Leader in the treatment of HERV-mediated diseases

Arrêter les maladies neurodégénératives et autoimmunes

Février 2018

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GeNeuro's mission

To develop therapies that improve the life of patients with neurodegenerative and autoimmune diseases

- Through leveraging the biology of human endogenous retroviruses (HERVs) to stop key causal factors associated with these disorders

- The HERV field is a new frontier pioneered by GeNeuro since 2006, based on 15 years of R&D at Institut Mérieux and INSERM.

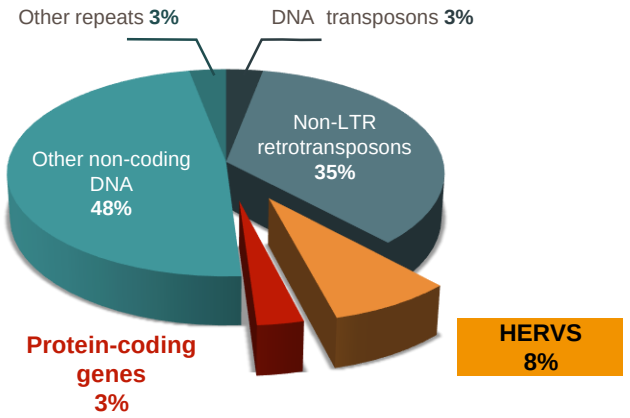
- Initially focusing on Multiple Sclerosis and Type 1 Diabetes, both in Phase II clinical trials

Human Endogenous Retroviruses (HERVs)

Ancestral retroviral genomic (DNA) insertions

HERV elements are latent in human genome

- Represent approximately 8% of total human genome
- Genetic transposition leads to variable copy number, with non-ubiquitous copies in individuals
- HERVs are normally latent but may be de-repressed and transcribed to produce viral proteins



Missing link between viral infections and poorly understood autoimmune / neurodegenerative diseases

- Strong epidemiology data associates environmental viruses with these diseases
- However environmental viruses do not appear to play a direct role in their development
- These viruses may de-repress HERV proteins upon infection of permissive cells
- Pathogenic HERV proteins have been implicated as causal factors in autoimmune / neurodegenerative diseases

nature medicine

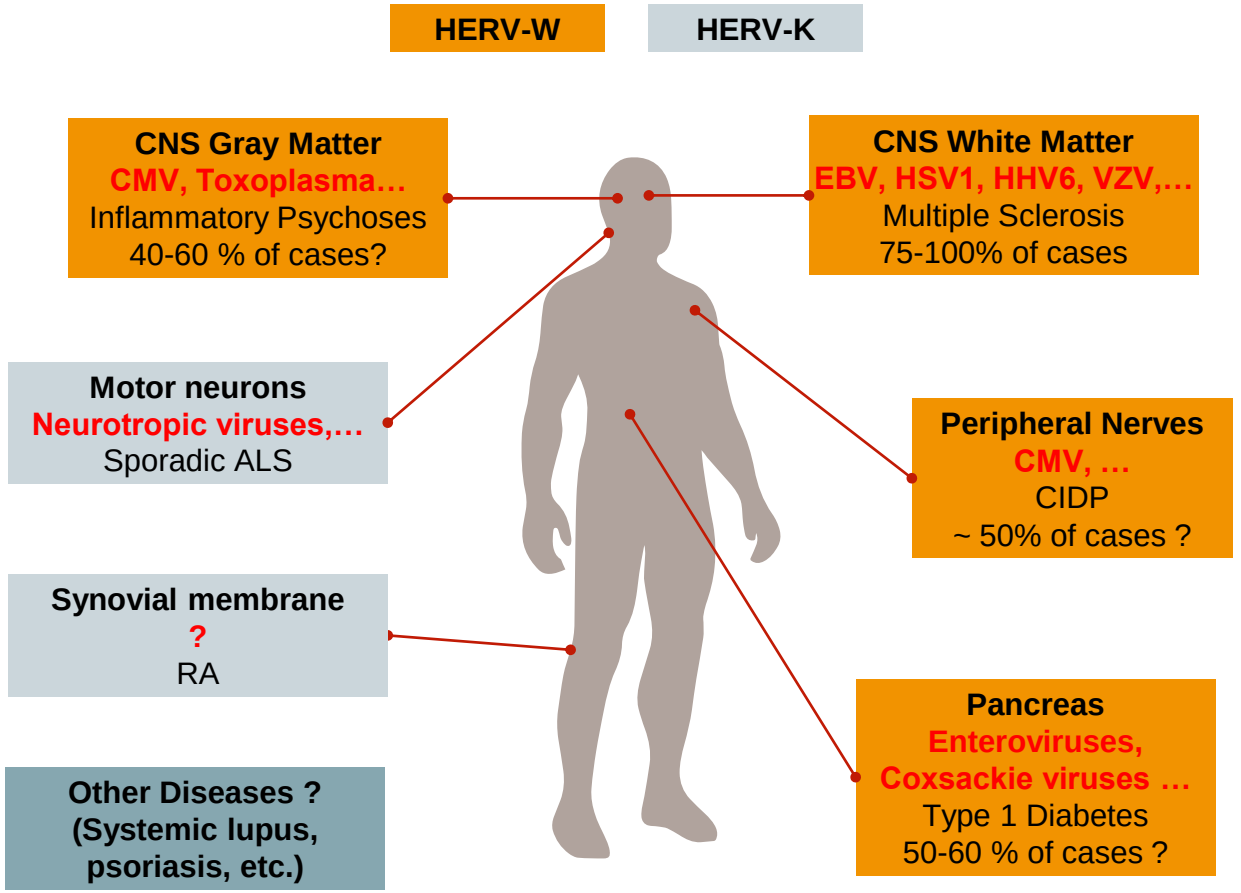
The enemy within: dormant retroviruses awaken
Engel & Hiebert, Nature Medicine, 2010

Regulatory evolution of innate immunity through co-option of endogenous retroviruses; Science, Vol. 351, Issue 6277
Discovery of unfixed endogenous retrovirus insertions in diverse human populations. Proc Natl Acad Sci U S A. 2016
Human Endogenous Retrovirus Type W Envelope Protein Inhibits Oligodendroglial Precursor Cell Differentiation; Ann Neurol. 2013;74(5)A

Viruses triggering HERV Proteins and link to disease

Examples of pHERV Env mediated diseases

Suspected transactivating viruses and affected organs



- Pathogenic HERV proteins found at high levels in affected organs
- Pathogenicity is generally mediated by (abnormally expressed) viral envelope proteins – pHERV Env
- pHERV Env directed toxicities found in:
  - Microglia
  - OPCs
  - Pancreatic beta islet cells
  - Neurons
  - Schwan cells
  - Others…

Antony Nature Neuroscience 2006; Perron et al.J Gen Virol 1993; Ruprecht & Perron JAMA 2005; Christensen Rev Med Virol 2005; Nellaker Retrovirology 2006 ; Frank et al. J Infect Dis. 2006; Brown AS. Schizophr Bull. 2006; Vandenberghe et al Amyotroph Lateral Scler. 2010; Arias et al. Schizophr Res. 2012; Leboyer et al.World J Biol Psychiatry. 2013; Fung et al. Cell Death Differ. 2015. Freimanis et al. A role for human endogenous retrovirus-K (HML-2) in rheumatoid arthritis Clin Exp Immunol. 2010

First mover in HERV-mediated diseases

Program	Pre-clinical	Phase I	Phase IIa	Phase IIb	Phase III
1. GNbAC1 Multiple Sclerosis – RRMS Multiple Sclerosis – SPMS	**270 patients / 50 centers** in the RRMS indication / Data expected 1Q2018 Review possible options after 48-week results				SERVIER Partnership (ex-US & Japan)
2. GNbAC1 Type1D	Proof-of-concept Phase IIa Launched April 2017 / Data expected 3Q2018				
3. GNbAC1 CIDP	Proof-of-concept Phase IIa trial in preparation				
4. Other Anti HERV-W products & approaches Inflammatory Psychosis					
5. Other anti-HERV approaches (HERV-K in ALS)	R&D Agreement with NIH in ALS				

A well-crafted partnership in MS with Servier GeNeuro retains US rights

1 Option agreement

- Option payment of €37.5 million
- Ongoing Phase IIb trial in MS led by GeNeuro
- Post Phase IIb option to license GNbAC1 in MS **ex-USA and Japan**
- Exercised in December 2015 its option to buy 8.6% of GeNeuro for €15 million
- Launch of ANGEL-MS study, fully funded by Servier

2 Licensing agreement

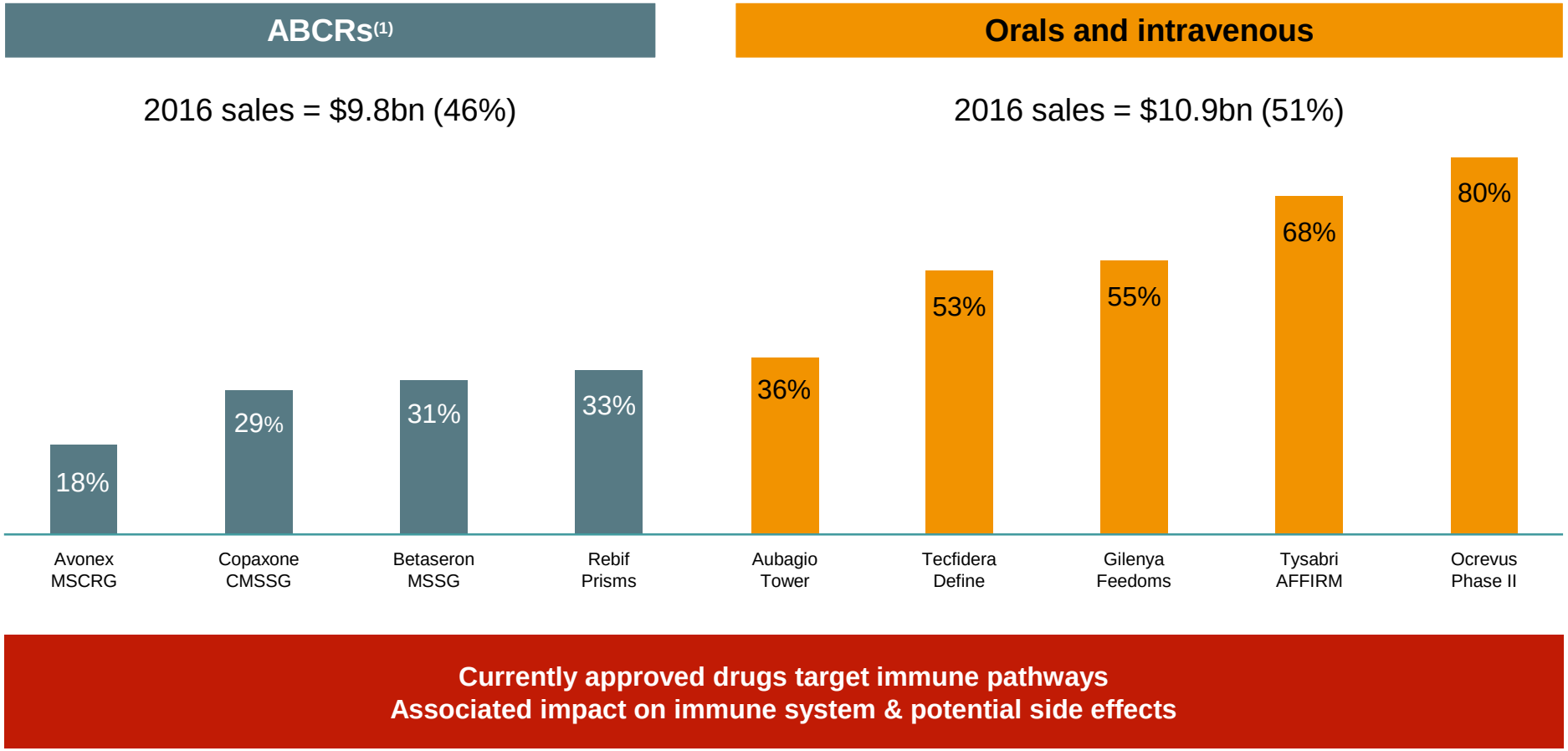
- Global Phase III financed by Servier
- Up to €325 million in development and sales milestones
- Tiered royalties on future sales up to mid-teens
- Right of first negotiation on GNbAC1 in other indications in Servier territories

GeNeuro retains rights for US & Japan (67% of WW MS) **and other GNbAC1 indications**

GeNeuro development in MS

RRMS landscape today: current treatment paradigm focuses on relapse control

Reductions of relapse rate by leading MS drugs (data from 2-year Phase III clinical trials)



(1) ABCR = Avonex-Betaseron-Copaxone-Rebif

Sources: 2016 company filings & announcements, Sorensen S. New management algorithms in multiple sclerosis, Current Opinion Neurology 2014,27,246-258.; Cohen JA. Lancet, 2012, L.Kappos Lancet 2011

Critical unmet medical need: MS inevitably leads to progressive disability

MS at first diagnosis (Post CIS)

Relapsing-remitting: 85%

Primary progressive: 15%

Few drugs for progressive forms of the disease

Patient evolution

8 out of 10 people who are diagnosed with relapsing-remitting MS develop secondary progressive MS

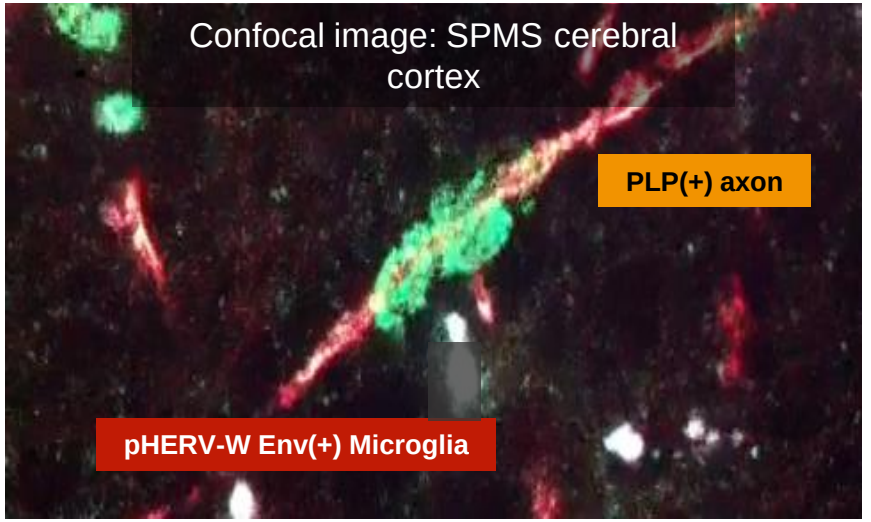
Secondary progressive

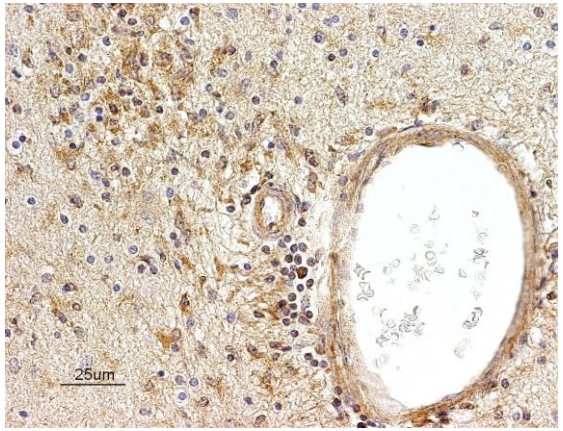
No drugs prevent conversion from RRMS to SPMS

Source: National MS Society; Atlas of MS 2013.

Presence of pathogenic HERV-W Env (pHERV-W Env) in the brain

- Pathogenic pHERV-W Env is highly expressed in MS patients
  - Found in 100% of MS brain lesions
  - Also found in 75% of patients' blood
  - Expression in the brain correlates with lesion activity
  - Detected in areas of active demyelination from earliest to latest stages of disease

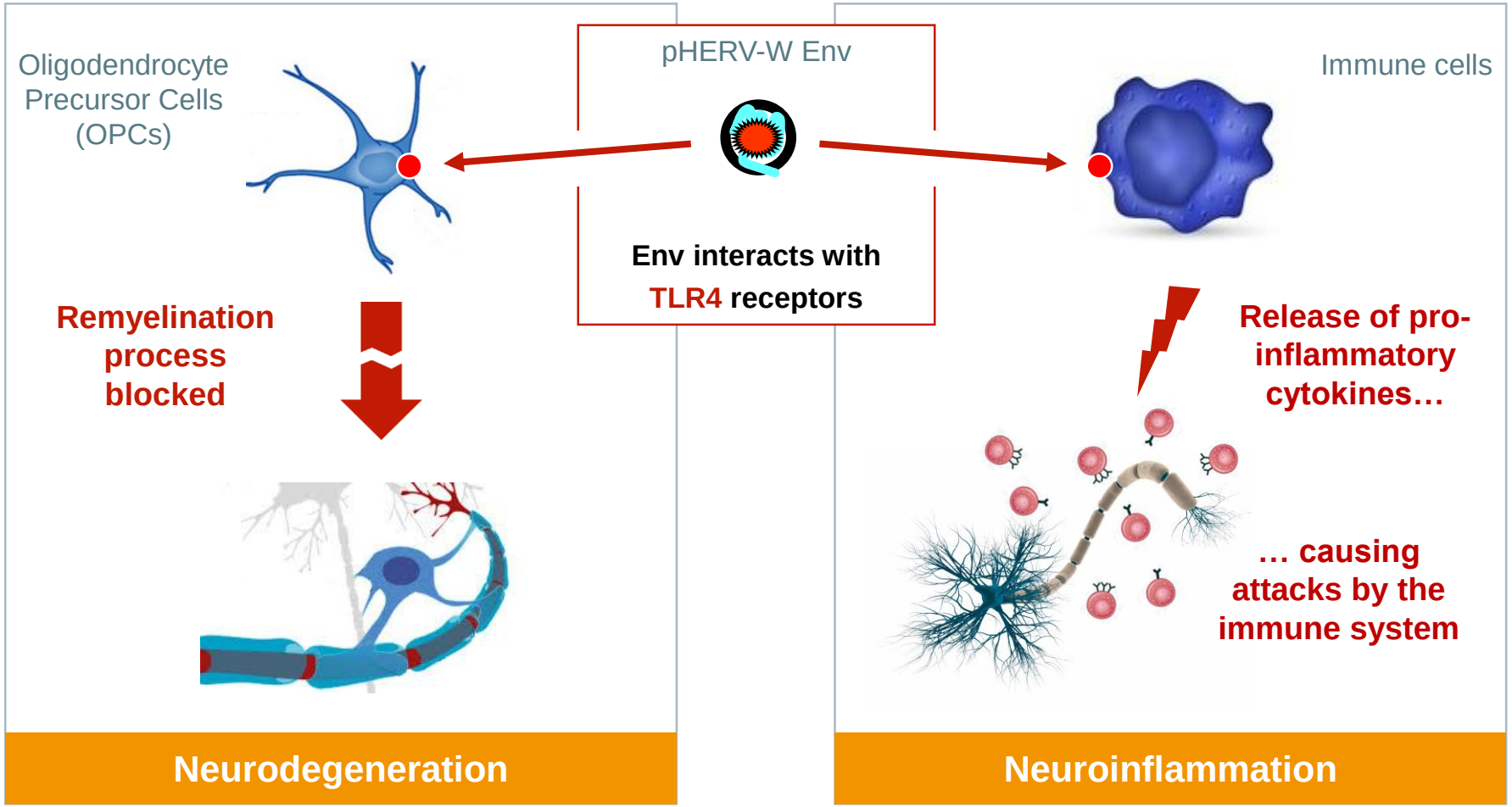




pHERV-W Env positive infiltrating perivascular macrophages in early demyelinating lesion
Van Horssen et al., MS & Related Disorders 2016

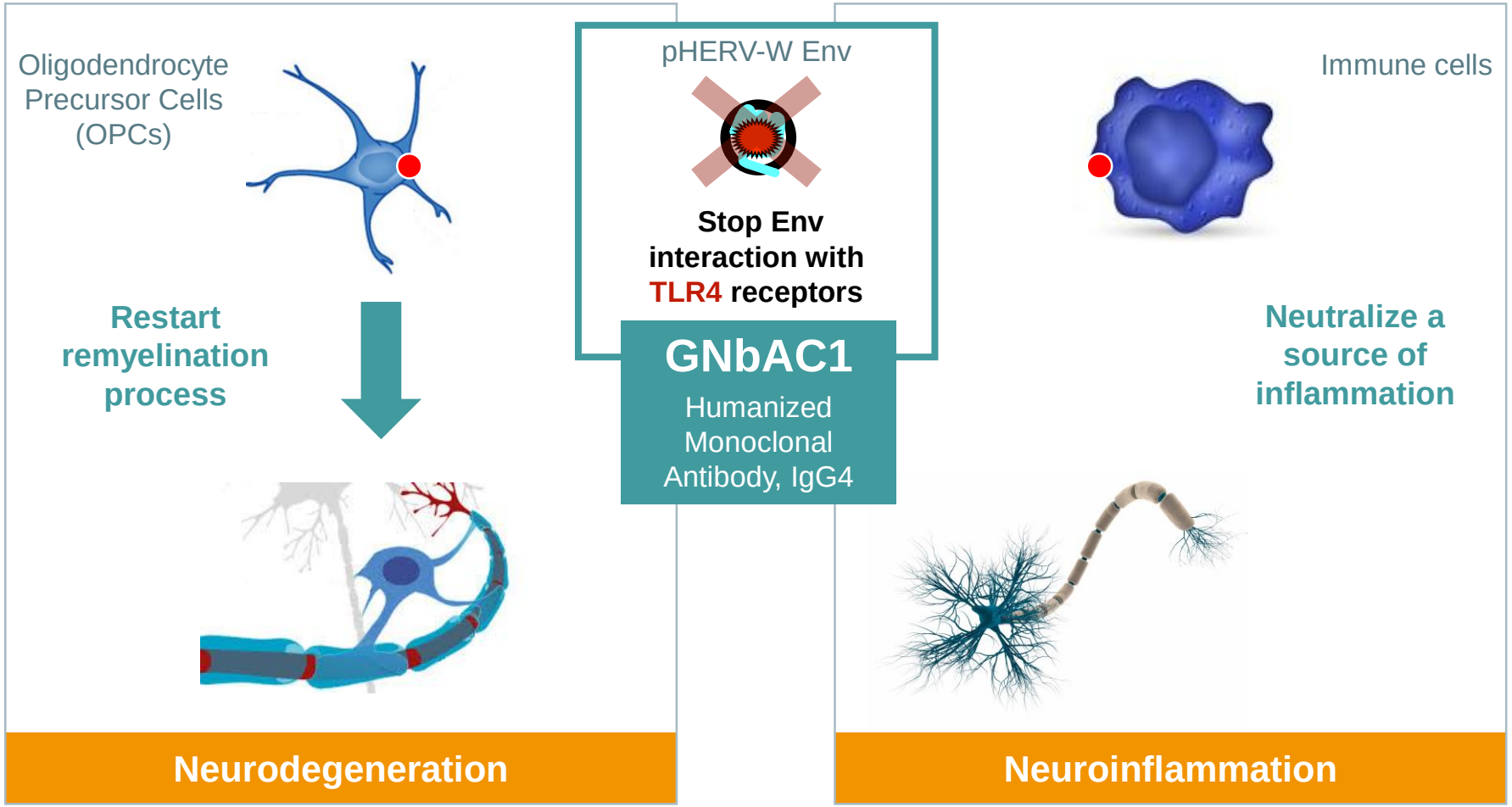
Sources: Perron et al., MS Journal, 2012 & Van Horssen et al.,MS & Related Disorders 2016 & Rolland et al., J Immunol, 2006 & Antony et al., Nat NeuroSci, 2004 & Kremer et al., Ann. Neurol, 2013 & Perron et al., PLOS One, 2013, Madeira et al., J Neuroimmunol 2016

pHERV-W Env's mode of action in MS: fueling inflammation AND neurodegeneration



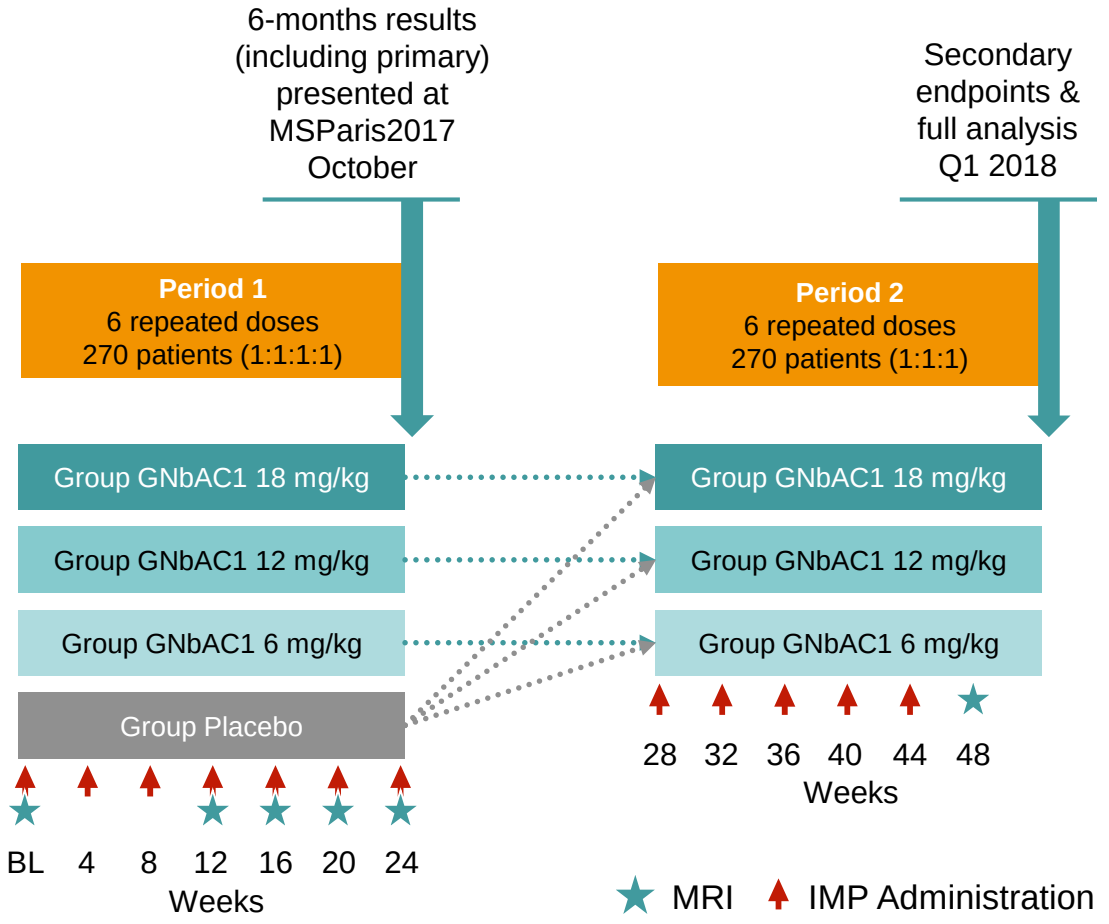
Sources: Antony Nat NeuroSci 2004; Rolland et al., J Immunol 2006; Kremer et al Ann Neurol 2013; Madeira et al., J Neuroimmunol 2016

GeNeuro's GNbAC1 targets pHERV-W Env, to act on inflammation AND neurodegeneration



CHANGE-MS Phase IIb trial: confirm GNbAC1's efficacy
Full results 1Q2018

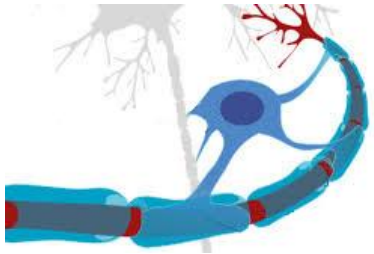
- International, randomized, double-blind, placebo-controlled Phase 2b study
- RRMS patients, 18 – 55
- EDSS 0 – 5.5
- 1 attack in the prior year or 1 Gd+ lesion within 3 months of screening, concomitant DMTs not allowed
- 1° Endpoint: Total # Gd+ lesions on brain MRI scans at weeks 12, 16, 20 and 24
- Remyelination endpoints: change in MTR in NAWM, cerebral cortex and lesions



Summary of CHANGE-MS 24-week results

Restart remyelination process

+ Strong increase in MT signal in NAWM and in Cortex already visible at 24 weeks



Neurodegeneration

GNbAC1

Humanized Monoclonal Antibody, IgG4

+ Excellent safety and tolerability

Neutralize a source of inflammation

– Failed **primary** of cumulative number of new Gd+ lesions and other inflammatory markers

+ Statistically significant reduction of lesions in active population at week 24 (post-hoc)

Neuroinflammation

GNC-003 (CHANGE-MS) week 24 safety results

No safety or tolerability issues over 24 weeks

	GNbAC1 **6 mg/kg N=67**	GNbAC1 **12mg/kg N=66**	GNbAC1 **18 mg/kg N=67**	Placebo **N=68**
24-week completers	60 (90%)	59 (90%)	64 (95%)	66 (97%)
SAE	1	1	0	2
Serious-related AE*	0	1	0	0
AE leading to early termination	2	1	1	0
AE leading to death	0	0	0	0

* Macroscopic hematuria: resolved

GNC-003 (CHANGE-MS) week 24 efficacy results

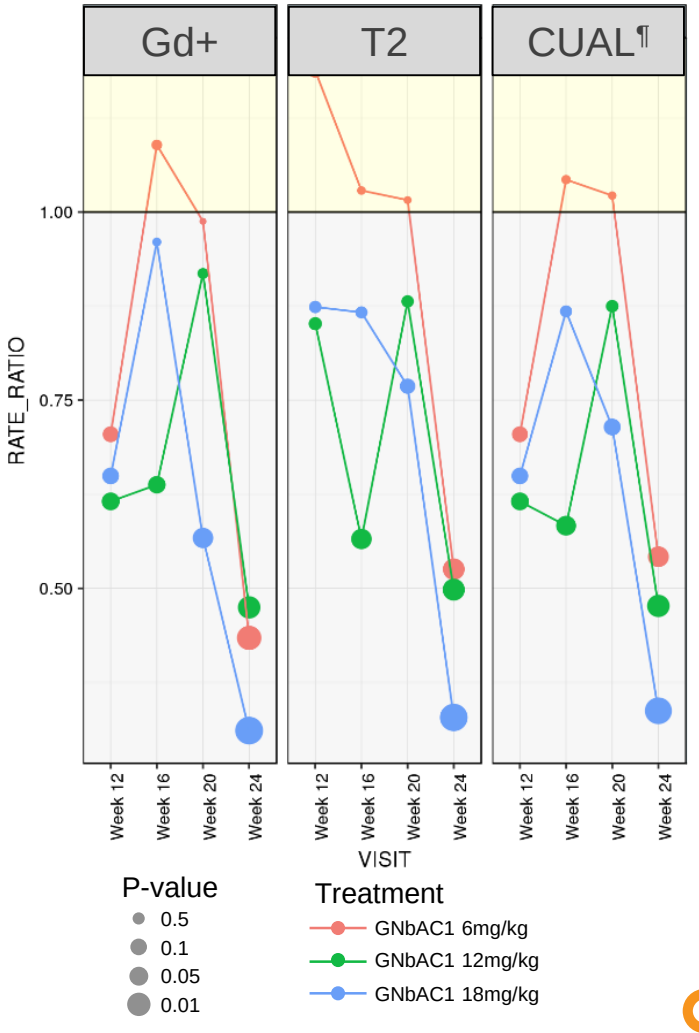
No effect on inflammatory measures over weeks 12 - 24

			GNbAC1 6 mg/kg	GNbAC1 12mg/kg	GNbAC1 18 mg/kg	Placebo
Primary Endpoint						
Total Gad+ lesions	Week 12 -24	# of lesions	510	407	339	666
		Mean (Med) P value	8.4 (2.0) p = 0.539	6.9 (2.0) p = 0.704	5.3 (1.0) p = 0.481	10.1 (1.5)
Secondary Endpoints Secondary endpoints include: total # new/enlarging T2 / CUAL / T1 BH; T2 / T1 BH volume, ARR, EDSS, MSFC, MSQOL-54						
% change in whole brain volume	Baseline – week 24	Mean (Med)	-0.32 (-0.13)	-0.35 (-0.22)	-0.24 (-0.16)	-0.34 (-0.35)
# of relapses	Baseline – week 24		18 p = 0.492	21 p = 0.217	21 p = 0.291	15
Total Gd+ lesions	Week 24	Mean (Med) P value	2.7 (1.0) p = 0.103	2.3 (0) p = 0.907	2.0 (0) p = 0.083	4.1 (0)

GNC-003 (CHANGE-MS) week 24 post-hoc analyses

Evidence for delayed onset of anti-inflammatory effect in active patients+ at 18 mg/kg

- When analyzing “Active* Population”, the potential benefit of treatment appears at week 24 for the 18mg/kg arm
- Effect appears to be consistent across MRI endpoints
- 18 mg/kg dose consistently numerically superior to other doses**
- Benefit to be confirmed in W48 data, due end 1Q2018

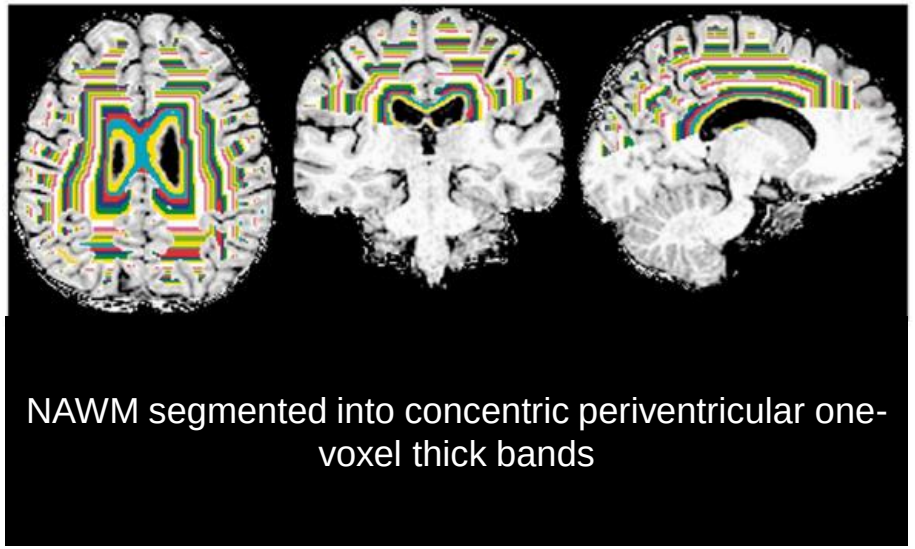


* Had at least 1 Gd+ lesion on their Baseline brain MRI scan
** No adjustment for multiplicity was made
¶ Combined Unique Active Lesions

Magnetization Transfer Ratio (MTR) measures at W24

Evidence for remyelination with highest dose vs. placebo in NAWM and Cortex

- In MS patients, MTR is reduced versus healthy controls throughout normal-appearing white matter (NAWM) and cerebral cortex
- The pathological gradient between MTR bands was reproduced in the CHANGE-MS study
- At 24 weeks, individual NAWM bands showed a positive increase of MTR, with statistical trends in favor of GNbAC1 at 18mg/kg
- At 24 weeks, individual Cortex bands showed a positive increase of MTR, with statistical trends in favor of GNbAC1 at 18mg/kg
- **To be confirmed in W48 data, due end of 1Q2018**



NAWM segmented into concentric periventricular one-voxel thick bands

Next steps for development in MS

Assess Phase IIb 48-week results at end of 1Q2018

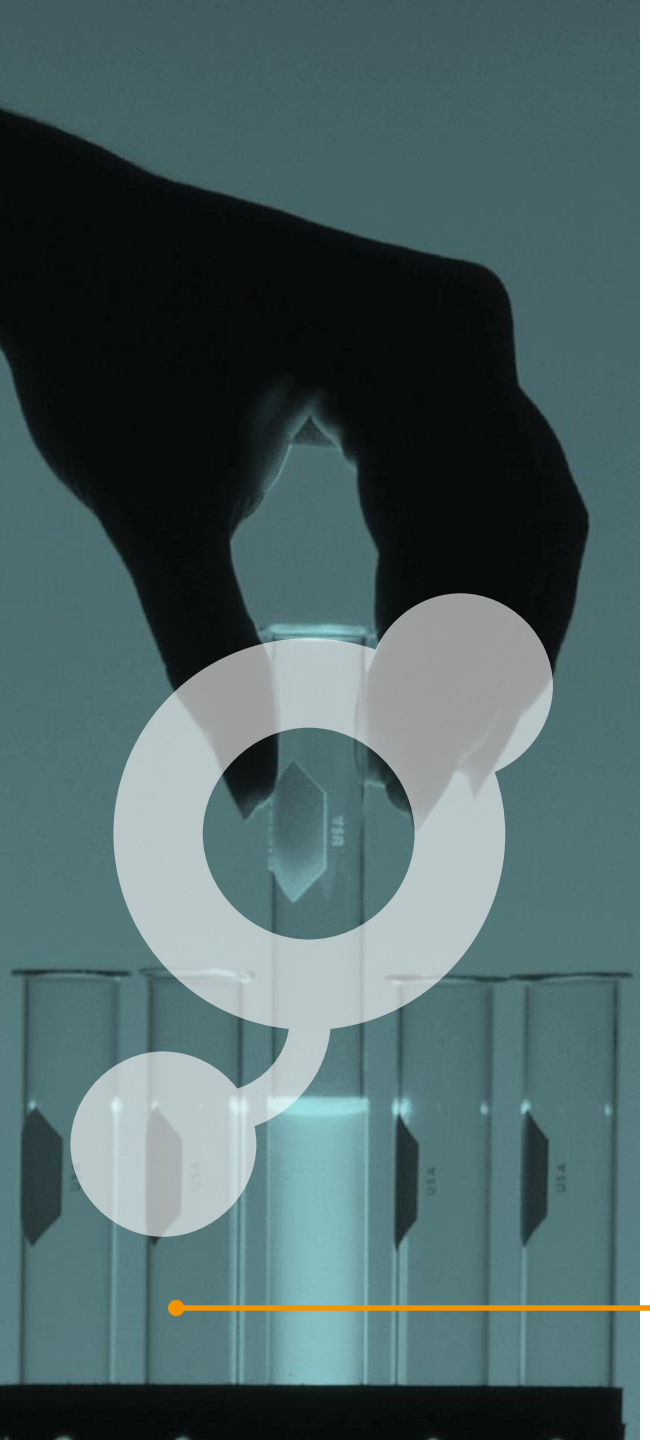
- Safety and tolerability
- Inflammatory endpoints
- Remyelination endpoints
- Biomarkers

Define path forward in terms of population to treat

- RRMS, and / or
- Progressive forms of MS
- MS subgroups
- Identification of responders based on biomarkers

Define path forward in terms of possible comparators / combinations

- As a single agent against comparator, and /or
- In combination with existing DMTs



GeNeuro development in T1D

T1D Unmet medical needs

No disease modifying therapies available today

Efficient management of glucose levels

- Insulin replacement therapies are not satisfactory over the long term
- >50% of adults with T1D have an A1C >8%
- Severe consequences of poor glucose level control include renal, ophthalmic, cardiac, vascular and nervous system dysfunctions and deficiencies
- Significant risk of coma and death by hyperglycemia or hypoglycemia

Preservation of remaining insulin production at diagnosis

- Residual β-cell function may prevent ketoacidosis for many years
- Preservation of endogenous insulin production is the best prognosis against T1D co-morbidities

Early diagnosis

- Understanding pathophysiology of T1D and early diagnosis with a biomarker could facilitate T1D treatment and possibly preserve pancreatic function

International Diabetes Federation (IDF) – Diabetes World Atlas 2015

Type 1 Diabetes : RAINBOW Study update
Fully recruited trial

- Placebo controlled randomized Phase IIa on GNbAC1 with 60 recently diagnosed T1D patients in Australia
  - Testing GNbAC1 6 mg/kg vs placebo (2:1 randomization) over 6 months
  - Safety and Pharmacodynamic efficacy endpoints as main objectives
    - Safety in new patient population
    - Link between response and pHERV-W Env biomarkers
    - Efficacy measures to assess maintenance of insulin production (C-peptide)
    - Other T1D-related biomarkers such as insulin consumption, glycaemia, anti-beta cells antibodies
    - Pharmacokinetics and Pharmacodynamics
  - 6 month open-label extension has started with first patients in November

- **6-month results in 3Q2018**

Next steps for development in T1D

RAINBOW – ongoing Phase IIa trial in Australia

- FPFV 2Q2017
- Recruitment completed end 2017, on schedule
- LPFV end 4Q2017
- Results by 3Q2018

Review of RAINBOW Results

- Safety and tolerability in this new population
- GNbAC1 impact on T1D clinical measures
- Relationship between response and levels of pHERV-W Env biomarkers

Discussion with the regulatory authorities for further development

- Pivotal Phase IIb/III in adults
- Pediatric development plan

Creating value in other indications

Develop new approach against ALS

Pathology

- Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord
- 60% of the people with ALS are men and 93% of patients are Caucasian

Rationale for HERV-K Env as a causal factor

- HERV-K proteins are expressed in the brains of ALS patients
- HERV-K Env was observed in the anterior horn of the spinal cord, the site of lower motor neurons that degenerate in ALS
- HERV-K Env expression induces toxicity in human motor neurons
- Signs of motor dysfunction observed in transgenic mice expressing HERV-K Env

Market

- 6,000 people in the U.S. are diagnosed with ALS each year. As many as 20,000 Americans have the disease at any given time.
- No cure today. Current treatments modestly extend life span and manage patient comfort (median survival time from onset is 20 to 48 months)

Development stage

- Partnership with the National Institute of Neurological Disorders and Stroke (NINDS), part of the U.S. National Institutes of Health (NIH)
- GeNeuro provides antibodies to block the activity of HERV-K envelope protein
- NINDS tests antibodies in cellular and animal models of HERV-K associated ALS
- Goal: to achieve preclinical proof-of-concept of this novel therapeutic avenue addressing ALS pathogenesis

Sources: “Human endogenous retrovirus-K contributes to motor neuron disease”, Li et al, Sci Transl Med. 2015 Sep 30; ALS Association (www.alsa.org)

Develop new approach against Inflammatory Psychosis

Pathology

- Inflammatory psychosis include schizophrenia and bipolar disorder observed in patients presenting an inflammatory syndrome marked with a increase in C-reactive protein
- Symptoms include hallucinations, delusions, paranoïa leading to social withdrawal, BD is characterized by episodes of agitation and elation or depression

Rationale for HERV-W Env as a causal factor

- HERV-W Env and Gag proteins are increased in the PBMC and serum of 50% to 60% of patients with SCZ and BD correlated with an increase of C-reactive protein
- HERV-W genes and proteins are expressed in the cortex of patients with psychotic disorders
- Demyelination due to HERV-W Env could participate to the neuropsychiatric dysfunction
- HERV-W triggered by Influenza, Herpes or T gondii – germs epidemiologically associated with SCZ

Market

- About 1% of the population worldwide suffers from psychotic disorders
- No curative treatments exist today: antipsychotic drugs or mood stabilizers are symptomatic treatments but frequently these drugs do not prevent mental handicap and social withdrawal, at the price of severe side effects

Development stage

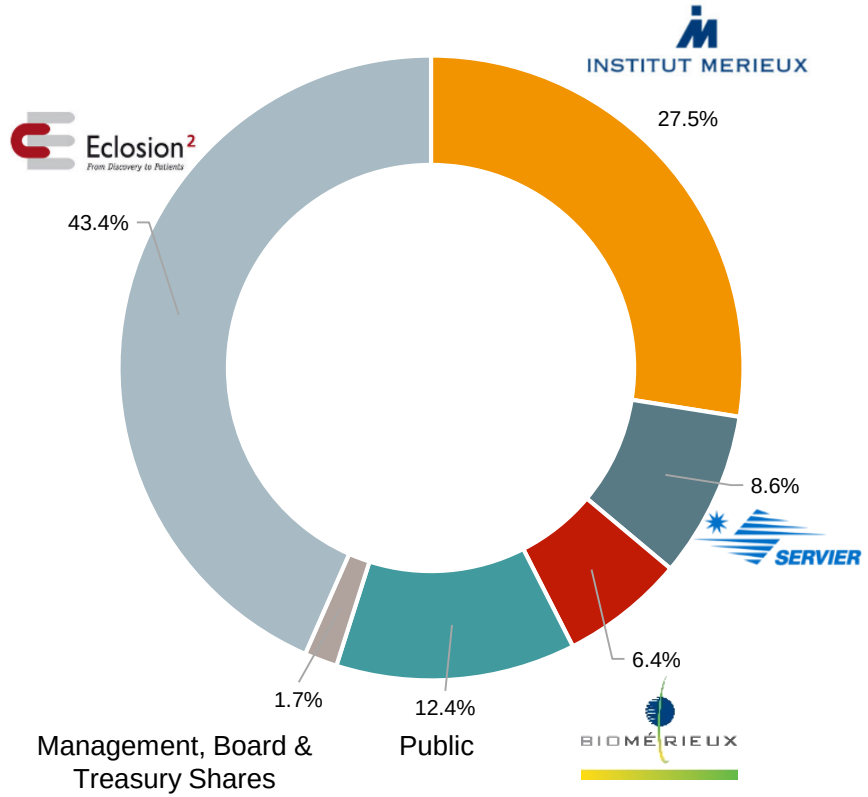
- Ongoing collaborations with research centers in France (Créteil and Bordeaux) on epidemiological studies and animal models of psychotic disorders

Qin et al. Elevation of Ser9 phosphorylation of GSK3beta is required for HERV-W env-mediated BDNF signaling in human U251 cells. Neurosci Lett. 2016. Huang et al. Human endogenous retroviral pol RNA and protein detected and identified in the blood of individuals with schizophrenia. Schizophr Res. 2006. Karlsson et al. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci U S A. 2001

Strong basis for growth

Financial Summary

Share capital as of December 2017



Note: excludes stock options and performance-based option units, representing a maximum 6% dilution

P&L and cash balance (in € millions)

	Unaudited 2017	FY 2016	FY 2015
Revenue	14.7	5.9	2.5
R&D Expenses	n.d.	(14.4)	(5.6)
G&A	n.d.	(5.5)*	(1.9)
Operating Income (loss)	n.d.	(14.0)	(4.3)
Cash & Equivalents	26.1	34.5	19.6

Note: * 2016: includes €1,801k of IPO-related fees

Multiple value enhancing milestones in the next twelve months, leading to Phase II results

- ✓ LPLV Phase IIb clinical trial in MS by end December 2017
- ✓ Full recruitment of Phase IIa trial of GNbAC1 in T1D by early February 2018
- Analysis of 48-week Phase IIb results, 1Q2018
- US IND & opening Phase II trial in Secondary Progressive MS patients
- New anti-pHERV antibodies (e.g. ALS, inflammatory psychosis)
- T1D Phase IIa results 3Q2018

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Leader in the treatment of HERV-mediated diseases

Arrêter les maladies neurodégénératives et autoimmunes