PLL Therapeutics

New paradigm for Neurodegenerative management:

Early and accurate detection, treatment of the root cause.

A first application on ALS (Amyotrophic Lateral Sclerosis) with a clinical Trial Phase I II in Australia

Jean-Pascal ZAMBAUX / Michel LARROCHE

BIOSHARES
Australia's Biotech Investment Resource

Hobart Tasmania 07/08/2025

PLL THERAPEUTICS

PLL THERAPEUTICS is a Biotech company developing a platform technology (diagnostic and therapy) in NeuroScience for neurodegenerative and auto immune disease which will focus on Amyotrophic Lateral Sclerosis (ALS)

Based on **the carrier properties of PLys®,**we have developed PLL001 **ALuSen®**, a multifunctional therapy that has demonstrated a breakthrough potential to treat ALS in preclinical studies.

PLL Therapeutics in the World

PLL US Share Holder

Headquarters in Bordeaux-France

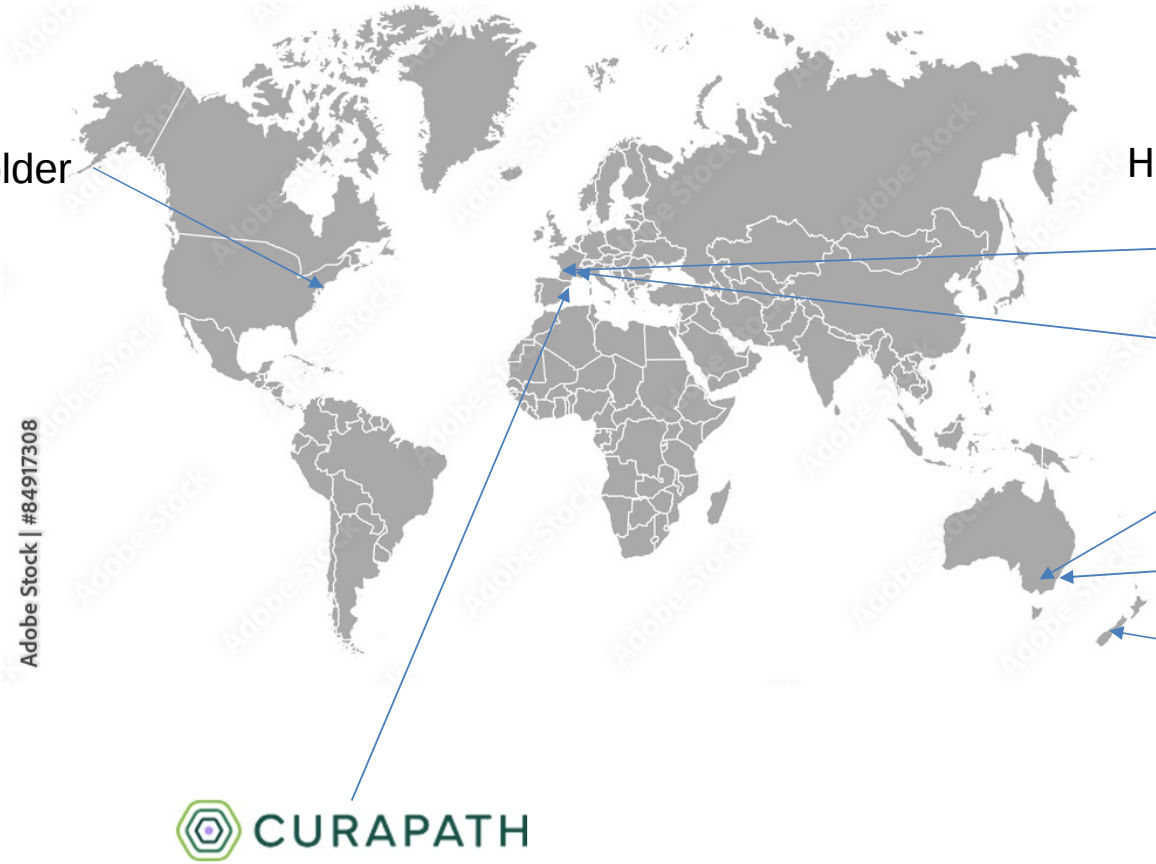
PLL Therapeutics

COPEXIS

PLL TX AUSTRALIA

lithia

PLL TX NZ



CURAPATH

Our Strategy

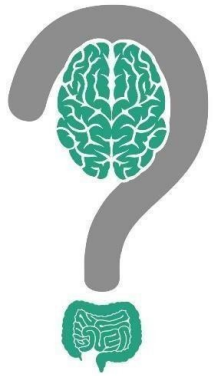
THE GI TRACK IS AT THE ROOTS OF THE DISEASE

The causal link between gastrointestinal injuries and Neurodegenerative Disease are supported by a growing body of recent research.

GASTROINTESTINAL ROOTS

- + Dysbiosis syndrome
- + Reduced butyrate producing bacteria
- + Reduced diversity
- + Paneth cells abnormalities
- + Endotoxins release in the blood

GUT BRAIN AXIS



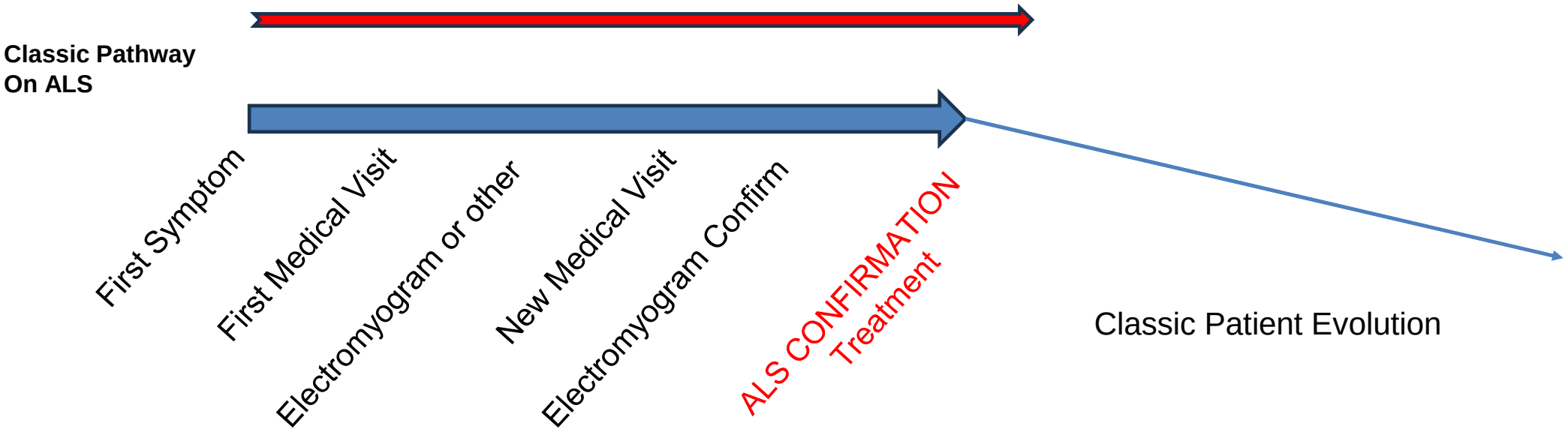
CNS INJURIES

- + CNS inflammation
- + Glial cells NO* & ROS** hyperproduction
- + Increased glutamate, reduced butyrate
- + IDO*** pathway activation
- + Autoimmunity

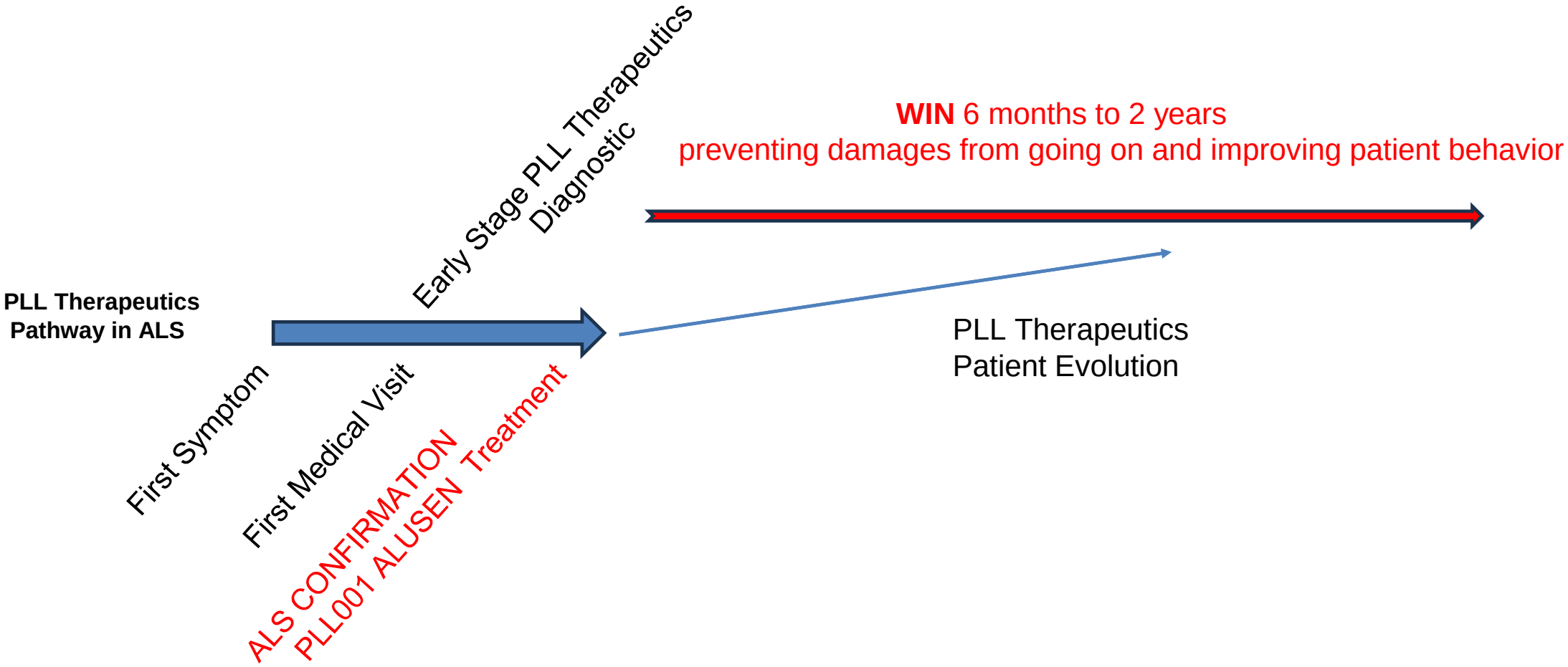
*Nitric Oxide pathway
**Reactive oxygen species
***Indoleamine 2,3 dioxygenase pathway

Classic ALS Pathway

Can be 6 months to 2 years or more during which nothing happens
but where the damages become irreversible



PLL Therapeutics Pathway



EARLY DIAGNOSTIC and THERAPY stopping the disease at an early stage

EARLY DIAGNOSTIC and THERAPY
stopping the disease at an early stage

Development of an accurate diagnostic solution to detect and follow the disease

PLL-Therapeutics has developed a solution to qualify and quantify blood biomarkers of amyotrophic lateral sclerosis (ALS).

Our technology is based on the detection of serum antibodies and their isotyping in patients with ALS; these antibodies recognize haptens on peptide epitopes. The presence of these anti-hapten antibodies is the physio pathological reflection of a disease and its chronicity.

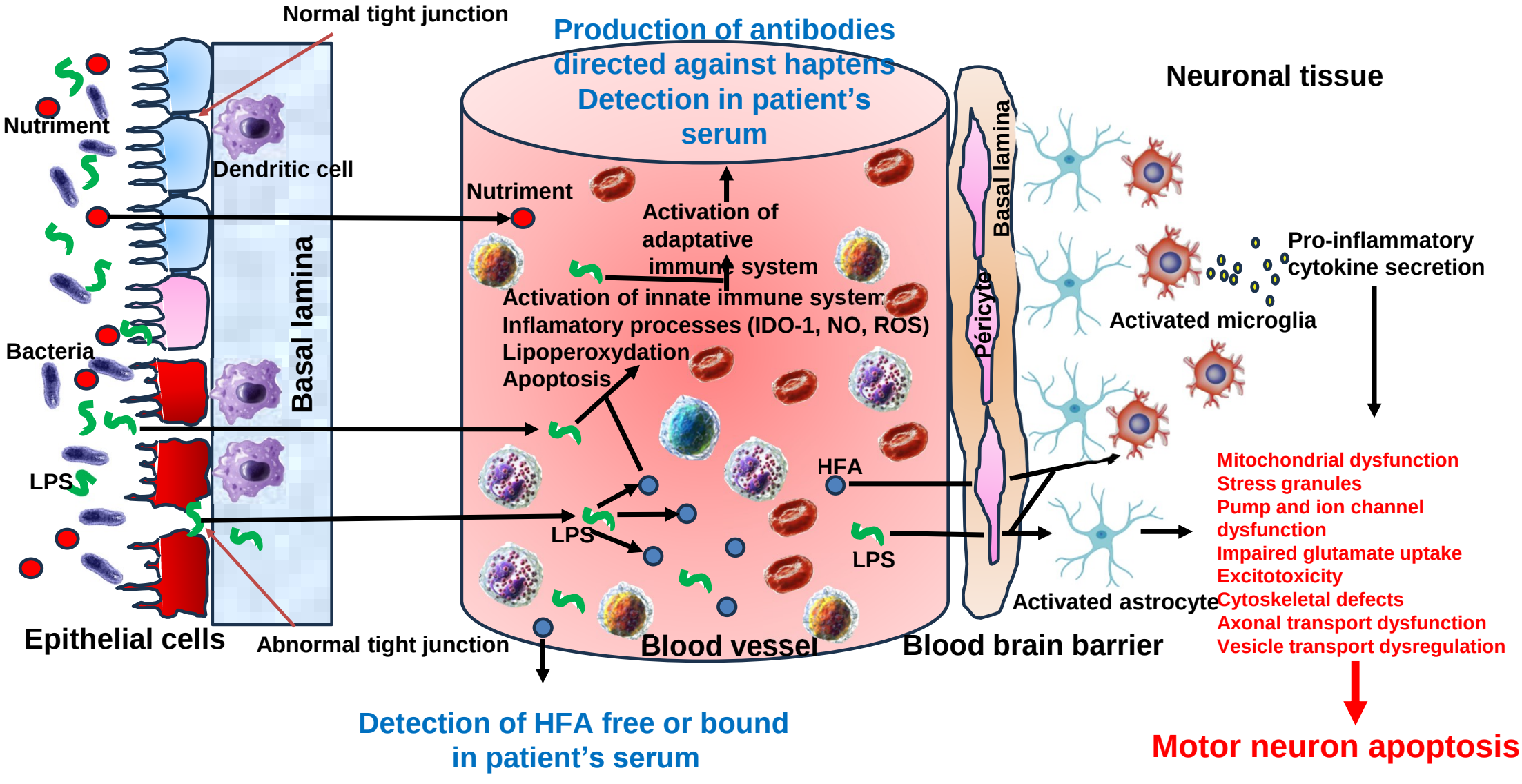
The presence of 12 Isotypes was identified in the sera of patients suffering from different forms of ALS for each gender (currently c. 150 sera samples).

In addition, we identified blood markers making it possible to demonstrate intestinal dysbiosis associated with intestinal bacterial elements which could be a trigger for the onset of the disease (validation is ongoing on a large sample of sera in Europe, Australia and USA).

These 2 types of markers will be monitored in patients treated with our therapy (PLL001) as a companion diagnostic

This technique makes it possible to **measure *in vitro* what happens *in vivo***.

New PARADIGM ON ALS

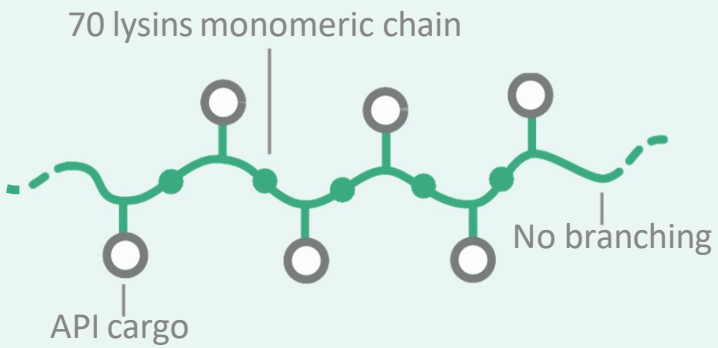


Our Technology

OUR THERAPY SOLUTION

Our DP, PLys® (PolyLlysine) is a drug carrier with best-in-class properties combining stability, high internalization and no immunogenicity.

STRUCTURE



FORMULATION

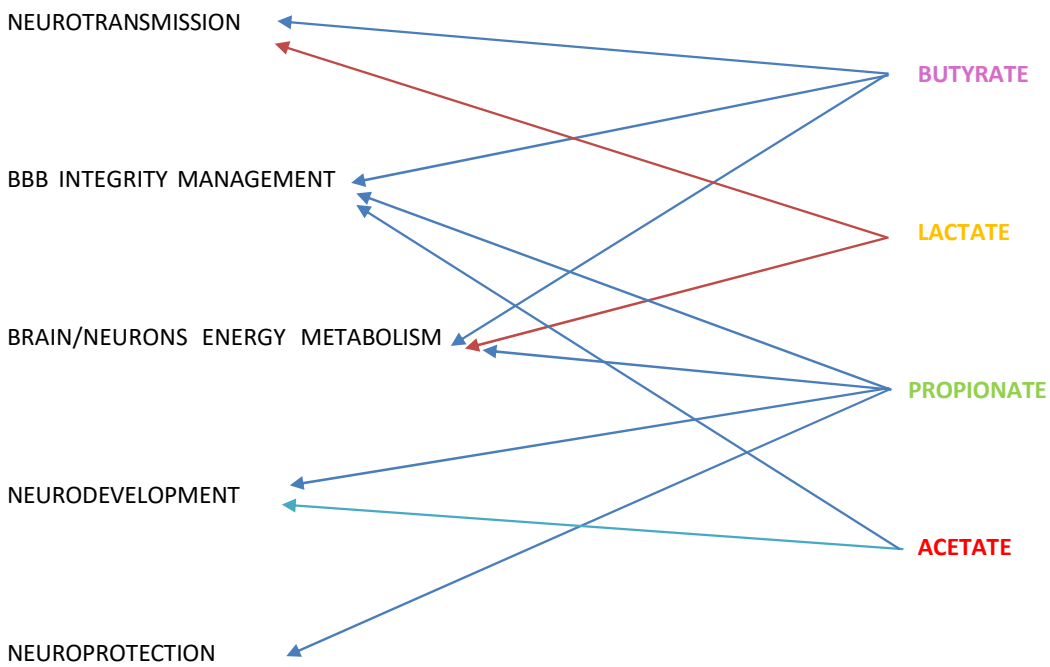
Our DP will transport 4 SCFA*s to the epithelium gut cells and as well on BBB and restore the Gut-Brain Axis, the microbiome balance and the dysbiosis.

INTERNALIZATION[1,3,4]

PLys® internalizes its cargo through endocytosis & charge >900-fold higher than the API alone.

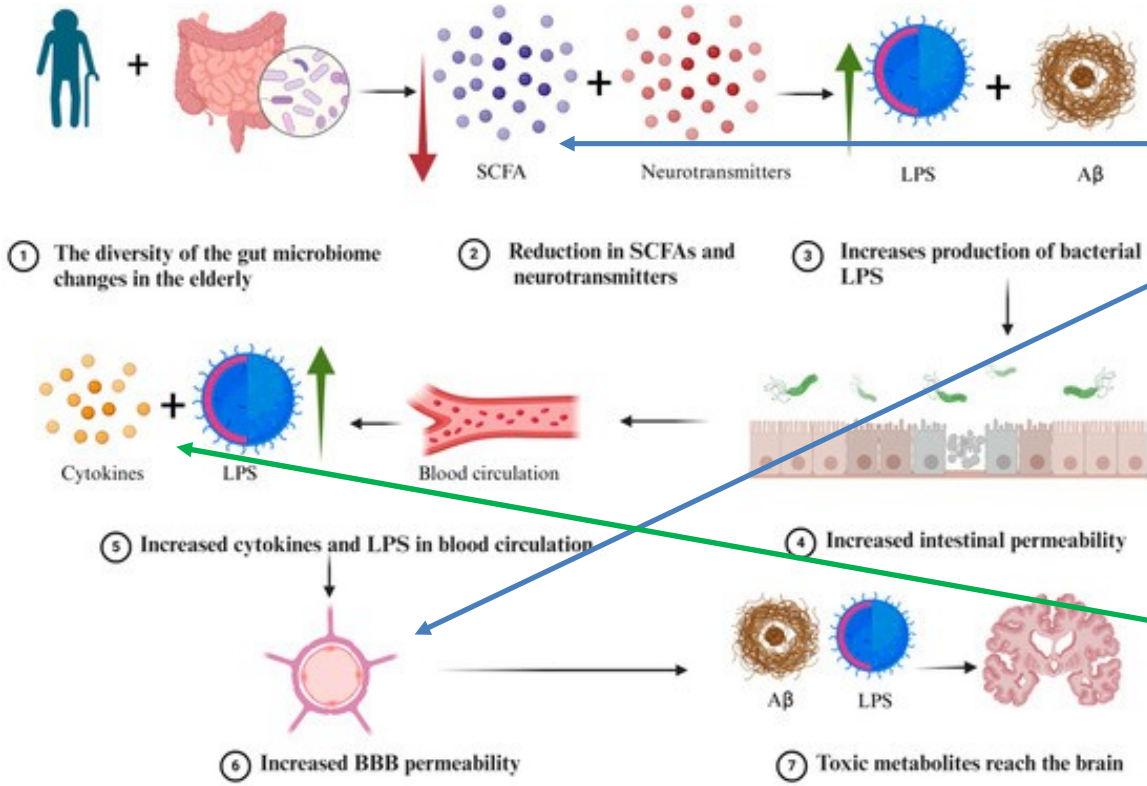
A patented polymer and potent carrier with a confirmed safety profile to restore the Dysbiosis

Small Chain Fatty Acid's (SCFA's)



New PARADIGM ON ALS

Neurodegenerative Pathway



THERAPY PLL

- **Increase SCFAS**
- « Restore » Gut Permeability
- « Restore » BBB permeability
  BBB (Brain Blood Barrier)

A comprehensive diagnostic and therapeutic approach for a holistic management of ALS

DIAGNOSTIC PLL

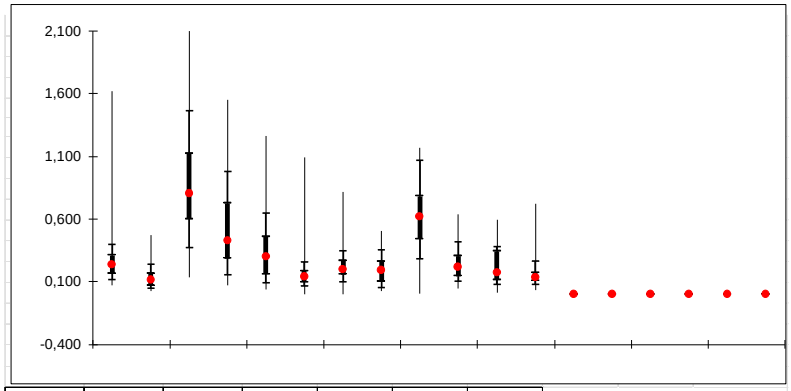
Early stage and Companion

- Tracking LPS and serum antibodies links to inflammation

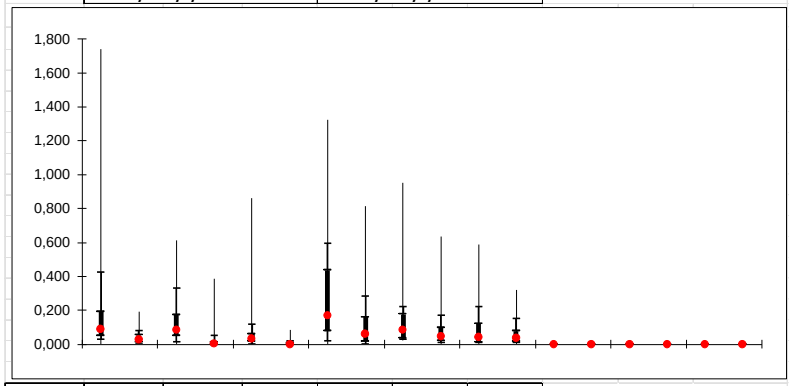
https://doi.org/10.3390/ijms25168619

DIAGNOSTIC APPROACH – Example of results

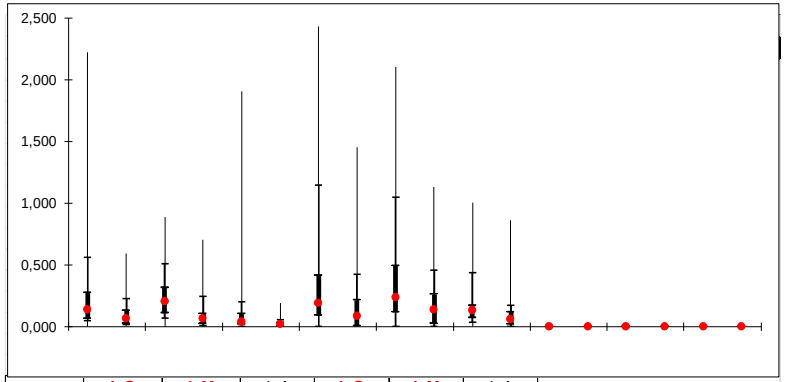
Percentile Distribution of ALS patients versus Healthy patients



Isotype	IgG	IgM	IgA	IgG	IgM	IgA
P value	0,0008	0,0004	0,0049	0,3263	0,0000	0,0696
sera's number	72/76	72/76	72/76	28/79	28/79	28/79
	DL-3-Hydroxykynurenin - Female			DL-3-Hydroxykynurenin - Male		



Isotype	IgG	IgM	IgA	IgG	IgM	IgA
P value	0,0022	0,0457	0,0034	0,0038	0,0228	0,6302
sera's number	71/76	71/76	71/76	29/60	29/60	29/60
Hapten	Myristic acid - Female			Myristic acid - Male		



Isotype	IgG	IgM	IgA	IgG	IgM	IgA
P value	0,0000	0,0011	0,0000	0,0192	0,0116	0,0044
sera's number	71/76	71/76	71/76	29/60	29/60	29/60
Hapten	Thioctic acid - Female			Thioctic acid - Male		

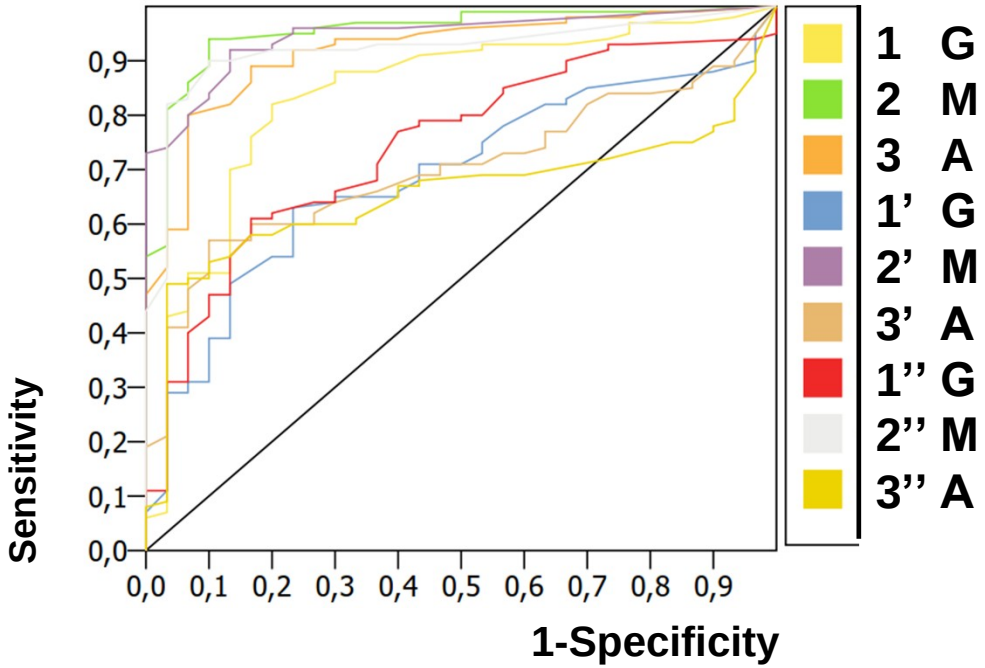
Markers Centiles: 0 10 25 50 75 90 100
Associated probability of Mann-Whitney "U" test
Number of patients versus number of controls

Production of antibodies directed against haptens Detection in patient's serum

The distributions of female and male ALS patient populations versus healthy controls show significant thresholds of serum antibodies against our haptens.

DIAGNOSTIC APPROACH – Example of results

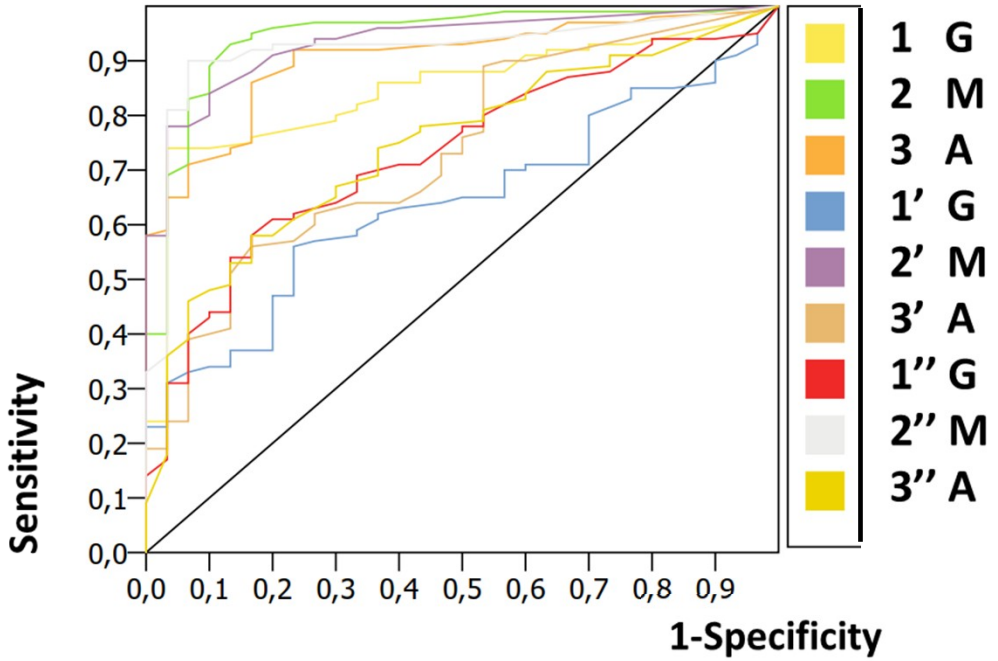
ROC curves and AUC between ALS patients and Alzheimer's patients



Surface située sous la courbe

Variable testée	Surface	Erreur standard	Sig. symptotique.	Intervalle de confiance asymp. 95%	
				Limite inférieure	Limite supérieure
OHKynG	,84	,04	,000	,77	,91
OHKynM	,95	,02	,000	,92	,99
OHKynA	,92	,03	,000	,88	,96
MyrG	,69	,05	,002	,61	,77
MyrM	,95	,02	,000	,92	,98
MyrA	,70	,05	,001	,63	,78
ThiocG	,75	,05	,000	,67	,83
ThiocM	,92	,03	,000	,88	,97
ThiocA	,66	,05	,009	,58	,74

ROC curves and AUC between ALS patients and Parkinsonian's patients

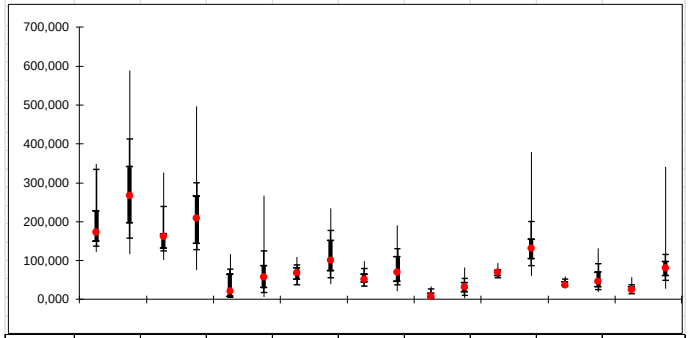


Surface située sous la courbe

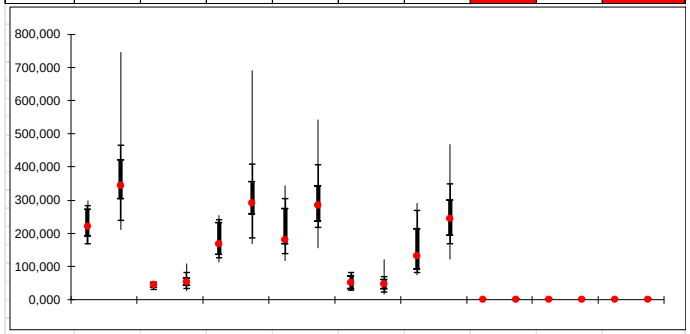
Variable testée	Surface	Erreur standard	Sig. symptotique.	Intervalle de confiance asymp. 95%	
				Limite inférieure	Limite supérieure
OHKynG	,85	,04	,000	,79	,91
OHKynM	,94	,02	,000	,90	,98
OHKynA	,90	,03	,000	,86	,95
MyrG	,64	,05	,018	,56	,73
MyrM	,94	,02	,000	,90	,97
MyrA	,74	,05	,000	,66	,82
ThiocG	,73	,05	,000	,66	,81
ThiocM	,92	,03	,000	,87	,97
ThiocA	,75	,05	,000	,67	,82

DIAGNOSTIC APPROACH – HFA from LPS-Dysbiosis

Percentile Distribution of healthy controls versus ALS patients for hydroxylated FA

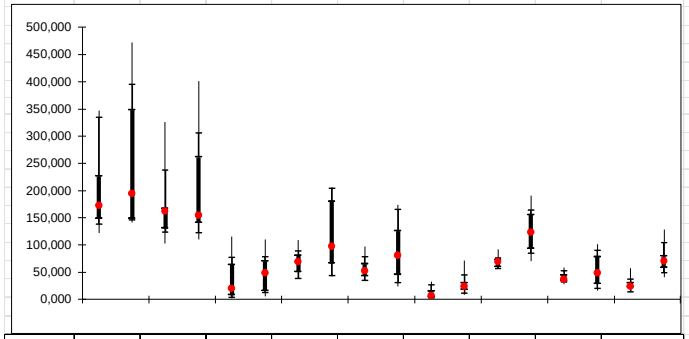


P value	0,9283	0,7873	0,8338	0,5826	0,6821	0,1974	0,0160	0,5356	0,0169
sera's number	9/53	9/53	9/53	9/53	9/53	9/53	9/53	9/53	9/53
HFA	1003OHT	1003OHF	1003OHB	1203OHT	1203OHF	1203OHB	1403OHT	1403OHF	1403OHB

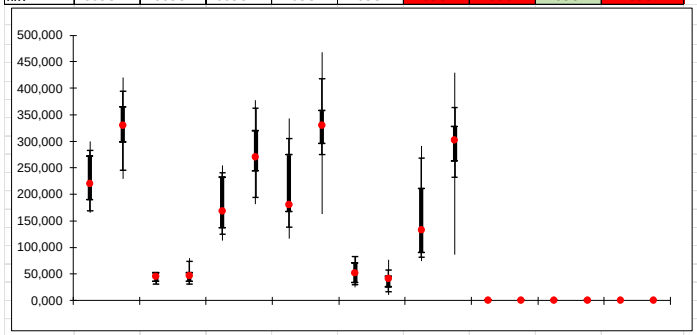


P value	0,0425	0,9920	0,0590	0,4781	0,4013	0,4536			
sera's number	9/53	9/53	9/53	9/53	9/53	9/53			
HFA	1603OHT	1603OHF	1603OHB	1803OHT	1803OHF	1803OHB			

Percentile Distribution of healthy controls versus Alzheimer's patients for hydroxylated FA

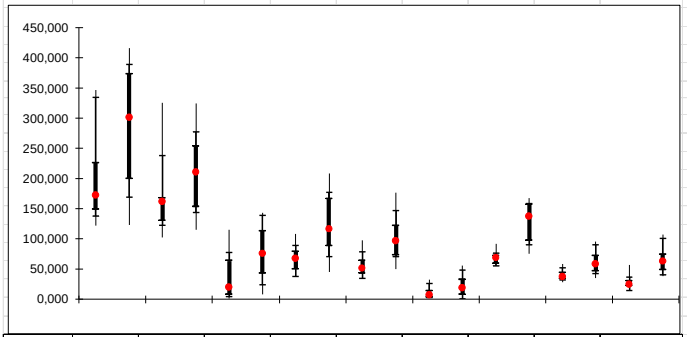


P value	0,5136	0,6242	0,2885	0,1025	0,2530	0,0179	0,0011	0,5676	0,0004
sera's number	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10
HFA	1003OHT	1003OHF	1003OHB	1203OHT	1203OHF	1203OHB	1403OHT	1403OHF	1403OHB

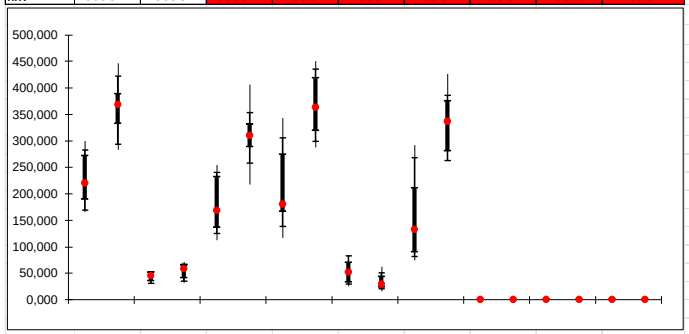


P value	0,0019	0,8703	0,0033	0,0114	0,1208	0,0090			
sera's number	9/10	9/10	9/10	9/10	9/10	9/10			
HFA	1603OHT	1603OHF	1603OHB	1803OHT	1803OHF	1803OHB			

Percentile Distribution of healthy controls versus Parkinsonian patients



P value	0,0604	0,1914	0,0275	0,0071	0,0055	0,2207	0,0003	0,0090	0,0008
sera's number	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10	9/10
HFA	1003OHT	1003OHF	1003OHB	1203OHT	1203OHF	1203OHB	1403OHT	1403OHF	1403OHB



P value	0,0004	0,0864	0,0006	0,0015	*0,0275*	0,0011			
sera's number	9/10	9/10	9/10	9/10	*9/10*	9/10			
HFA	1603OHT	1603OHF	1603OHB	1803OHT	*1803OHF*	1803OHB			

INSIGHTS FROM PRE-CLINICAL RESULTS

Restore intestinal epithelium barrier. In Trans Epithelial Electric Resistance in vitro model, PLL001 accelerates intestinal barrier maturation (dose dependant)

Reduces neurodegeneration and muscle waste. In SOD1 mice models, PLL001 reduced neurodegeneration and muscle cell apoptosis (microscopy) and improved motor capabilities

Restores healthy microbiota. In SOD1 mice models, PLL001 reverted the microbiota observed in sick mouse to the microbiota observed in wild type mice

Shows no toxicity. In SOD1 mice models, PLL001 showed no toxicity at the predicted therapeutic dose.

PLL-001 is the first therapy showing dysbiosis and ALS microbiota healing as well as improvement of motor capabilities in SOD1 G93A- SOD1 transgenic mice (ALS models).

The proof-of-concept study was conducted by **Charles River** and **INRAE** (Clermont-Ferrand, France) on behalf of PLL. We also confirmed that G93A-SOD1 transgenic mice that received PLL001 showed a greatly reduced incidence and severity of nervous system and skeletal muscle pathologies compare to control mice after 3 weeks treatment.

WHERE ARE WE TODAY ?

- Phase I and II in Australia on ALS

  The HREC approval is from 23 October 2024

  First Patient in Phase I in April 2025

  Cohort 1 Safety Review Committee Meeting Minutes in June 2025

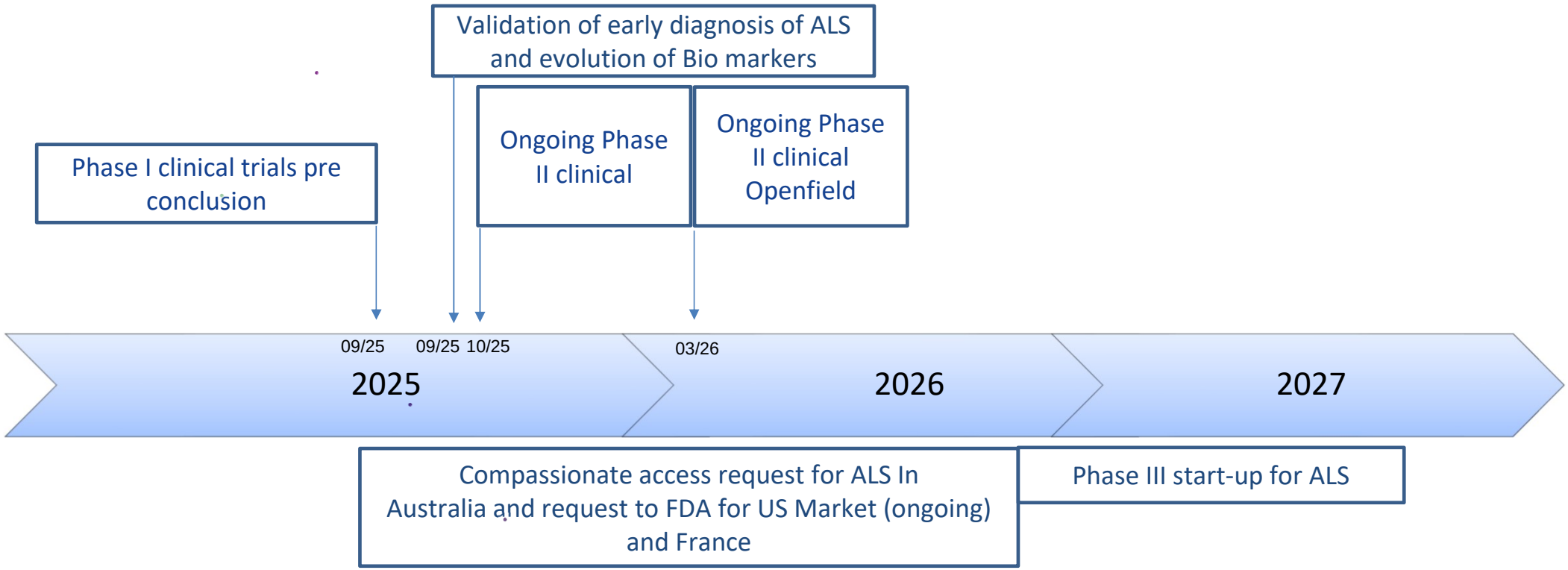
  Cohort 2 on the way with a review Committee in Sept 2025

  Cohort 3 will be close in October 2025

  Launch on Phase II in November 2025 with 9 hospitals in Australia and 1 in NZ

- Development of our R&D in Australia with PLL TX Australia our Australian company and Sponsor of our Trial

PLL THERAPEUTICS NEXT MILESTONES



PLL Therapeutics

PLL TX AUSTRALIA PTY LTD

Melbourne Victoria

Tel: +61 487 190 569

Mail: jpzambaux@pll-therapeutics.com

WWW.PLL-THERAPEUTICS.COM