Programa Cooperación Farma-Biotech
Neurociencias

Methylthioadenosine (MTA)

Immunomodulation and Neuroprotection for the Multiple Sclerosis Treatment

DIGNA BIOTECH

Barcelona, 15 de febrero 2011

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Associació catalana d'empreses de biotecnologia

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Plataforma Tecnológica Española

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DIGNA BIOTECH is a company that "manages" science

- DIGNA BIOTECH is a clinical-stage biopharmaceutical company developing therapeutic and diagnostic products discovered primarily at the University of Navarra's CIMA (Center for Applied Medical Research).

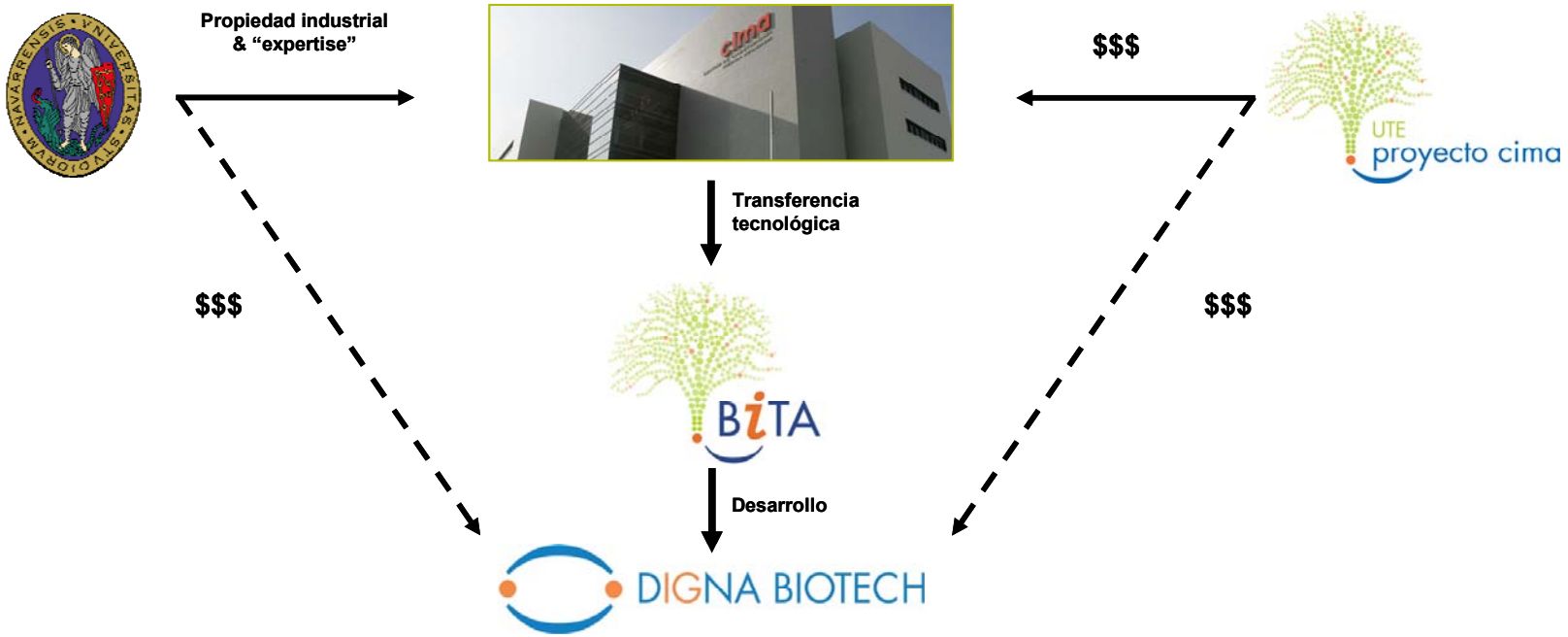
- The company started operations in 2004 and is funded jointly by two Foundations - linked to the University of Navarra -, and a group of 15 investors.

- Currently, DIGNA BIOTECH has a portfolio of 31 products to be developed in 36 different indications under a €66.1 M investment plan (€32.9 M already invested).

- The company expects its first therapy product to be in the market in 2014.

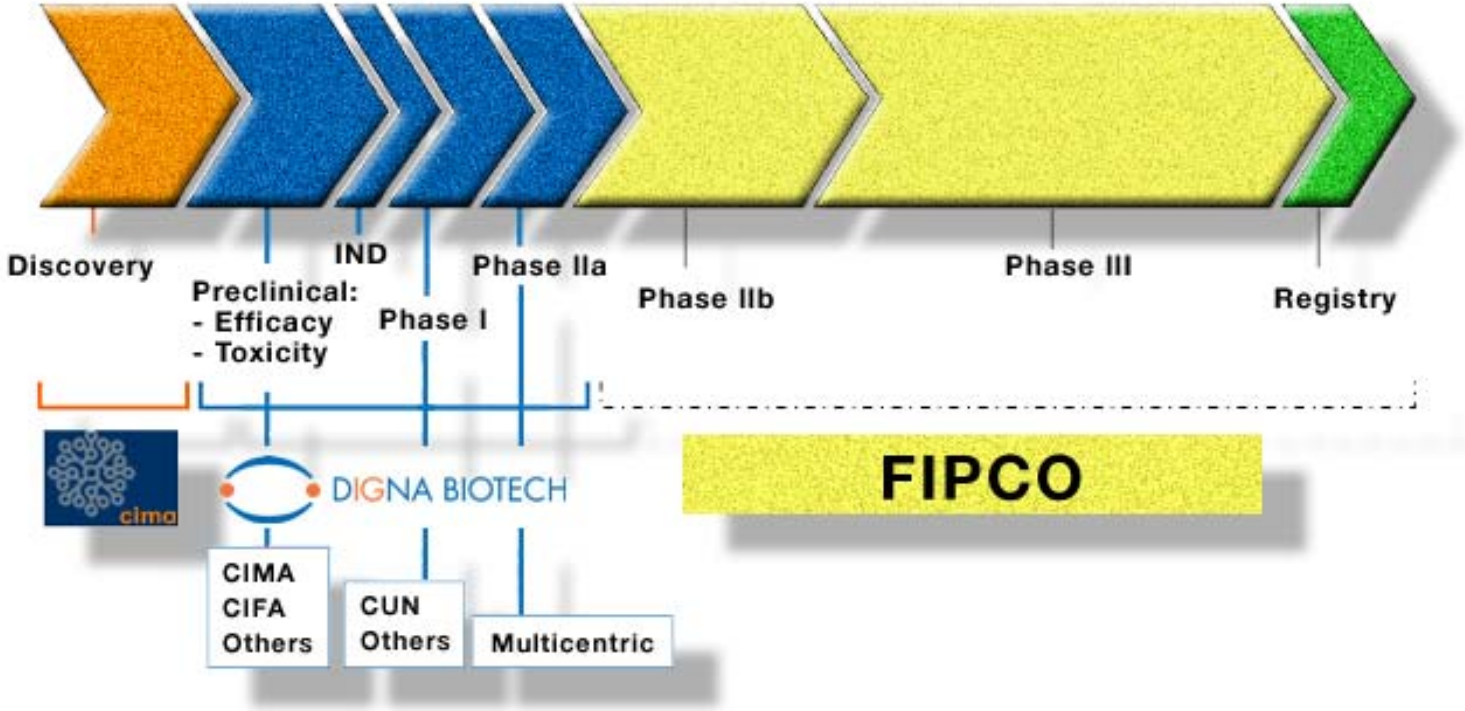
CIMA is one of the most important private biomedical research center of Europe

- The University of Navarra is a Spanish private academic institution with internationally recognized medical research.
- The University together with a group of 15 investors have committed €152 M during the 2003-2012 period to create Spain's largest private biomedical research center.



DIGNA BIOTECH'S GOAL

- DIGNA BIOTECH intends to bring the products discovered at CIMA into clinical development - up to the "proof of concept" stage -, and to reach licensing agreements with the pharmaceutical industry to ensure the marketing of those products.



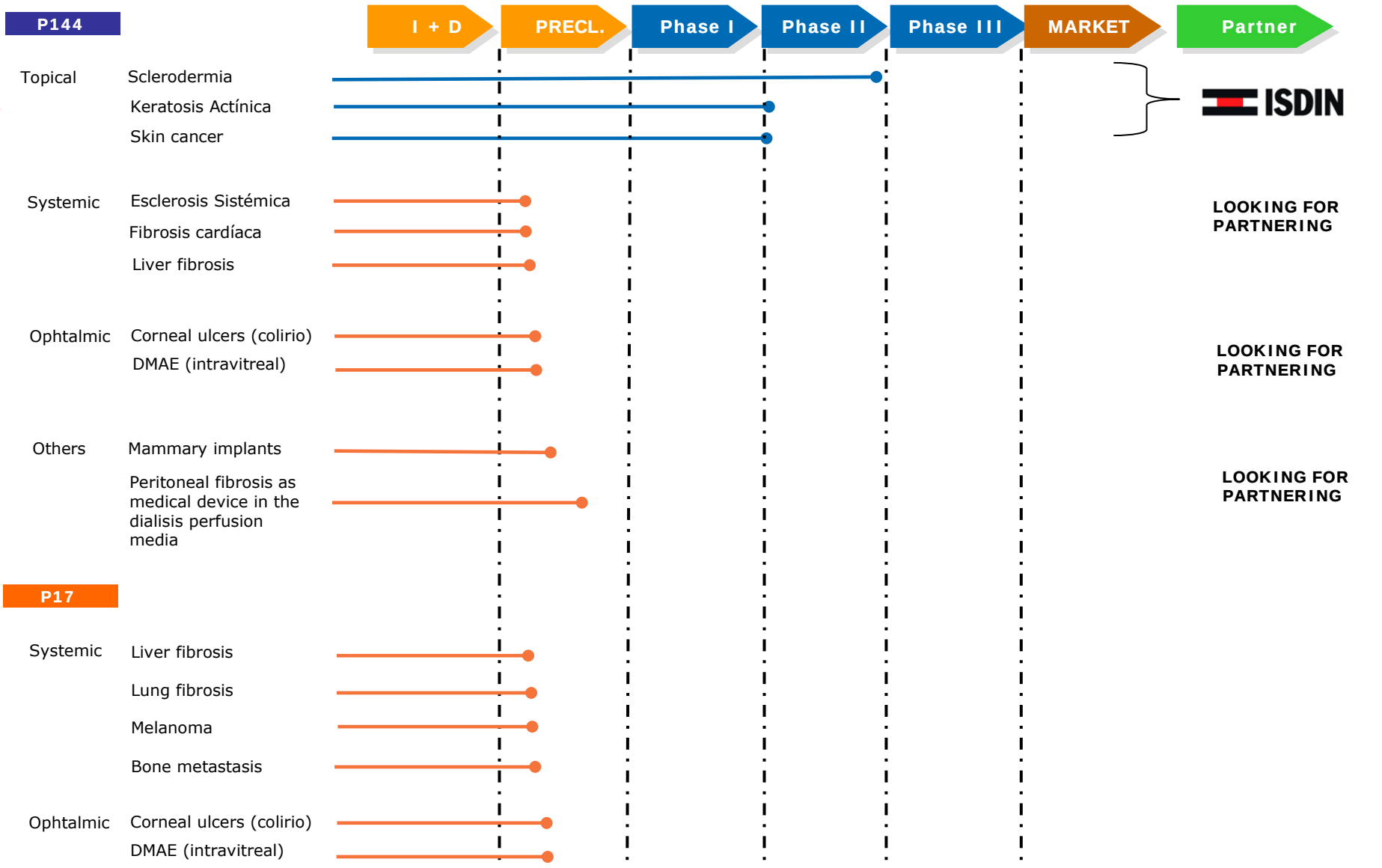
The University of Navarra provides additional structure for the development of new drugs

UNIVERSITY OF NAVARRA
Additional Research Centers

University Schools	• Medicine • Pharmacy (GMPs) • Biology	
C.I.F.A. (GLPs)	• Preclinical efficacy assays • Toxicology • Pharmacokinetic	
University of Navarra Clinic (GCPs)	• Phase I unit • Ethical Review Board • Biology	

THERAPEUTIC PIPELINE: PRODUCT CHARACTERISTICS

Candidate	Mechanism Of Action	Competitors	IP Expiration	Status
PEPTIDES				
P144	TGF-β1 inhibitor topic	1st topical iTGFb	2019	Orphan
P17	TGF-β1 inhibitor i.v	2 Clinical (Ph. I & III); 10 Precl.	2023	---
RECOMBINANT PROTEINS				
CT-1	IL-6 cytokine family	1st-in-class	2021	Orphan
IFN α5	Type I IFN	INF alfa 2	2019	----
EDA	TLR-4 agonist	1st-in-class	2024	----
SMALL MOLECULES				
MTA	Inmunomodulador antioxidante	1st-in-class	2025	
4-PBA	Histone deacetylase inhibitor	1st-in-class	2029	----
GENE THERAPY				
AAV Deaminase	Gene replacement	1st-in-class	2027	Orphan



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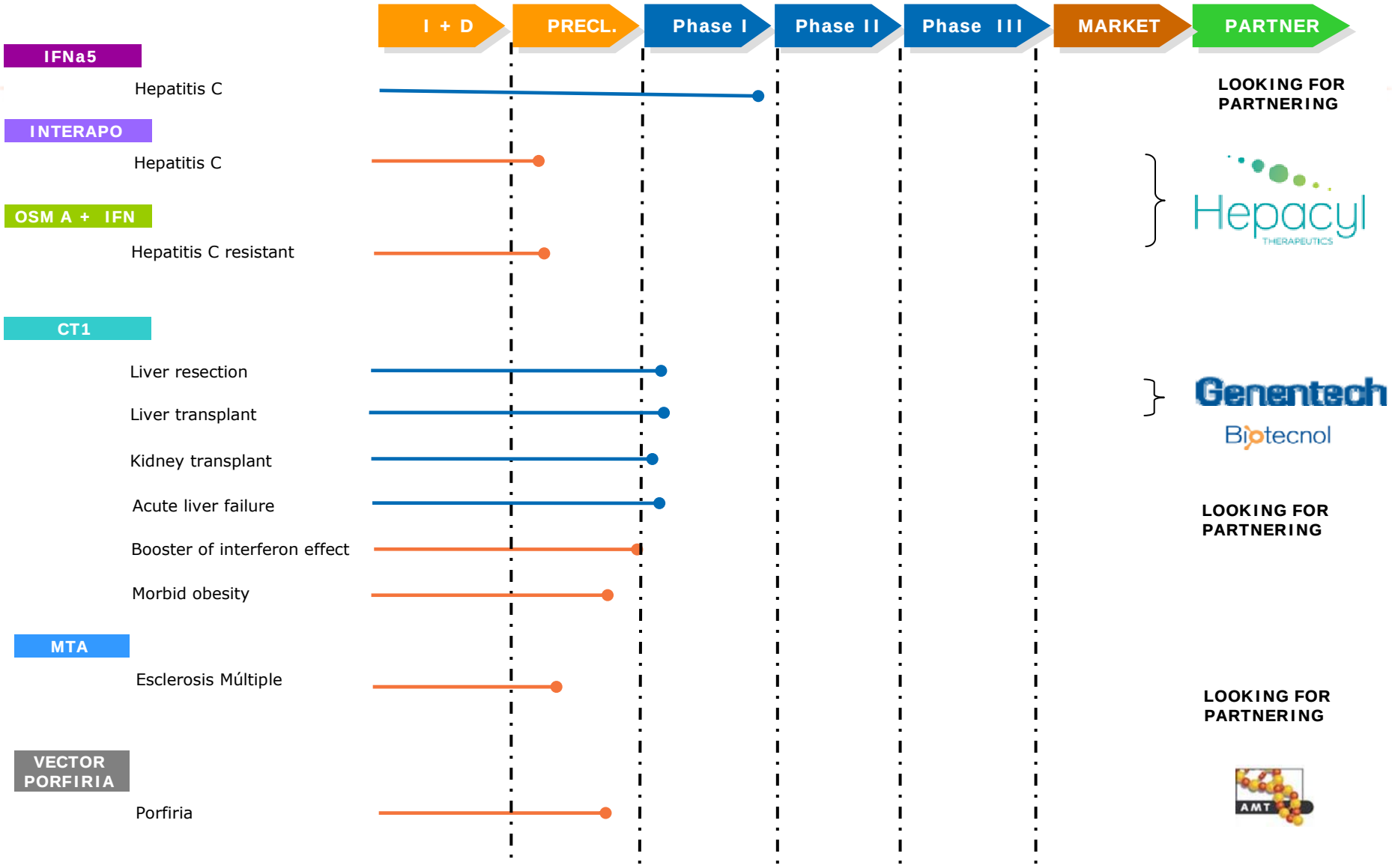

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DIGNA BIOTECH evolution
2005-2010

2005:	**7 patents**	**4 products**	**4 people**	**Capital: 1,7 M**
2010:	**30 patents**	**31 products**	**20 people**	**Capital: 15,5 M**

Total revenues:	11,4 M
Public funding:	15,5 M
Total Investment:	32,4 M

Licensing products: 6

Compromised investment in licesing (2007-2012): 20,5 M

Products with in vivo PoC: 31

Phase II/III	1
Phase I/II	2 (1 reprofiling)
Phase I	1
Pre-clinic late stage	2
Pre-clinic early stage	9
Research	16

THE PRODUCT
Methylthioadenosine (MTA)

- Digna Biotech holds the IP rights for three patents filled **worldwide**:

- Use of 5'-Methylthioadenosine (MTA) in the prevention and/or treatment of autoimmune diseases and/or transplant rejection (2025).
  Granted in EU, US, RU and MX.

- Synergystic combinations of 5'-Methylthioadenosine (2029)

- Neuroprotective properties of 5'-Methylthioadenosine (2029)

THE PRODUCT
Methylthioadenosine (MTA)

- Active ingredient GMP production available.
- Positive PoC in MS animal models (Acute and chronic relapsing EAE) via i.p. / oral.
- Novel MoA: exogenous MTA inhibits in a reversible, non-toxic, and dose-dependent manner, the activation of peripheral human lymphocytes. *Ann Neurol. 2006 Sep: 60(3):323-34.*
- PoC neuroprotection.
- Preliminary PK i.p / oral available
- Genotoxicity studies available: no genotoxic.
- Development plan designed until Phase I:

  18-24 months

  3 M €
- Failure risk before end of Phase I is very low:

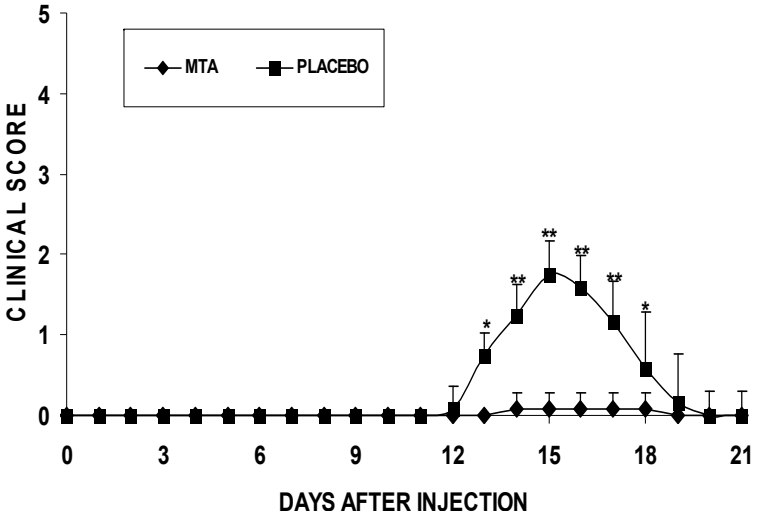
  Available (as reference only) documentation of a failed development of MTA as AINE.

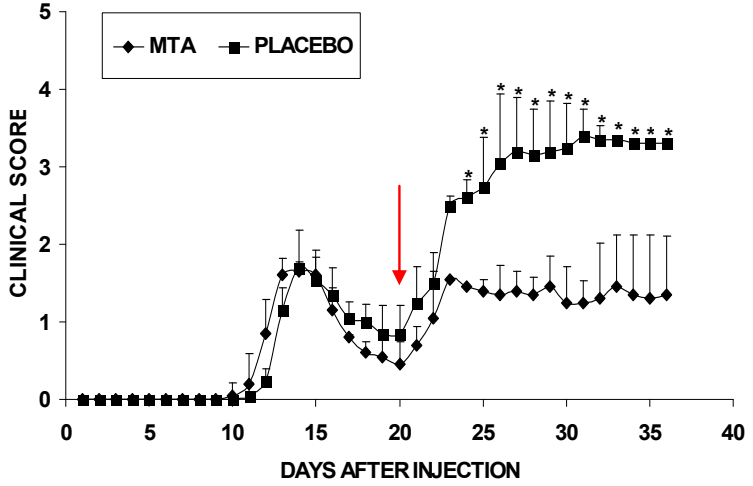
  MTA has been previously tested in 53 humans without relevant signs of toxicity:

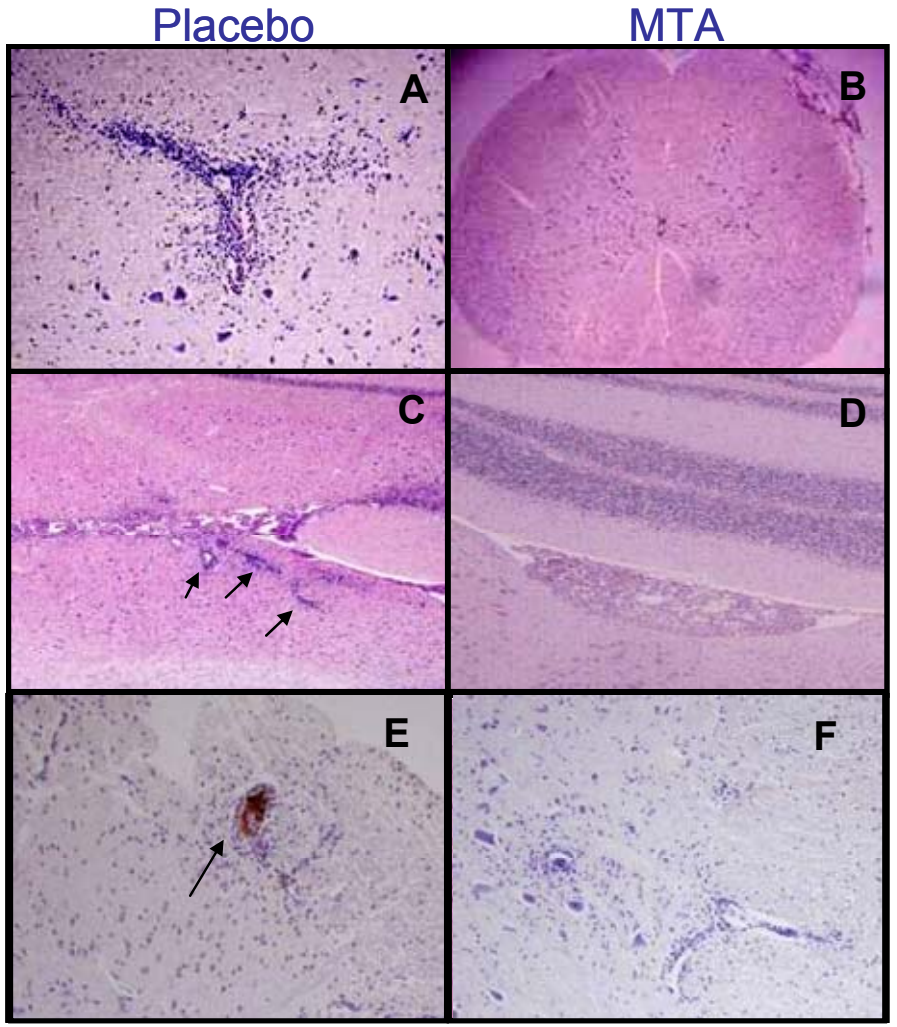
  100 mg every 8 hours for 3 days in 3 HC *(Stramentinoli U.S. patent 4,454,122. Filed: Aug 6, 1982; Issued: Jun 12, 1984).*

  600 mg/day for 1 month (*Moratti U.S. patent 5,753,213. Filed Mar 13, 1990; Issued May 19, 1998*).

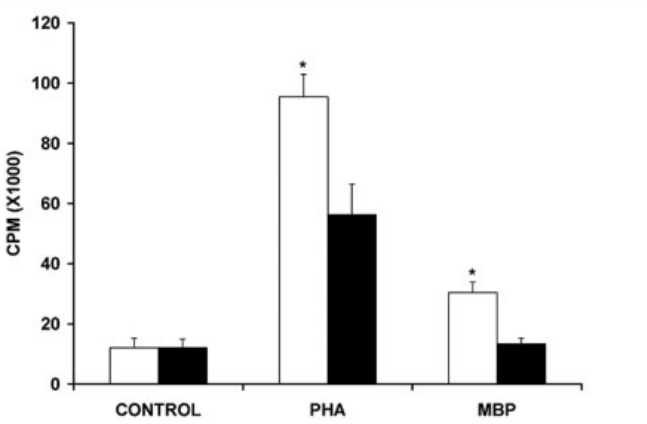
MTA treatment is effective in the acute and chronic-relapsing model of the disease

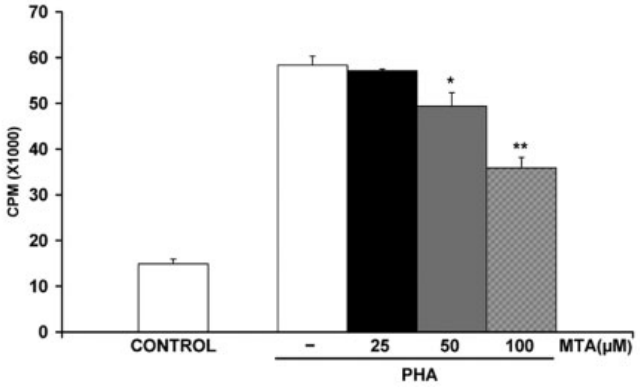


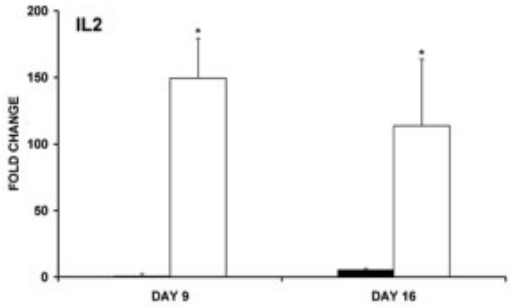


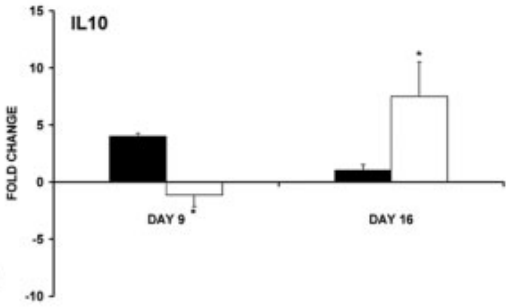


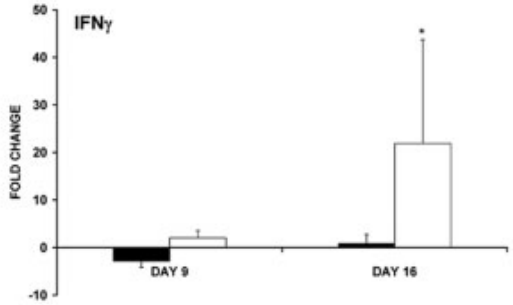
MTA inhibits the T-cell proliferation, redeuces the expression of proinflammatory cytokines and enhances the expression of IL10

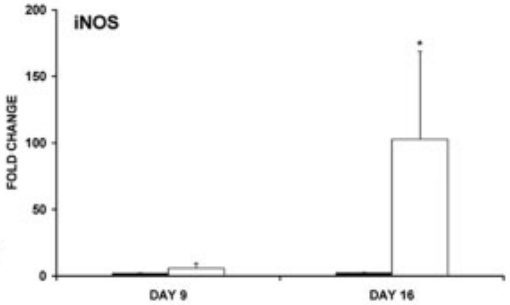


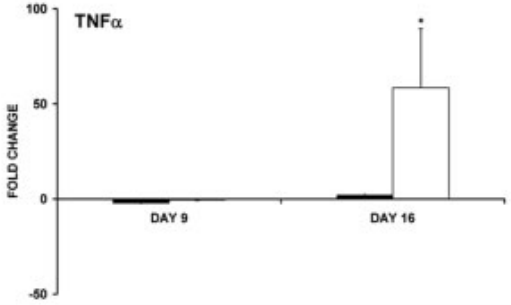












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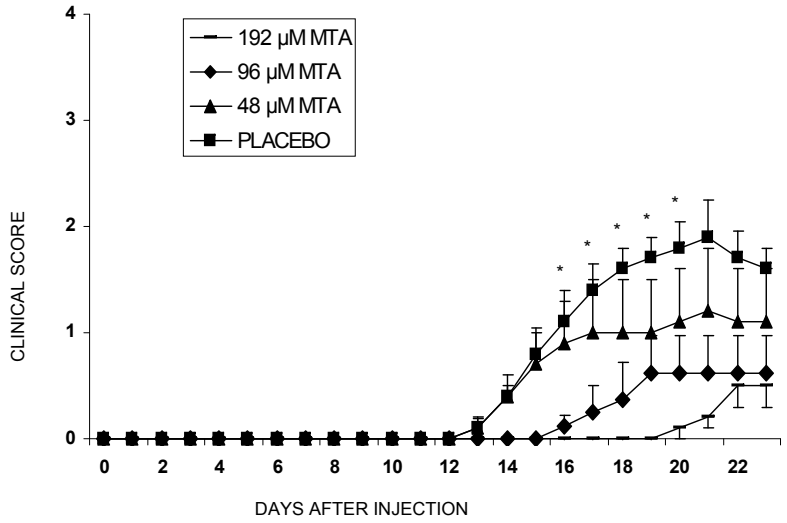
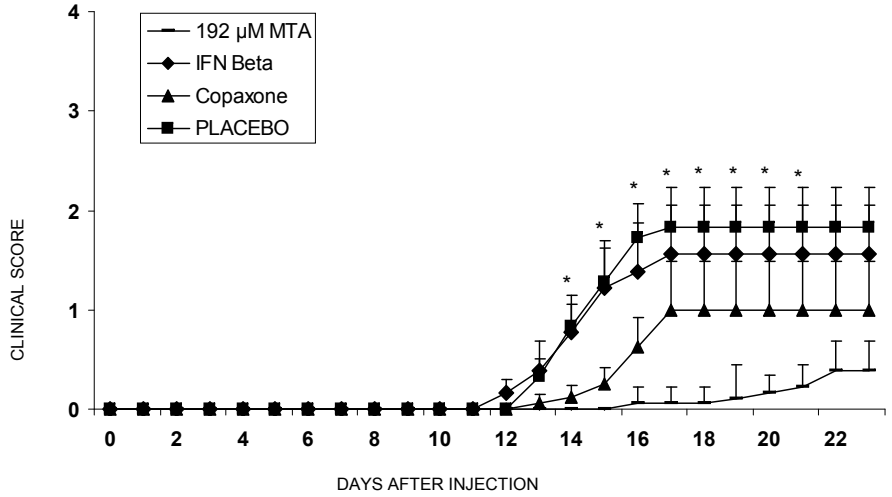
MTA effect is dose-dependent and the higher dose showed the best result when compared with Interferon-β and Copaxone





Promotes the greatest benefit compared to approved therapies

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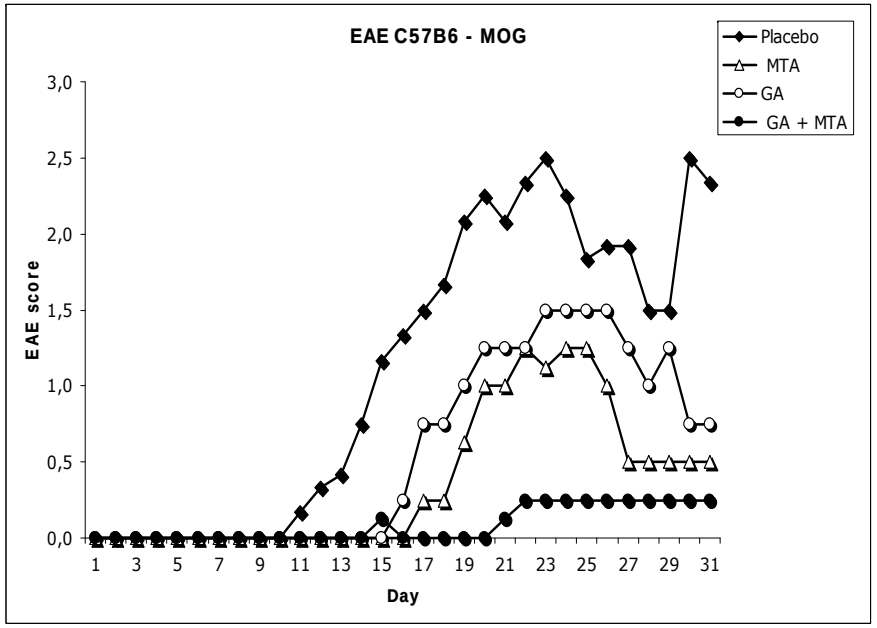
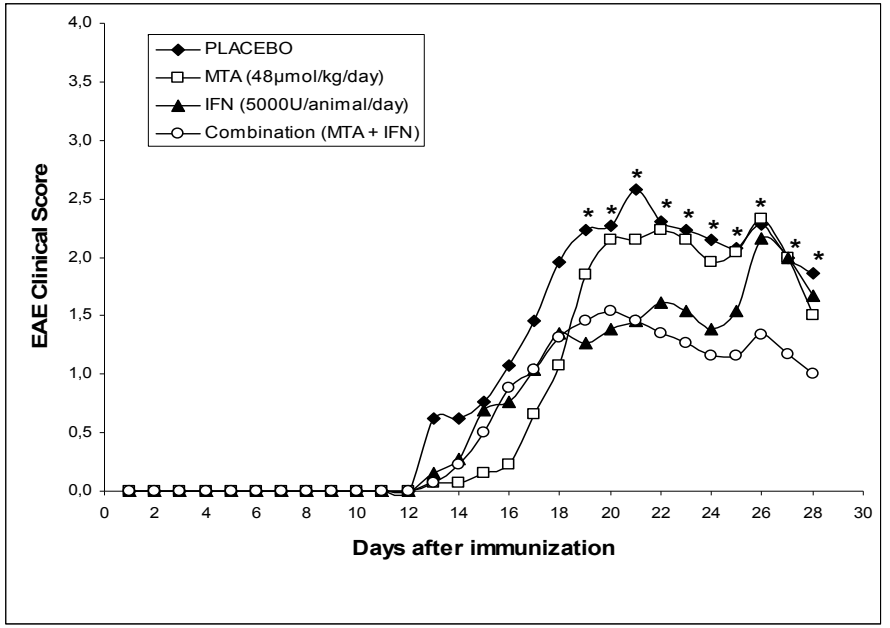
MTA shows synergistic effects with the current therapies for Multiple Sclerosis





Suitable for polytherapy

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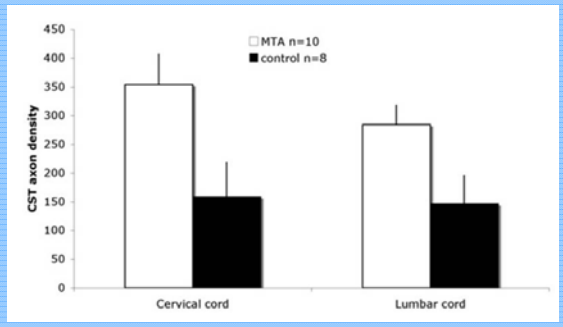
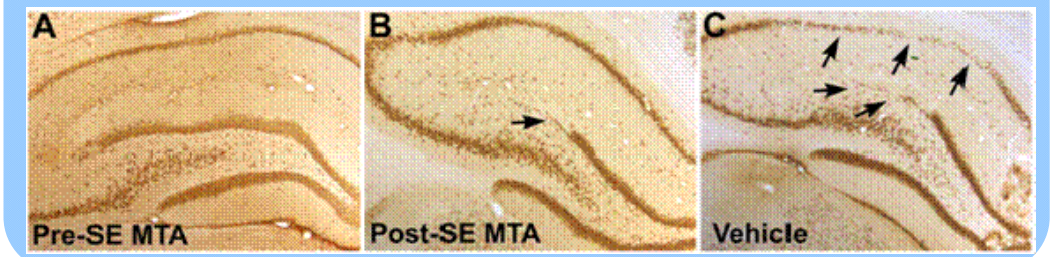
MTA not only has an immunomodulatory effect, but also it has a neuroprotective effect

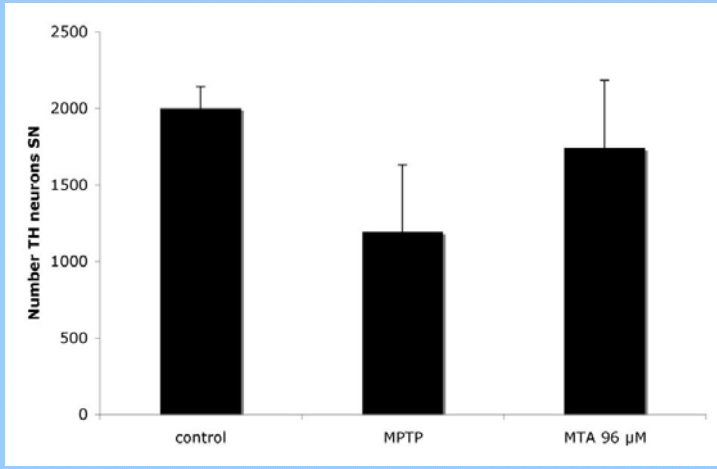
Multiple Sclerosis



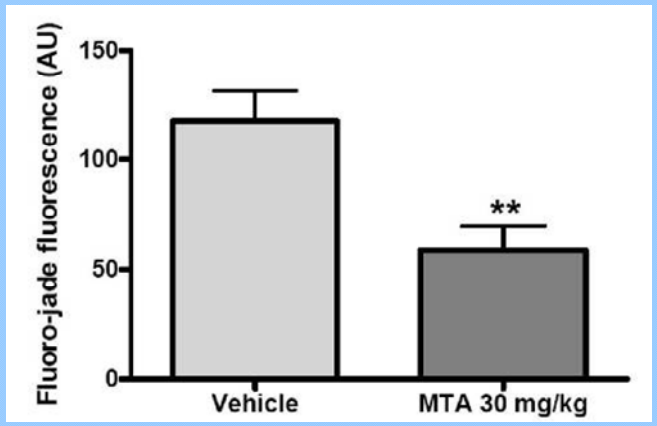
Epilepsy



Parkinson



Global ischemia



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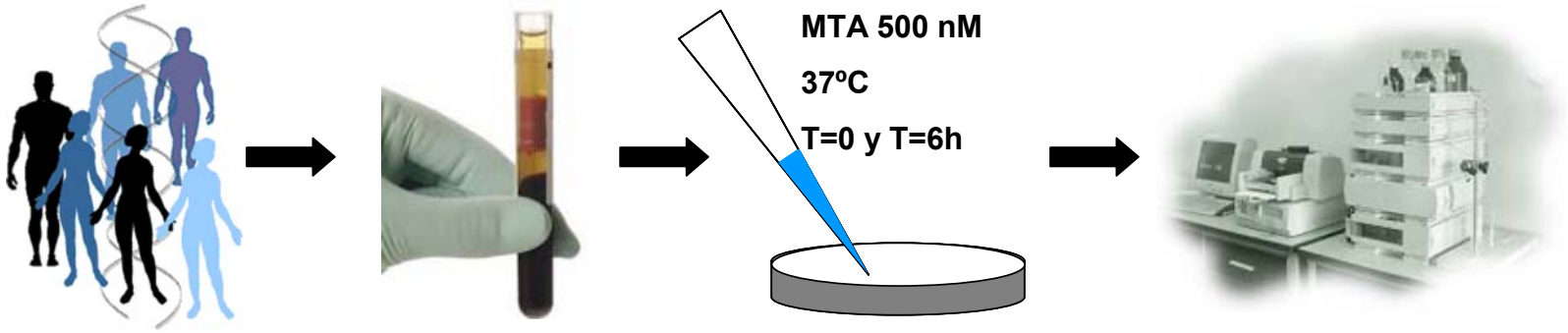
A potential biomarker for individuals with high or low consumption of MTA has been identified



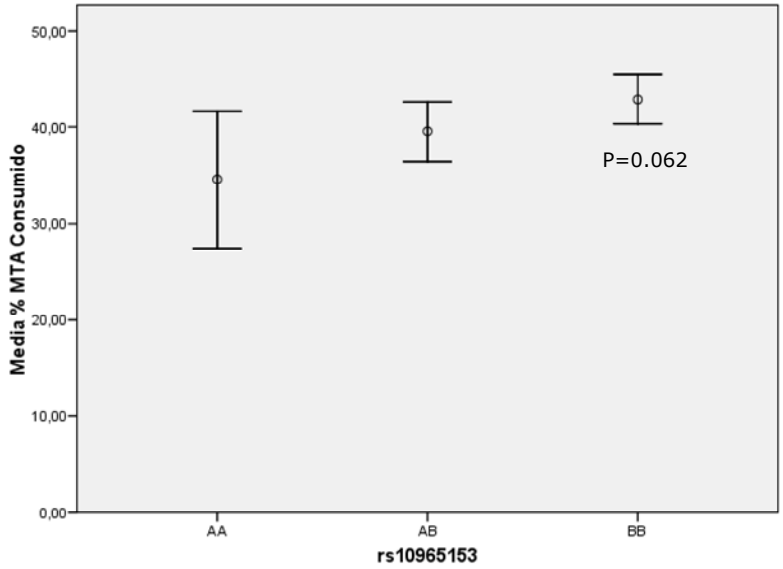


Figure 1: MTA consuption in the different rs10965153 SNP (A= Thymine y B= Cytosine). Results show percentage of consumption as mean ± SD.

In summary

- MTA exibits a novel MoA: exogenous MTA inhibits in a reversible, non-toxic, and dose-dependent manner, the activation of peripheral human lymphocytes (Ann Neurol. 2006 Sep: 60(3):323-34).
- Positive PoC in MS animal models (Acute and chronic relapsing EAE).
- MTA administration promotes the greatest benefit compared to interferon-β or Copaxone in the EAE models.
- In combination studies, MTA synergizes with Copaxone in the EAE model.
- Synergistic studies with interferon-β showed additive effect.
- Oral administration reproduced i.p. effect.
- Neuroprotection studies were positive.
- A potential biomaker has been identified and could be use to adjust the therapeutic dose.