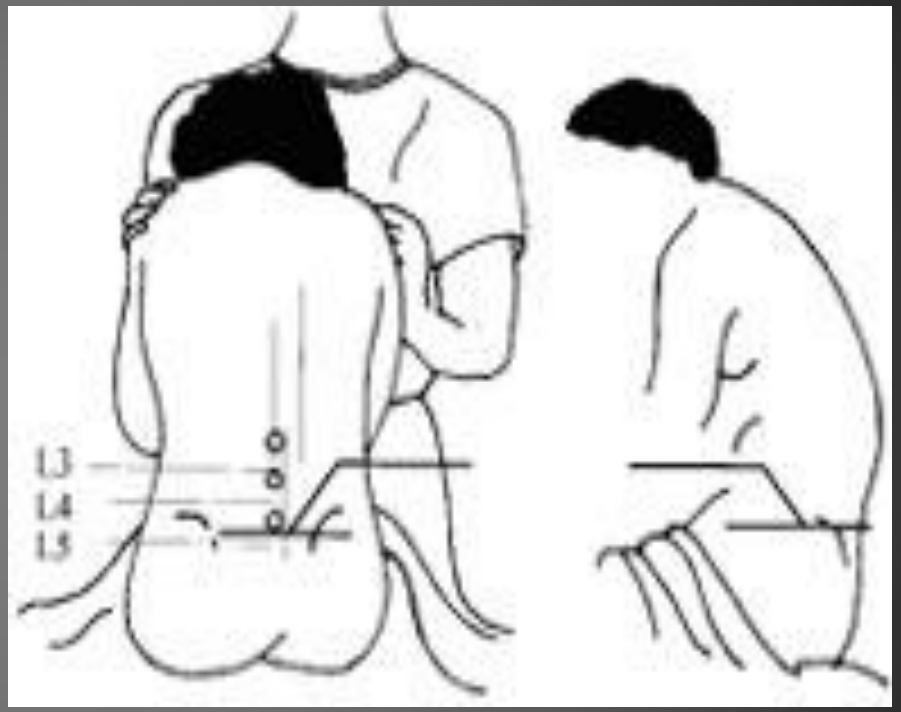
25 months (plus follow-up)

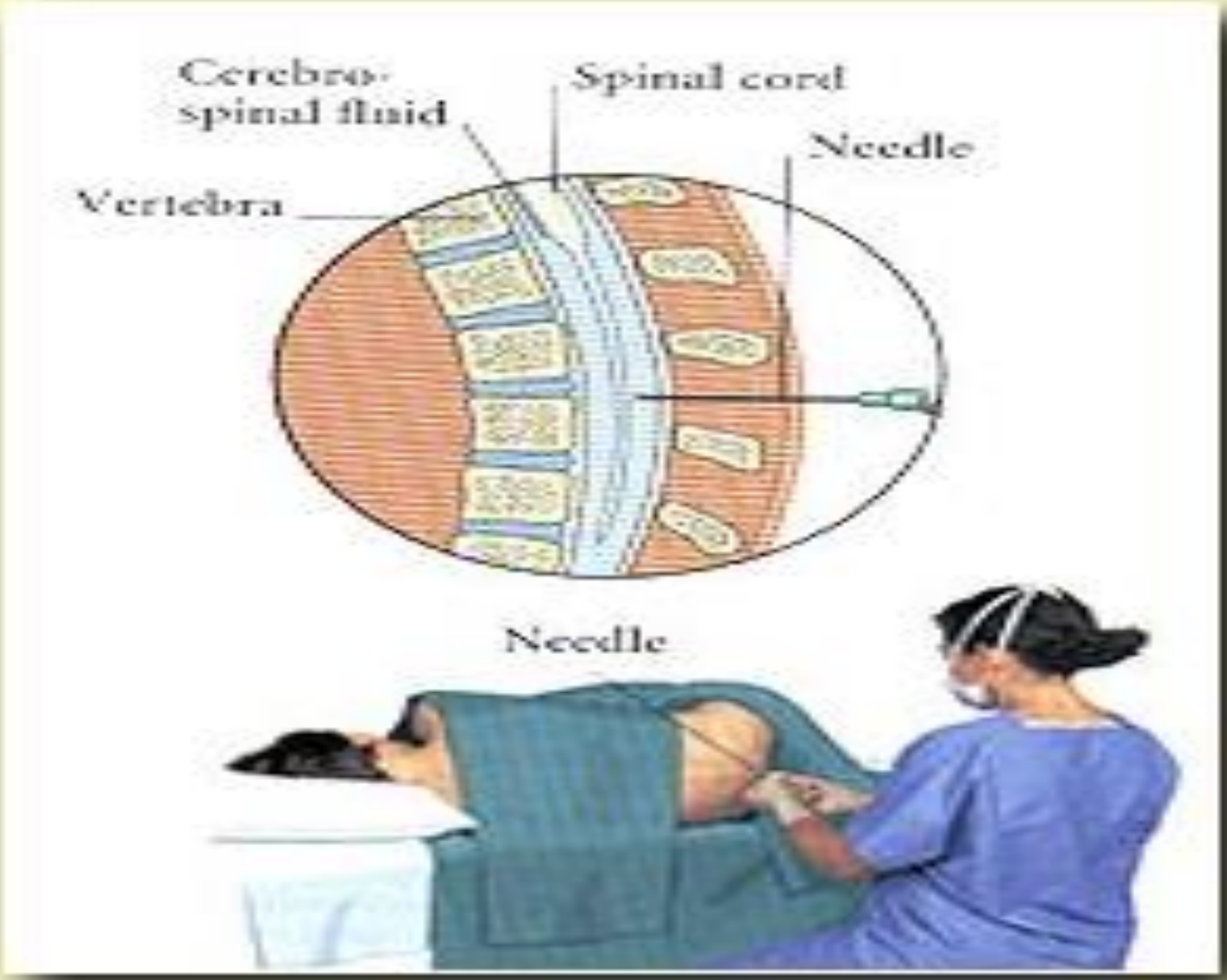
Open-label extension RG6042 monthly or bimonthly (optional)*

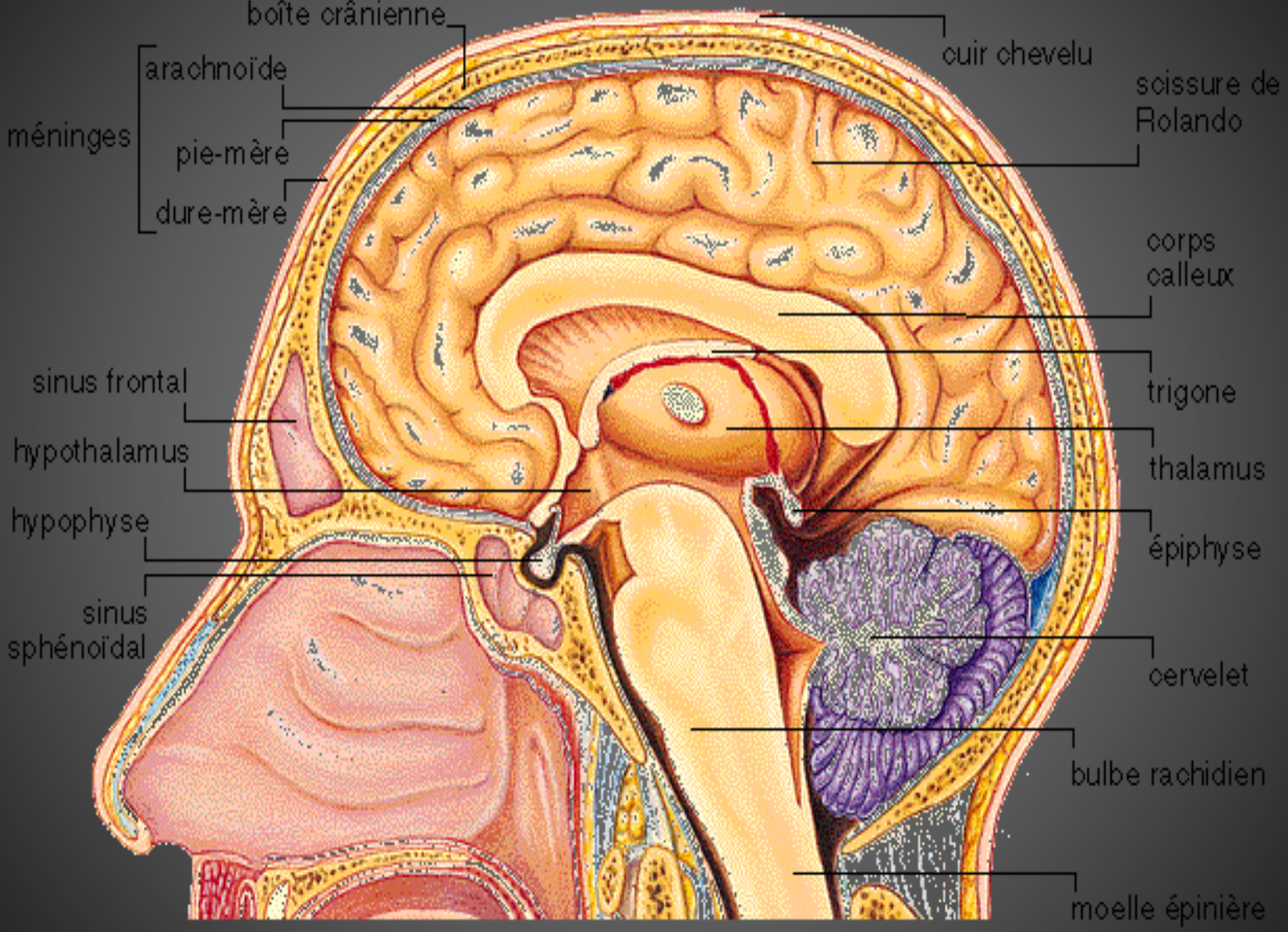
Inclusion criteria for pivotal study are broader than OLE and HD NHS studies†

*Provided participants meet eligibility criteria, the data for RG6042 support continued development and the study is approved by Authorities and Ethics Committees/Investigational Review Boards.
†Pivotal Phase III study protocol is pending approval by Health Authorities, Investigational Review Boards and Ethics Committees.
CAP, CAG-age product; DCL, diagnostic confidence level; GENERATION HD1, Global EvaluatioN of Efficacy and Safety of Roche/Genentech AnTIsense OligoNucleotide for Huntington's Disease; HD, Huntington's disease; IT, intrathecal; NHS, Natural History Study, OLE, open-label extension; Q4W, once-a-month.




L3
L4
L5


Cerebro-
spinal fluid
Spinal cord
Needle
Vertebra
Needle


boîte crânienne
cuir chevelu
méninges
arachnoïde
pie-mère
dure-mère
scissure de Rolando
corps calleux
sinus frontal
trigone
hypothalamus
thalamus
hypophyse
épiphyse
sinus sphénoïdal
cervelet
bulbe rachidien
moelle épinière

Céphalées post PL

- **Il existe une relation entre l'incidence des céphalées et la taille de l'aiguille.**
- Le décubitus ne prévient pas leur survenue
- Il faut encourager une ***bonne hydratation*** (boissons, perfusion si nécessaire).
- Des antalgiques simples comme le paracétamol, ou la codéine sont peu efficaces, tout comme l'augmentation de la pression abdominale qui augmente la pression péridurale. Le sumatriptan utilisé pour le traitement des migraines a été proposé. La ***caféine*** du thé, du café et du Coca-Cola sont utiles.
- Les céphalées prolongées peuvent être traitées par la réalisation d'un ***blood-patch*** péridural de 15 à 20 ml de sang prélevé au patient et injecté selon une procédure stérile


Merci pour votre
attention