BIOTECH INDUSTRY

CLEAR & BOOST CD38+ CELLS: NEURONS INTRACELLULAR CLEARANCE & INFLAMMATION RESOLUTION AGAINST NEURO-DEGENERATIVE DISEASES

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THE ORGANIZATION

Spin-out from Paris Brain Institute (Pitié Salpêtrière Hospital, France). Incorporated in 2016.

https://www.encefa.com/

Encefa develops First-in-Class CD38 drugs (3 international patents filed) against a large range of age-related diseases. 2 ongoing programs: NC-B8 against neurodegenerative diseases, starting with ALS, and NC-P7 against Cardio-Metabolic Diseases.

THE NEED

Neuro-Degenerative Diseases (NDD) are a major unmet medical need that affects more than 60 million people worldwide.

While gene therapy emerges as promising for familial forms, there is no disease-modifier treatment against sporadic forms, and when .

NDD (ALS PD, MS, AD and HD) share the same deleterious mechanisms. Increasing evidences place Autophagy-Lysosomal Pathway as a key promising therapeutic approach against these proteino-inflammatory pathologies.

EXECUTIVE COMMITTEE

Mrs. Laurence Bressac

Executive Chairman & CEO, co-founder, formerly consultant within Deloitte, development of SME

Dr Damien Toulorge

CSO, co-founder, PhD, Neuroscientist, formerly in academic and private sectors, with Pitié Salpêtrière Hospital and Pharnext

Mr Serge Guerreiro

Neuroscientist, drug with Pitié Salpêtrière Hospital and Pierre Fabre.

FIRST-IN-CLASS DRUGS LEVERAGING ON AN AGE-RELATED TARGET TO ACT ON THE DEGRADATION PATHWAY OF RELEVANT CELLS (NEURONS & IMMUNE)

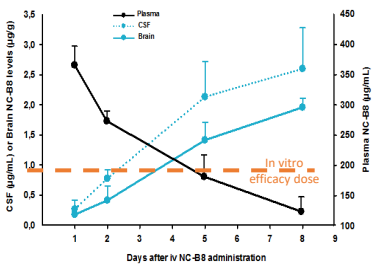
- **Encefa** drugs bind a specific epitope on CD38 to directly activate CD38+ cells entire **AUTOPHAGY-LYSOSOMAL FLUX** (up to lysosomal exocytosis) and **ENERGY METABOLISM**, in a **NAD-independent pathway**, while boosting **NAD+ levels**.
- **CD38** is an **AGE-RELATED TARGET**, known to be heavily expressed on activated immune cells (incl. microglia, T Cells), and on suffering cells (incl. neurons, muscles). CD38 expression is directly linked to senescence mechanisms and thereby increases with aging and furthermore with CNS diseases. **Genetically validated** for PD, validated for AD (KO mice) and for ALS (levels of expression).

Encefa CD38 drugs are FIRST-IN-CLASS: they uniquely and specifically act on suffering and pro-inflammatory cells, to (i) restore their energy metabolism, (ii) activate their degradation pathway → to protect the brain.

NC-B8 A FIRST LEAD PRODUCT READY FOR CMC DEVELOPMENT

NC-B8 is **Encefa**'s lead product for neurodegenerative diseases (**intravenous** inj.).

- NC-B8 is a proprietary **humanized IgG4-S228P monoclonal antibody**, with optimized efficacy and development properties, cross-reactive (H, C, D, R, M), generated from a cutting-edge humanized synthetic bank of phages.



- NC-B8 was selected for its efficacy and ability to **cross the Blood Brain Barrier (BBB)**:
  - ✓ highly effective (human cells and in vivo),
  - ✓ good safety profile (**no immuno-supp.**),
  - ✓ good brain penetration (3.5% at D8) after intravenous injection,
  - ✓ chronic treatment (once a month).
- NC-B8 is **18 months from the IND/IMPD filing**.

MULTI-SCALE BENEFICIAL EFFECTS TO POSITION NC-B8 ON A WIDE RANGE OF NEURODEGENERATIVE DISEASES (BOTH SPORADIC AND FAMILIAL FORMS)

NC-B8 *in vivo* POC-efficacy -- five mice models:

Lysosomal impairment (CBE)
- Protein accumulation repression
- Microglia & Astrogliosis repression

Oxidative stress induced neurodegeneration (6OHDA)
- Neuro-protection (curative setting)

Auto-immune neuro-inflammation (EAE)
- Motor activity improvement > Rituximab
- Anti-demyelination

Mitochondrial impairment induced neurodegeneration (MPTP)
- Neuro-protection

TransGenic SOD1 G93A mice model (gold standard mice model for ALS)
- Protection against weight loss
- Motor activity improvement (rotarod)
- Protection against endplate degeneration
- Neuroprotection (number of MN & NfL)
- Neuroinflammation repression
- Survival increase

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ADVISORS

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INTELLECTUAL PROPERTY

ICOSA
European Patent & Trade Mark Attorneys

MABDESIGN

REGULATORY & CMC

VCLS
Vivian Consulting Life Sciences

INTELLECTUAL PROPERTY FREEDOM TO OPERATE

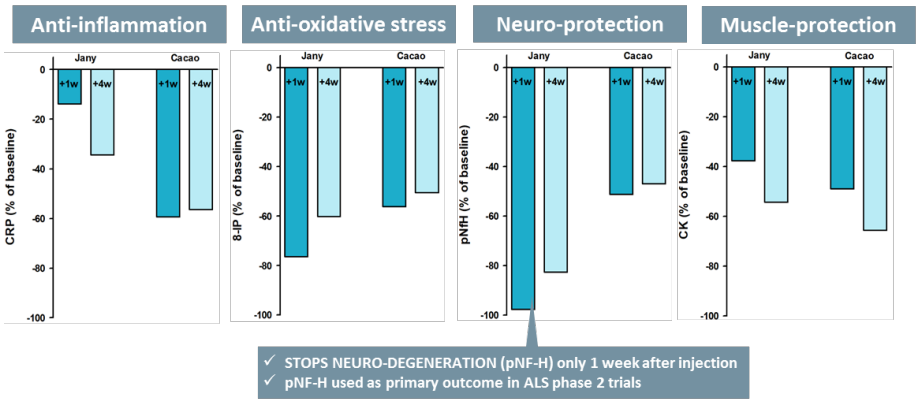
Encefa fully owns its entire IP covering all CD38 compounds which activate its specific MOA for neurodegenerative diseases, and from the IP protecting NC-B8 sequences. Portfolio of 3 patents recently filed.

Encefa's CD38 DRUGS – PILOT CANINE STUDY – REAL ALS-LIKE DISEASE

Pilot investigation of **Encefa** CD38 drug efficacy in **two old owner's dogs** naturally affected by Canine Degenerative Myelopathy (CDM), an actual **ALS-like disease**.

SOD1 mutated dogs, single **intravenous injection**, 8 mg/kg, curative, changes from baseline 1 week and 4 weeks after treatment, half-life = 27 days

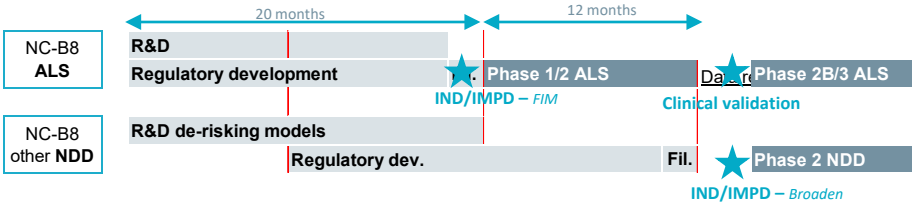
UNPRECEDENTED REDUCTION OF INFLAMMATION, NEURO-DEGENERATION, MUSCLE-DEGENERATION AND OXYDATIVE STRESS



Encefa CD38 drug is the first therapeutic to reach such results, in an actual ALS-like disease, for which canine studies are deemed to be predictive of human results.

Neurofilaments level is a recognized biomarker of neurodegeneration, correlated with disease severity and treatment response. Increasingly used as an unavoidable outcome in ALS clinical trials, it will be one of ENCEFA key outcome in its phase 1/2a study. **NC-B8 already triggered an exceptional reduction of their level in SOD1 mice and ALS dogs.**

Encefa DEVELOPMENT PLAN



PARTNERING

NC-B8 Unique differentiating features

Therapeutic Benefits	A disruptive MOA serving an innovative ANTI-AGING approach against NDD and involving the whole **Autophagy-Lysosomal Pathway** activation	✓
	Strong **preclinical data** to be **translational to human**: (1) In vivo efficacy in 5 mouse models, (2) efficacy in an ALS-like disease in dogs, (3) MOA validated on human cells, (4) no safety red flag	✓
	Companion biomarkers for (1) patient inclusion, (2) dose-finding studies, (3) personalized medicine	✓
	Clear **clinical strategy** to accelerate approval	✓
Commercial Benefits	**Breakthrough innovation**	✓
	Strong patent Protection: Large coverage, sequences protection, Coverage until 2040 to be extend through **2045**	✓
	Unique competitive advantages	✓

• **Encefa** is looking for funding upcoming stages of preclinical and clinical development of its CD38 lead candidate product NC-B8 until first clinical trial results of efficacy (Phase 1/2A, ALS), and IND/IMPD for other neurodegenerative diseases.

• **Encefa** is also open for early partnering with a pharmaceutical company to co-develop NC-B8 against neurodegenerative diseases.

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