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Gene Therapy for Neurodegenerative Diseases

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Neurodegenerative diseases targeted by Brainvectis

Huntington's disease (HD):

- 60 000 patients in Europe
- leads to death after 15-20 years

Alzheimer's disease (AD):

- > 35 millions patients today
- 115 millions in 2050

Spino-Cerebellar Ataxias (SCA)

- Rare disease, 3/100 000
- Ataxia, severe disability

Other rare diseases

→ **Severe diseases**

→ **Life threatening**

→ **No treatment today**

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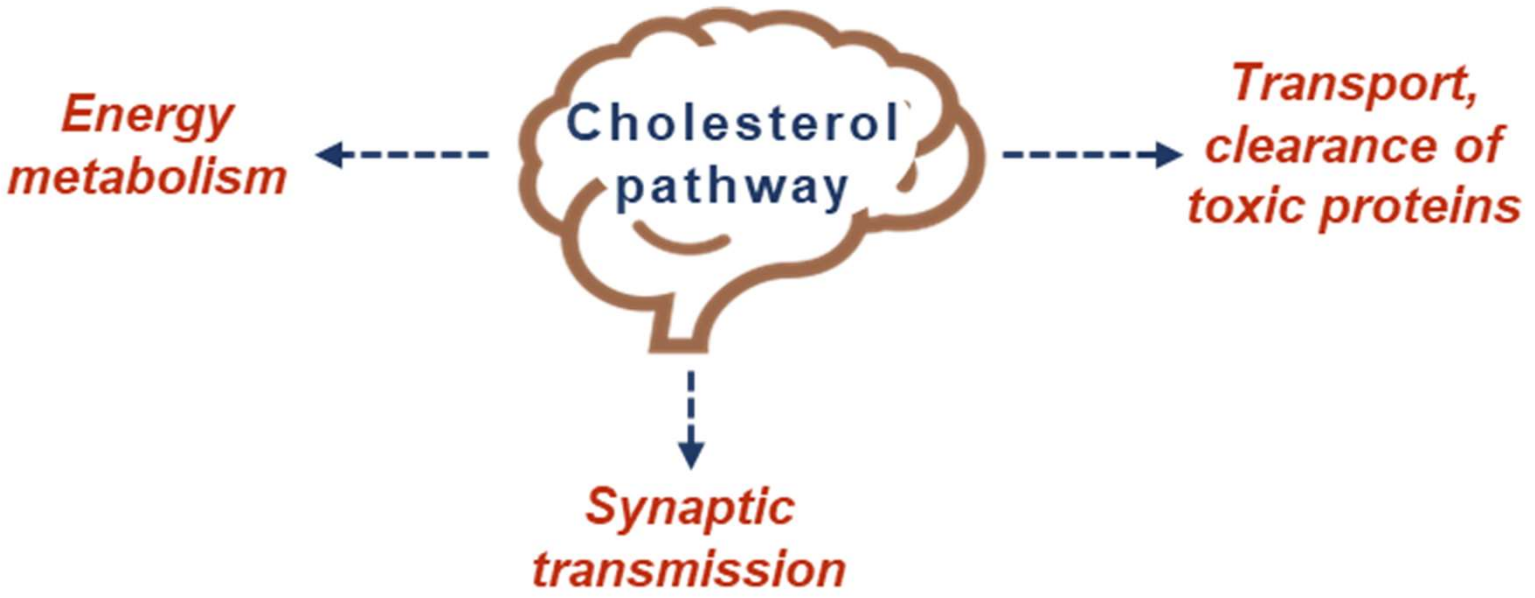
Therapeutic strategy (1)

We restore **cholesterol pathway in the brain,** a key mechanism which is impaired in neurodegenerative diseases.



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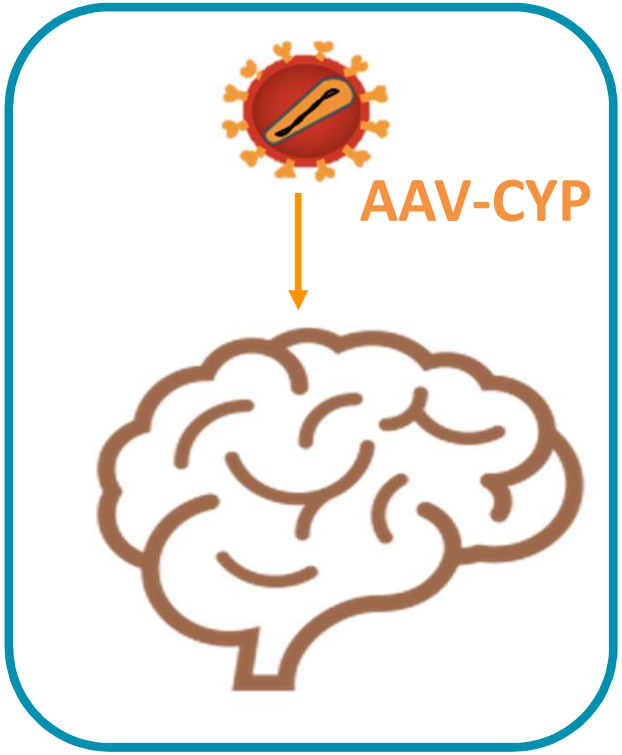
Therapeutic strategy (2)

- Target **CYP46**, the key enzyme to normalize brain cholesterol level
- Overexpress **CYP46** in specific disease brain areas
- By gene therapy
- Using an AAV vector
- **One-time administration**



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Results obtained

CYP46 validated as a relevant therapeutic target

- Converging results in patients and in mouse models of the diseases

Proof of concept obtained with AAV-CYP46

- 2 animal models of HD
- 4 models of AD
- 2 models of SCA
- Other PoC on going.

6 articles
3 patent families

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Results obtained: Highlights

AAV-CYP46

- Restores cholesterol metabolism
- Decresases toxic protein aggregates: Amyloïd (AD), Tau (AD), Huntingtin (HD)
- Prevents neuronal death, cerebral atrophy and memory deficits
- Corrects coordination and behavior defects
- In a dose dependent manner

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Brainvectis pipeline

Time to clinic : 2 years for Huntington

	Target validation	Proof of concept	Primate studies	Regulatory preclinical studies	Clinical phase 1/2
HUNTINGTON	2 mouse models			2018	2020
ALZHEIMER	4 mouse models				
SC ATAXIA	2 mouse models		2018		
Rare dis. N					
Rare dis. R		2018			
Rare dis. A		2018			

- 2M€ raised up to now + 1,1 M€ grants and public aids

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Brainvectis core team

- Jérôme Becquart, PhD CEO
- Nathalie Cartier, MD Inserm, CSO
- Sandro Alves, PhD director preclinical research
- LS, PhD Project leader Huntington, non-clinical development

- Alexandra Durr, MD, PhD, clinical ref. center HD and SCA, Paris
- Anne-Catherine Bachoud-Lévi, MD, PhD, clinical ref. center HD, Paris
- Michel Zerah, MD neurosurgeon, Necker Hospital, Paris
- Nicolas Ferry, MD, PhD, Regulatory consultant

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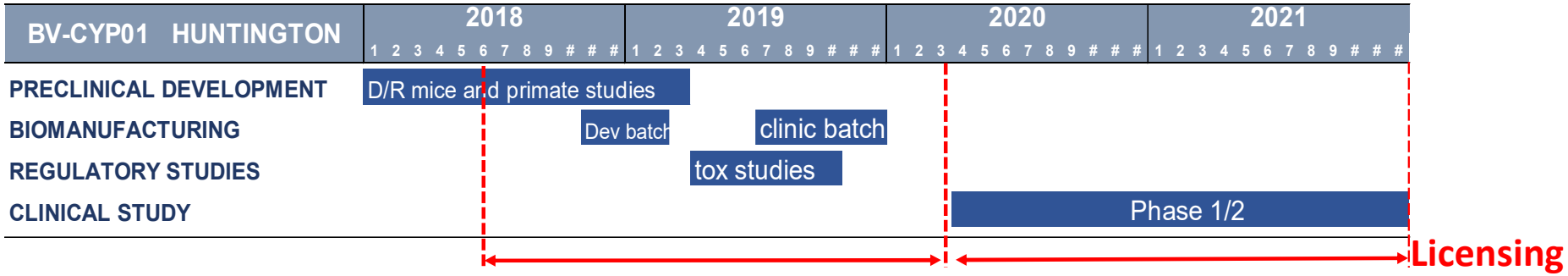
Business model and financial needs

Business model:

- Set up a Gene Therapy platform for neurodegenerative diseases
- License to Pharma after clinical proof of concept: in 2022 for Huntington

Needs : 9M€ to finance clinical proof of concept in Huntington's disease (pre-money valuation: 10M€)



Total needs :	6,5 M€	5 M€
Investors	5 M€	4 M€
Grants & aids	1,5 M€	1 M€

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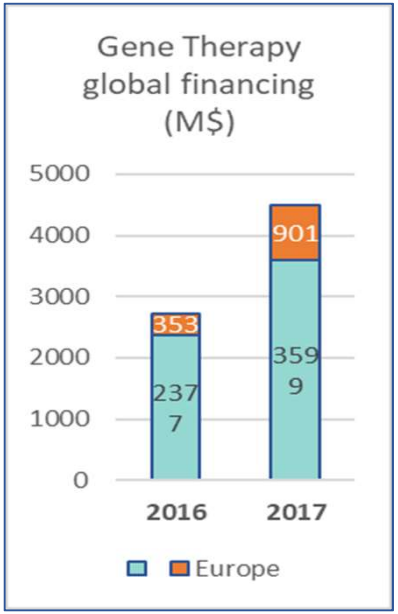
Gene Therapy: a favorable environment

- Increasing investments: $4.5 Billion in 2017
- **IPO**: AveXis (2016) , Audentes (2016), Gensight (2016), Cellectis (2016), Lysogene (2017)
- **Industrial deals**: Isis/Roche, Voyager/Sanofi-Genzyme, Spark/Pfizer, Bamboo/Pfizer, Sangamo / Pfizer, AveXis/Novartis (8,7 MM$, may 18)



- **On the market**: Glybera (LPLD, UniQure 2012), Strimvelis (ADA-SCID, GSK 2016), Zalmoxis (GVHD, Molmed 2016), Imlygic (Melanoma, Amgen 2016), Luxterna (Retinal disease, Spark 2017)
- **Clinical trials**: 313 in 2017: 113 (Ph. I), 170 (Ph. II), 30 (Ph. III)
- Encouraging clinical results for : adreno-leukodystrophy, hemophilia, spinal amyotrophy, Parkinson disease, retinal disseases,…

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Key points

Brainvectis targets cholesterol metabolism in the brain to treat neurodegeneratives diseases

Validated approach

Curative Therapy

One time administration

For multiple neurodegenerative conditions

We are 2 years from the clinic in Huntington's disease

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Backup slides

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Brain cholesterol is essential to neuronal functions

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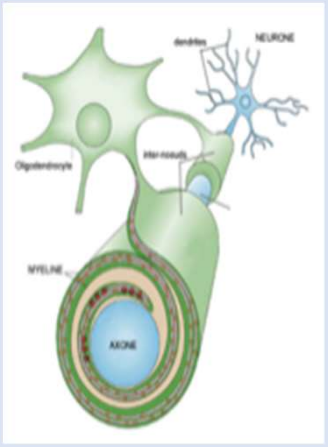
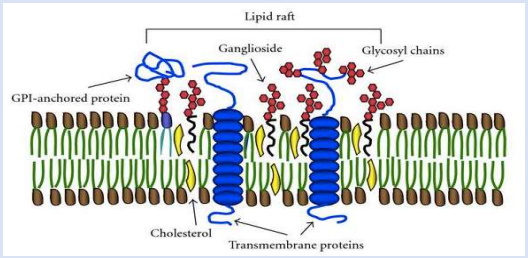
2% body weight

25 % total cholesterol

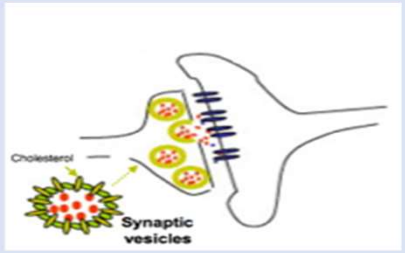
Myelin (70%)



Neuronal membrane (30%)



Synapses



Signaling

Synaptic functions

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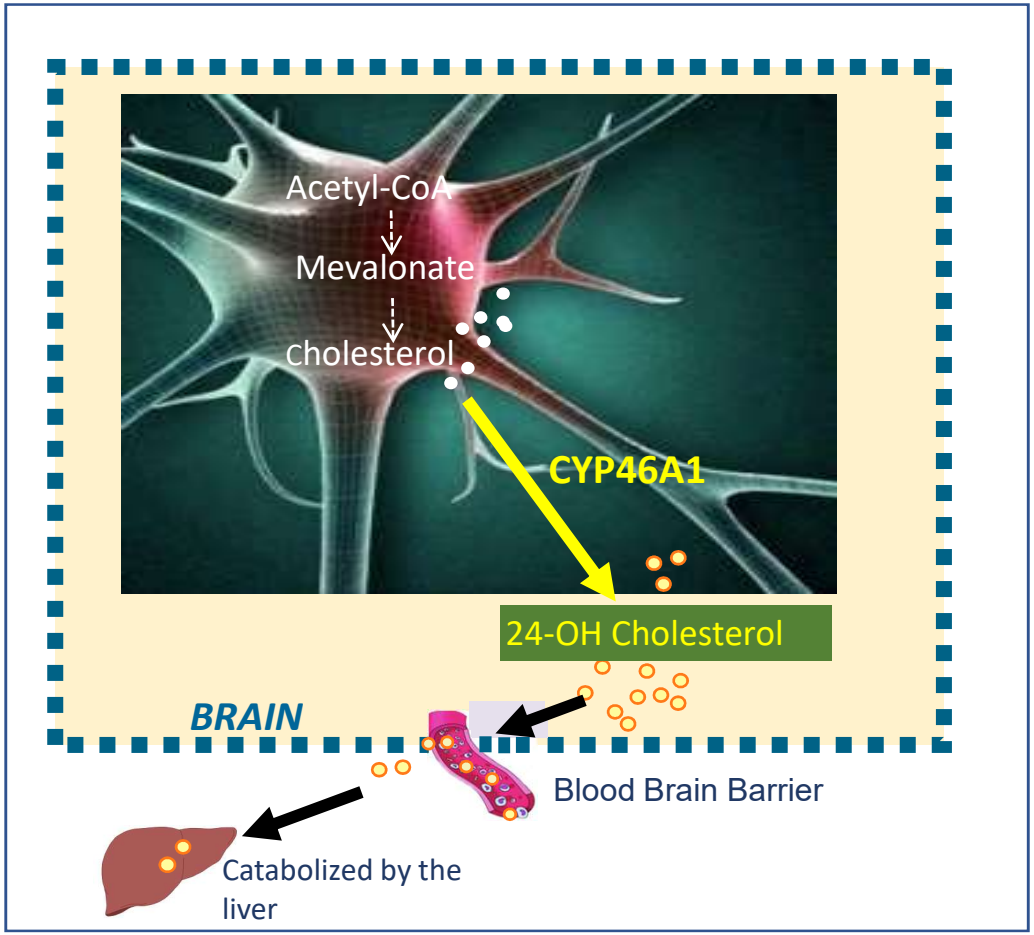
CYP46A1, a key brain enzyme

- **CYP46A1** controls membrane cholesterol removal from the brain[1]
  - **CYP46A1** converts cholesterol into 24-OHcholesterol
  - Cholesterol cannot cross the blood brain barrier, 24-OH cholesterol does
- **CYP46A1** is brain specific[1]
- **CYP46A1** is a major stress response factor in the brain (aging, oxidative stress, neurotoxic conditions, aggregates)[2]



1- Lund et al PNAS 1999, Lutjohann et al PNAS 1996
2-Sodero et al., J Neurochem 2011

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CYP46A1 is a validated target

Converging results validate CYP46A1 as a relevant therapeutic target

- **CYP46A1 is decreased** in affected regions of the brain in patients and mouse models of neurodegenerative diseases[1-4]
- **Cholesterol precursors** are decreased in the brain of patients and mice models
- **CYP46A1 inhibition** in specific brain regions mimics disease phenotype in normal mice[1-4]
- **CYP46A1 polymorphism** was associated with increased risk for AD [5] and retinal diseases (AMD, glaucoma)[8]
- **CYP46A1 KO** mice show **cognitive defects** [6]
- **CYP46A1 improves cognition** in aged transgenic mice [7]

1- Hudry et al Mol Ther 2010
2- Burlot et al Hum Mol Gen 2015
3- Dielti et al Brain 2015
4- Boussicault et al Brain 2016
5- Russell et al Annu. Rev. Biochem. 2009
6- Kotti et al PNAS 2006, 2008
7- Maioli et al PloS One 2013
8- Bretillon et al Invest. Ophtal. 2005

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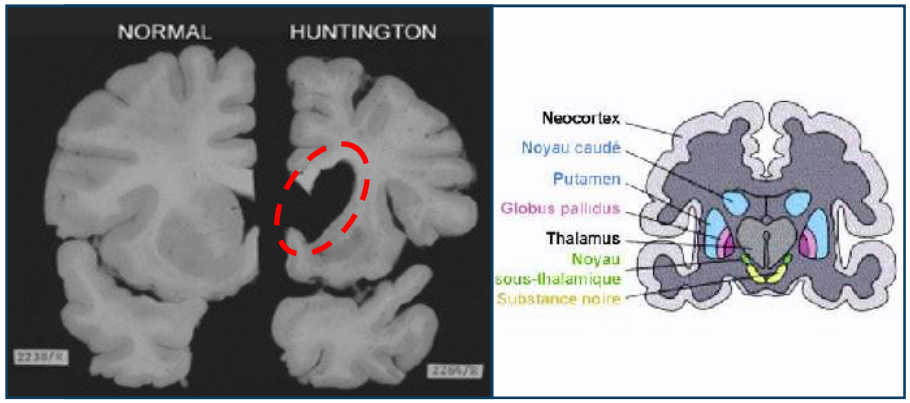
Huntington's disease (HD)

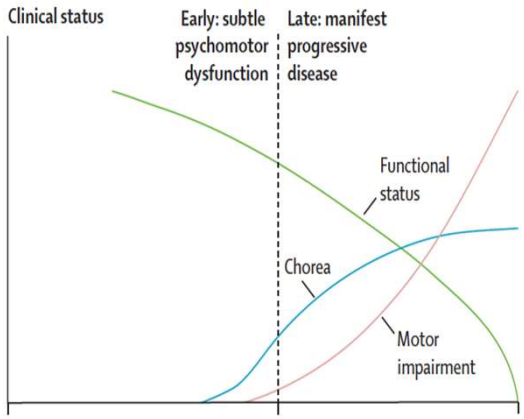
Huntington's disease is a chronic, progressive and irreversible condition

- HD is an autosomal dominant genetic disease (1/10.000).
- HD affects adults (30 to 50 years) and leads to death 15 to 20 years after disease onset.
- HD is caused by an elongated CAG repeat (> 36 repeats) in the Huntingtin gene leading to abnormal polyglutamine **(polyQ) accumulation** in the mutant Huntingtin (muHTT) protein.
- HD is caused by both accumulation of muHTT and deficit of normal HTT.

HD leads to progressive loss of medium spiny neurons



Ross, Tabrizi, lancet neurol 2011



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Intellectual property

- BrainVectis has obtained a worldwide exclusive license to use AAV-CYP46A1 to treat Alzheimer's disease and Huntington's diseases.
- Both patents have been granted in Europe and in the US.
- We filed in January 2017 an application for polyQ Ataxias
- FTO analysis : no licensing agreement for our AAV vector is needed since they will be in the public domain at NDA time.

Huntington

- PCT/EP2011/068033, priority 15 Oct 2010
- US 9,132,173 granted
- EP 2 627 359 granted, national phase in 12 countries: FR,GE,UK,ES,IT,BE,LU,CH,IRL,NT,FI,HO

Alzheimer

- PCT/EP2008/062047, priority 12 Sept 2007
- US 8,198,257 B2 granted
- EP 2 187 898 granted, national phase in 12 countries: FR,GE,UK,ES,IT,BE,LU,CH,IRL,NT,FI,HO

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