

**VI CONGRESSO NAZIONALE SINUT,
Bologna 27-28 maggio 2016**

**NUOVE PROSPETTIVE PER LA
NUTRACEUTICA: LE
PATOLOGIE “INCURABILI”**

Prof. Cesare Sirtori
Direttore Centro Dislipidemie
A.O. Niguarda Ca' Granda, Milano

Presidente Onorario Sinut

Hypertension



proteins, milk,
soy, lupin
(VPP, IPP)

chocolate
(flavanols)



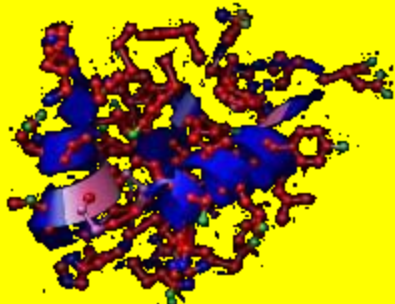
Nutrients for a
Happy Heart



psyllium



β -glucan



Diabetes



fish, n-3

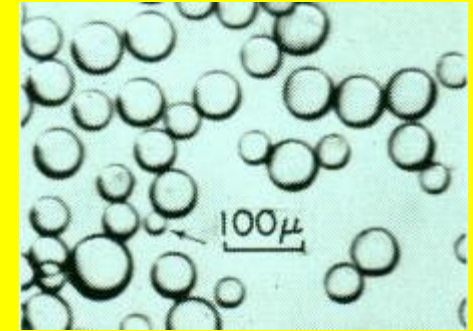


lupin



soy

Hyperlipidemia



psyllium



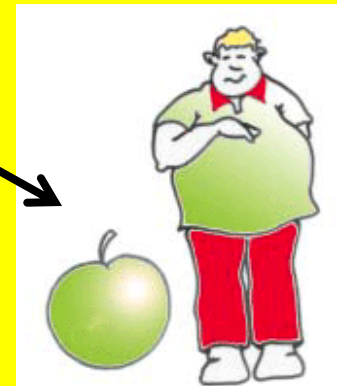
β -glucan



phytosterols



soy proteins



Obesity

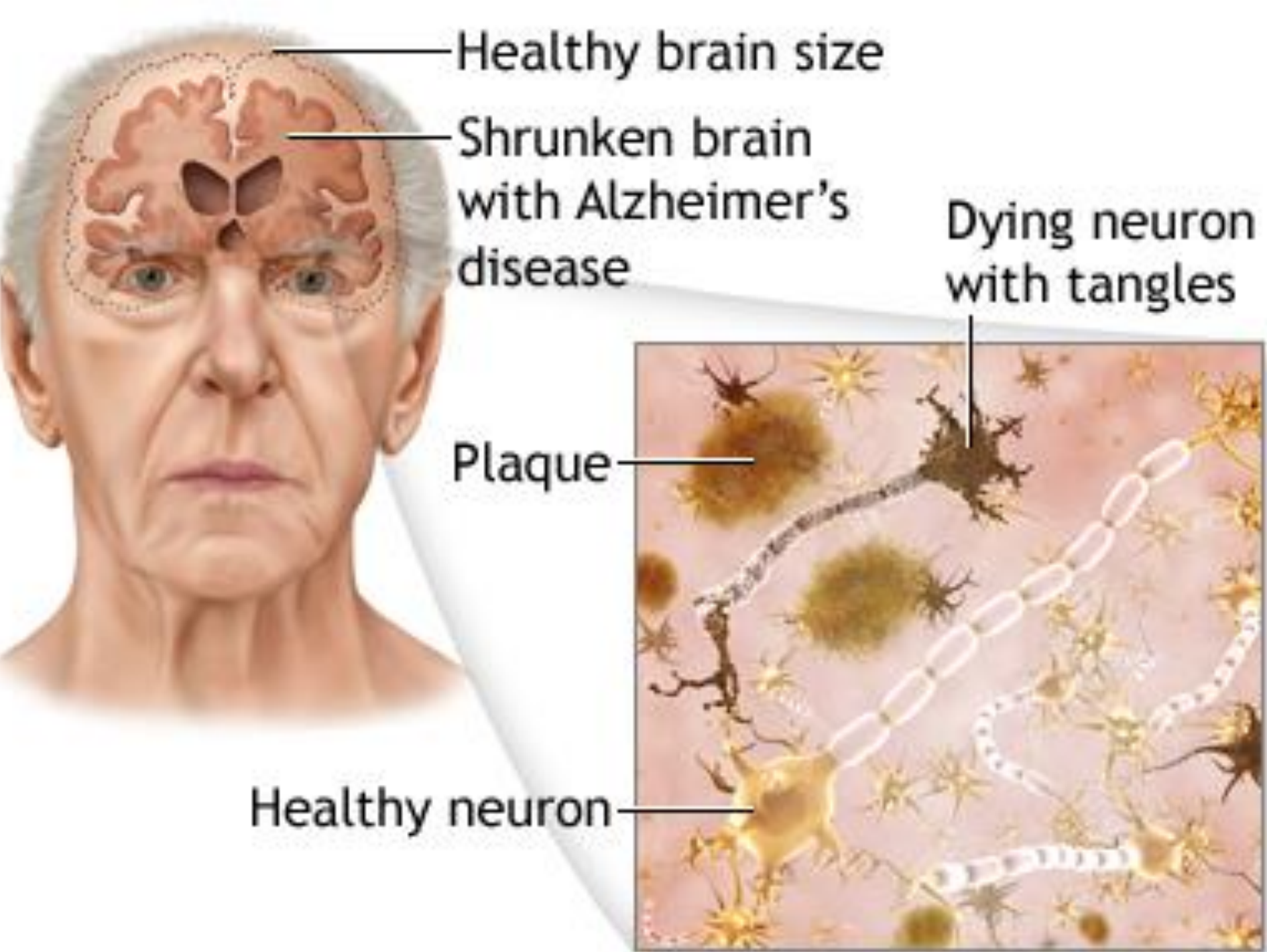
PATOLOGIE DI DIFFICILE TRATTAMENTO CON FARMACI: UN APPROCCIO NUTRACEUTICO?

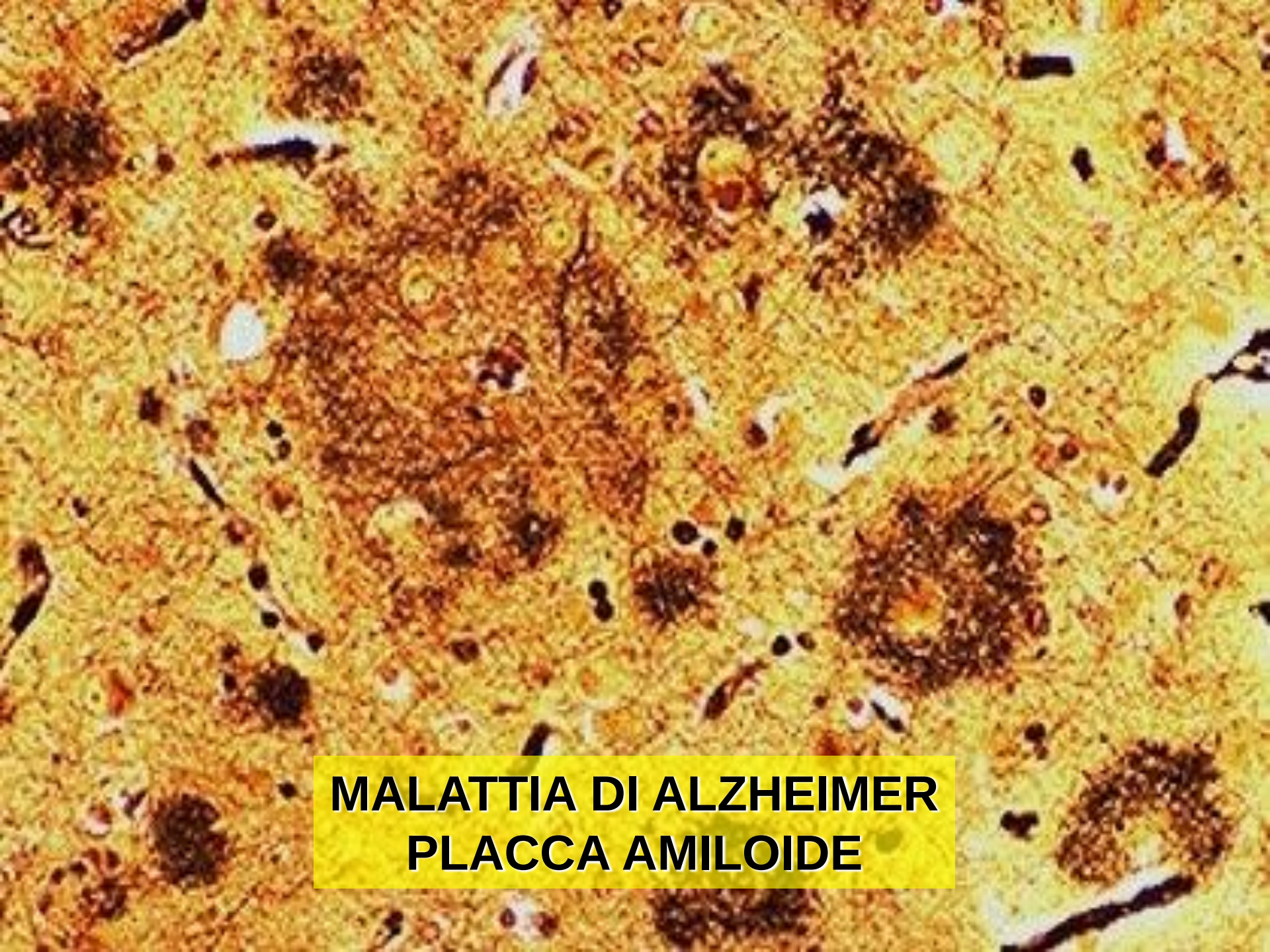
M. di Alzheimer

Autismo

Antibiotico-resistenza

Tumori



A microscopic image of a brain tissue section showing an amyloid plaque. The plaque is a large, dense, brownish-yellow mass with a granular texture, surrounded by a halo of smaller, less dense material. The surrounding brain tissue is lighter yellow and contains various small, dark-staining structures, likely neurons and glial cells. The overall appearance is characteristic of an amyloid plaque in Alzheimer's disease.

**MALATTIA DI ALZHEIMER
PLACCA AMILOIDE**

ALZHEIMER: β - AMILOIDE O NO?

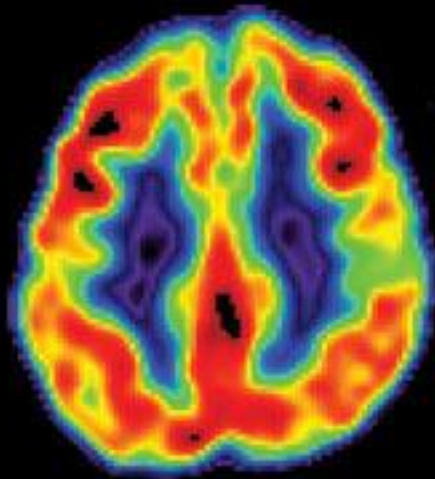
- Casi di Alzheimer senza β -amiloide e viceversa
- Fino ad ora non grande efficacia delle terapie anti- β -amiloide
- Deficit energetico cerebrale sembra il fenomeno più frequente

Alzheimer: β -amiloide ?

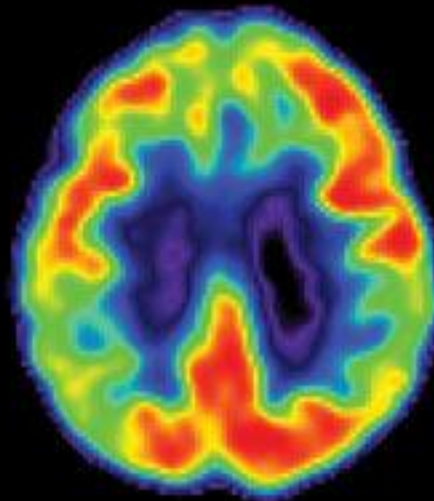


*Sister Matthia + 104 anni, neuropatologia Alzheimer
4° grado corteccia entorinale, ippocampo*

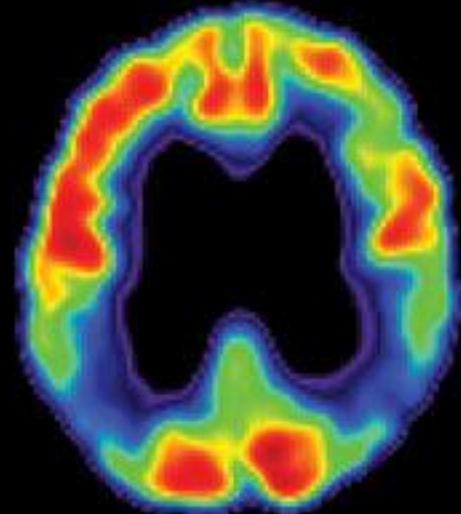
Snowdon DA, Ann. Intern. Med. 139, 450, 2003



Normal



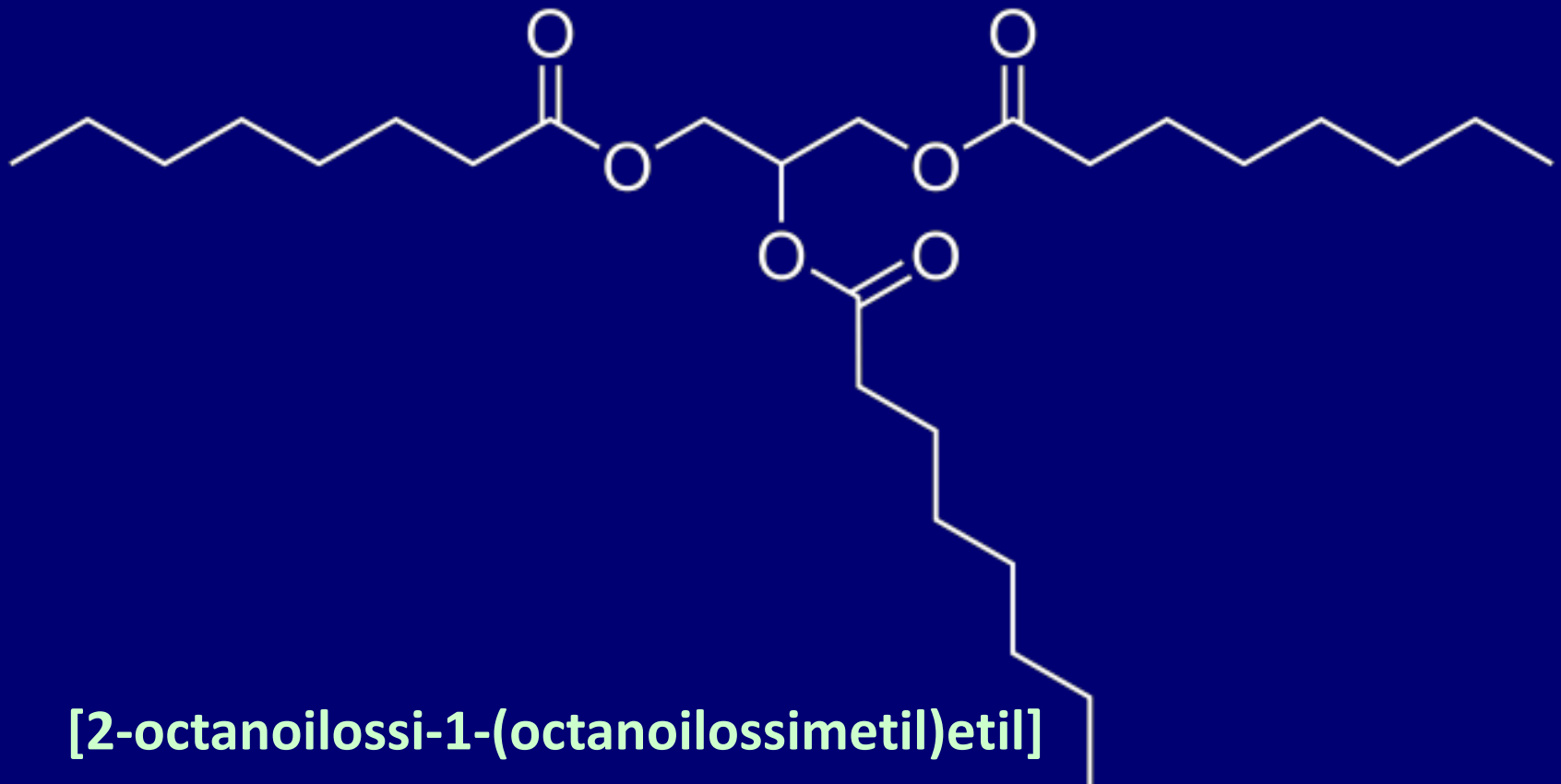
Mild cognitive
impairment



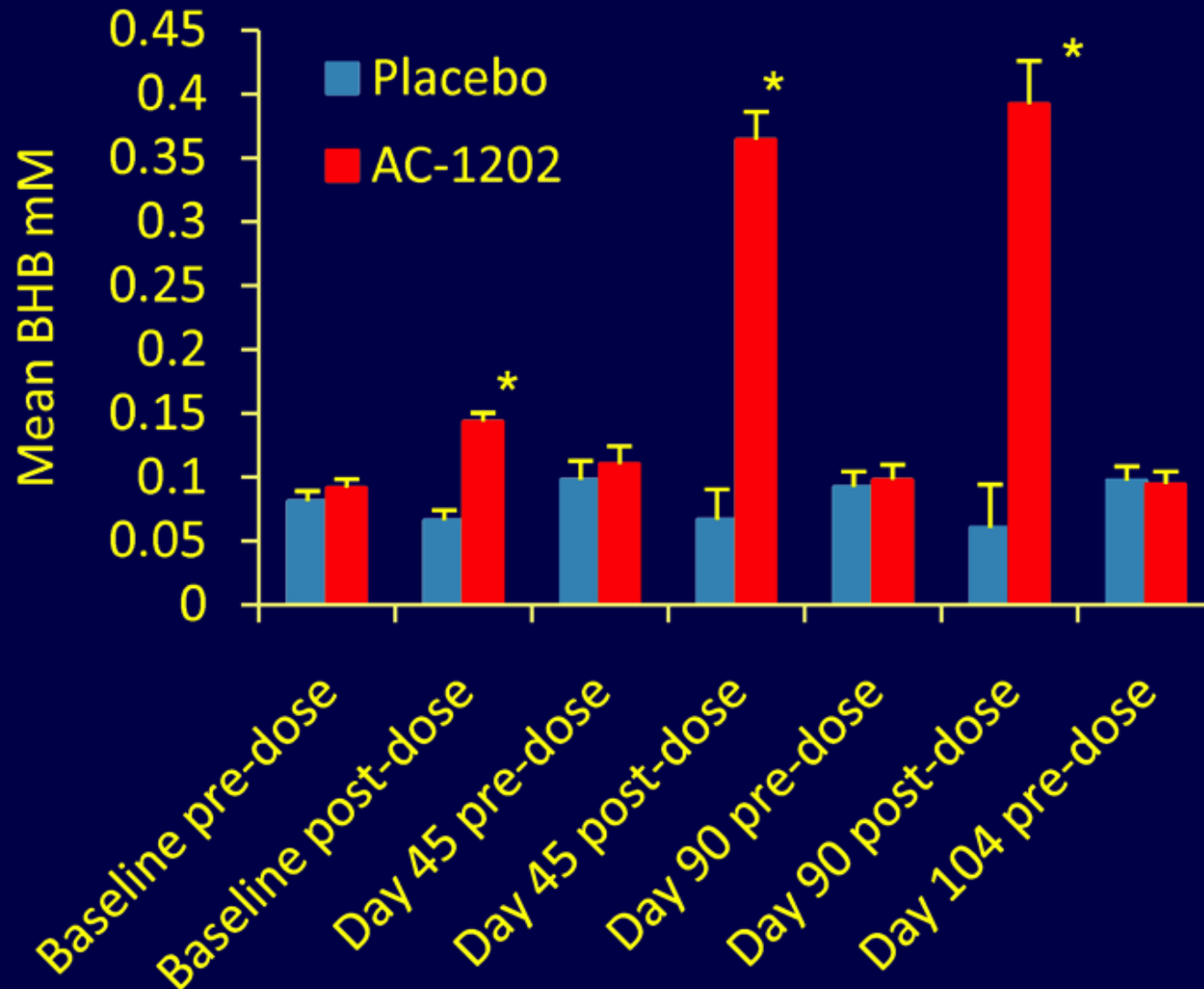
Alzheimer's
disease

**IPOMETABOLISMO DEL GLUCOSIO NEL DEFICIT
COGNITIVO E NELL'ALZHEIMER**

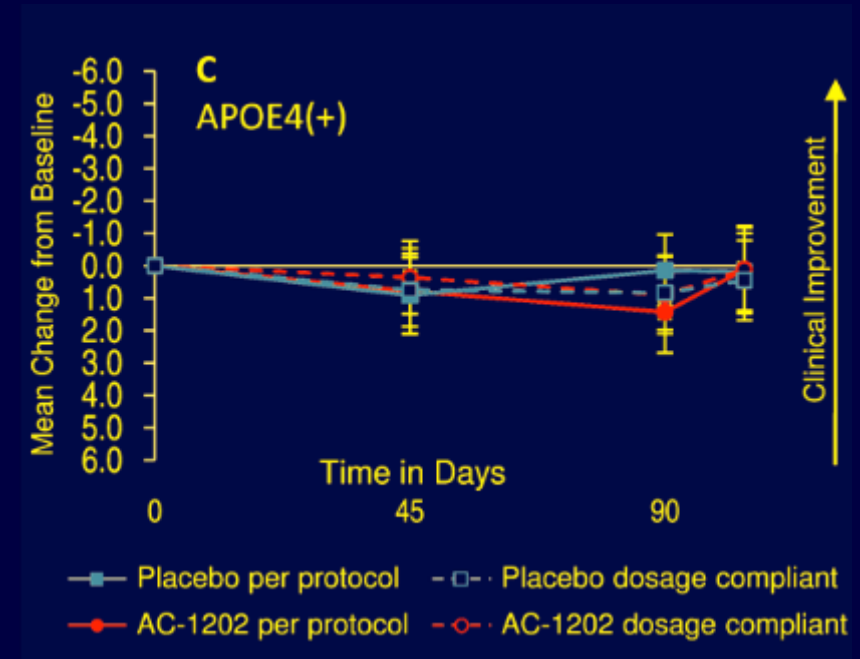
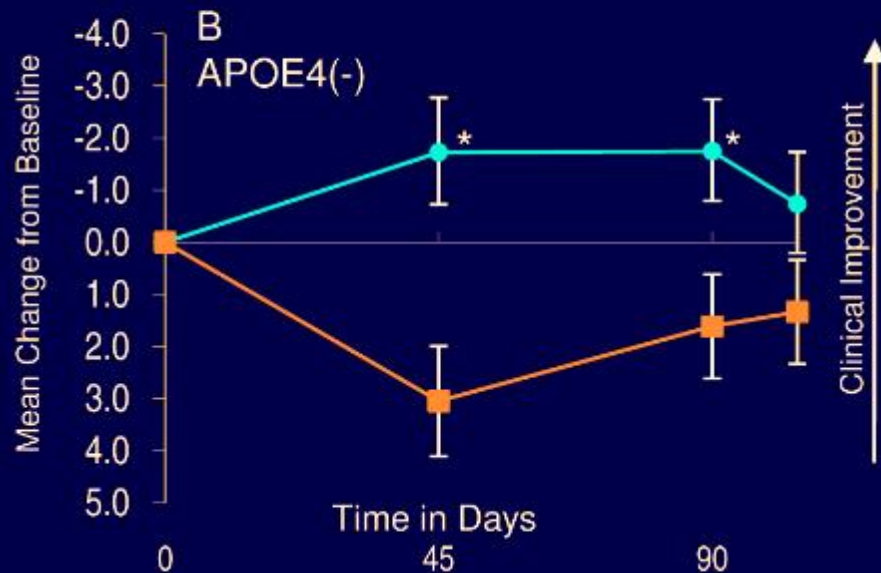
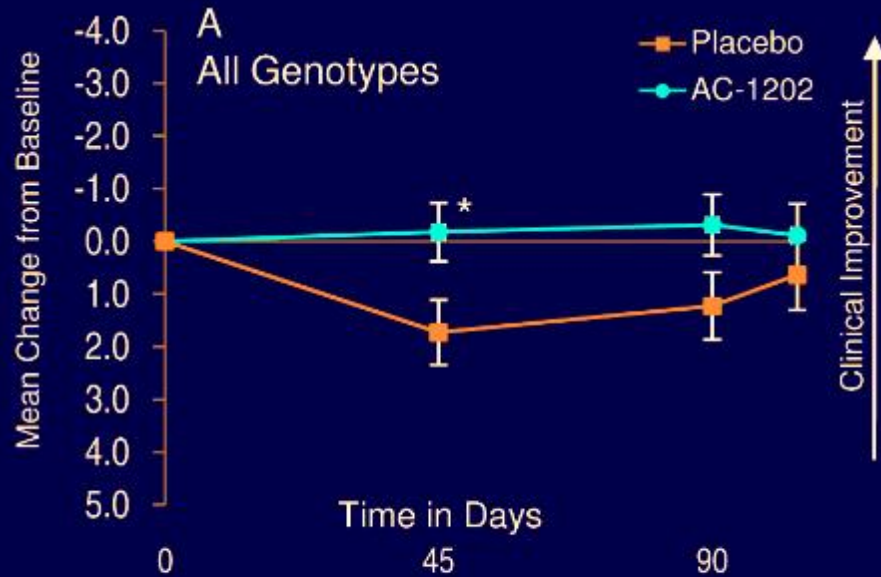
Axona (*caprylidene*) medical food approved in March 2009 by the U.S. FDA for the “clinical dietary management of the metabolic processes associated with mild to moderate Alzheimer’s disease”



Mean pre- and post-dose serum BHB levels at each study visit



Mean change in ADAS-Cog scores from baseline in populations stratified by E4 status



DETERMINANTI NUTRIZIONALI DELL'ALZHEIMER: LO STUDIO "MIND"

Dieta Mediterranea e diete DASH riducono il declino cognitivo

Mediterranean–DASH Dietary Intervention for Neurodegenerative Delay (MIND)

Follow up di 4,7 anni dei partecipanti al Memory and Aging Project (MAP).

1556 soggetti dal 1997 al 2011

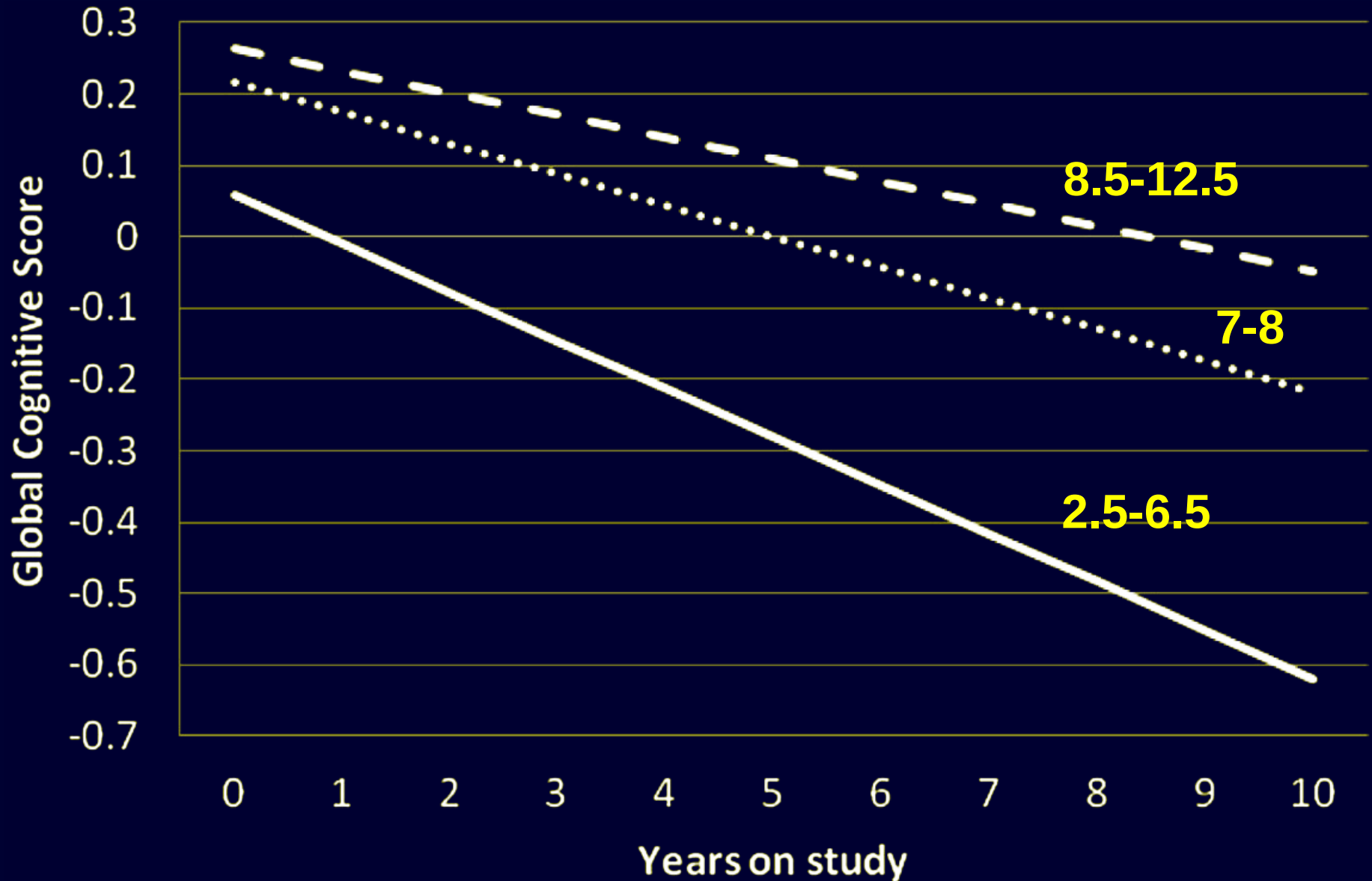
73.1% donne, età media 80.1 a

(Bennett et al. Curr Alzheimer Res 9, 644, 2012)

DIETA MIND: I PUNTEGGI

Diet component	0	0.5	1
Green leafy* vegetables	≤2 servings/wk	>2 to <6/wk	≥6 servings/wk
Other vegetables [†]	<5 serving/wk	5 to <7 wk	≥1 serving/d
Berries [‡]	<1 serving/wk	1/wk	≥2 servings/wk
Nuts	<1/mo	1/mo to <5/wk	≥5 servings/wk
Olive oil	Not primary oil	→ Primary oil used	
Butter, margarine	>2 T/d	1–2/d	<1 T/d
Cheese	7 + servings/wk	1–6/wk	<1 serving/wk
Whole grains	<1 serving/d	1–2/d	≥3 servings/d
Fish (not fried)	Rarely	1–3/mo	→ ≥1 meals/wk
Beans [§]	<1 meal/wk	1–3/wk	>3 meals/wk
Poultry (not fried) [¶]	<1 meal/wk	1/wk	≥2 meals/wk
Red meat and products [#]	7 + meals/wk	4–6/wk	→ <4 meals/wk
Fast fried foods**	4 + times/wk	1–3/wk	<1 time/wk

Punteggi MIND: Declino cognitivo



Morris MC et al, *Alzheimer's & Dementia* 11, 1015, 2015

DIETA SOUVENAIID

125 ml una volta al giorno

Eicosapentaenoic acid, 300 mg

Docosahexaenoic acid, 1200 mg



Phospholipids 106 mg

Choline, 400 mg

Uridine monophosphate, 625 mg

Vitamin E (alpha-tocopherol equivalents), 40 mg

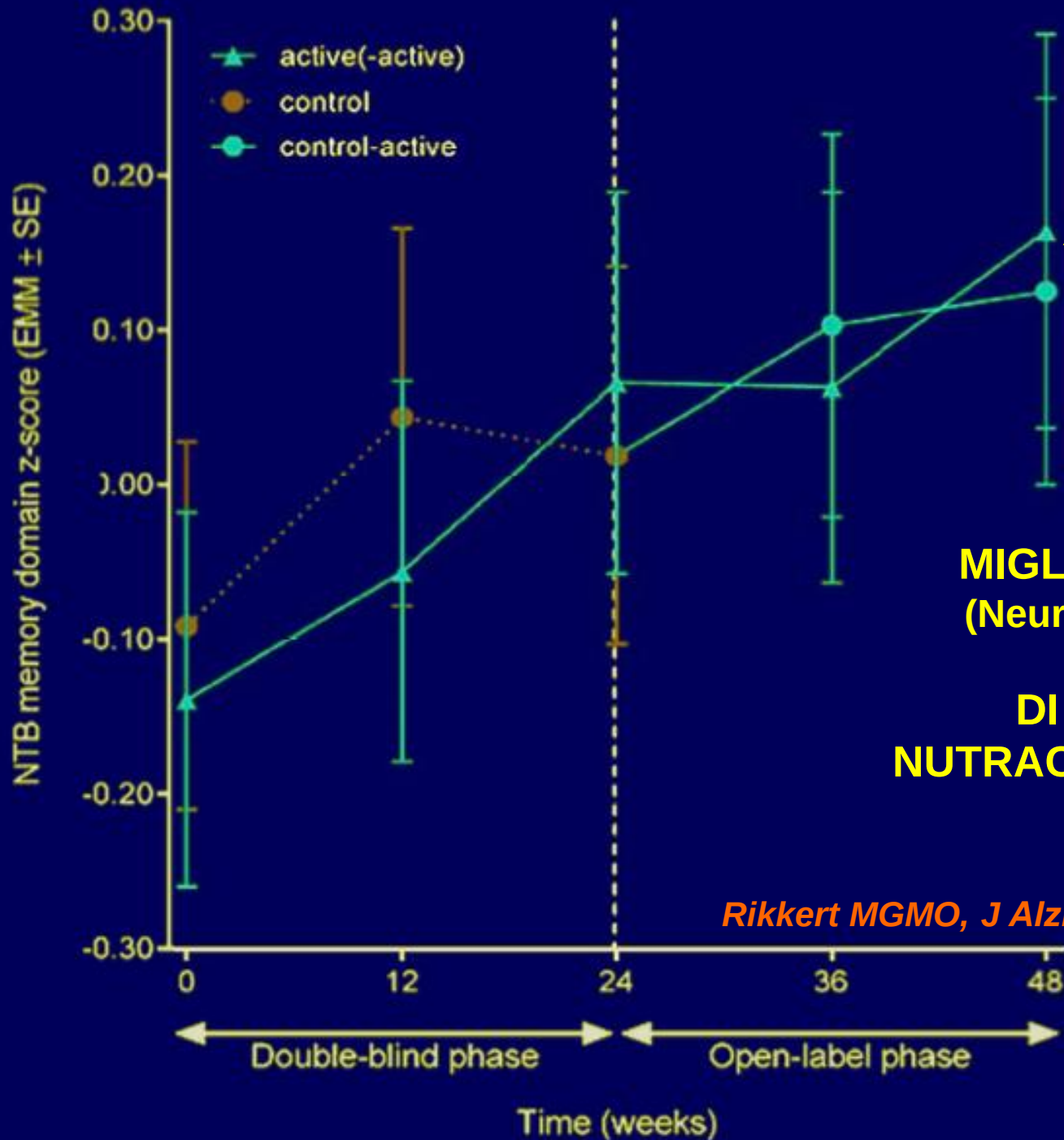
Selenium, 60 µg

Vitamin B12, 3 µg

Vitamin B6, 1 mg

Folic acid, 400 µg

Vitamin C, 80 mg



Attivo-Attivo



**MIGLIORAMENTO NTB
(Neuropsychological Test
Battery)
DI MEMORIA CON
NUTRACEUTICO SOUVENAID**

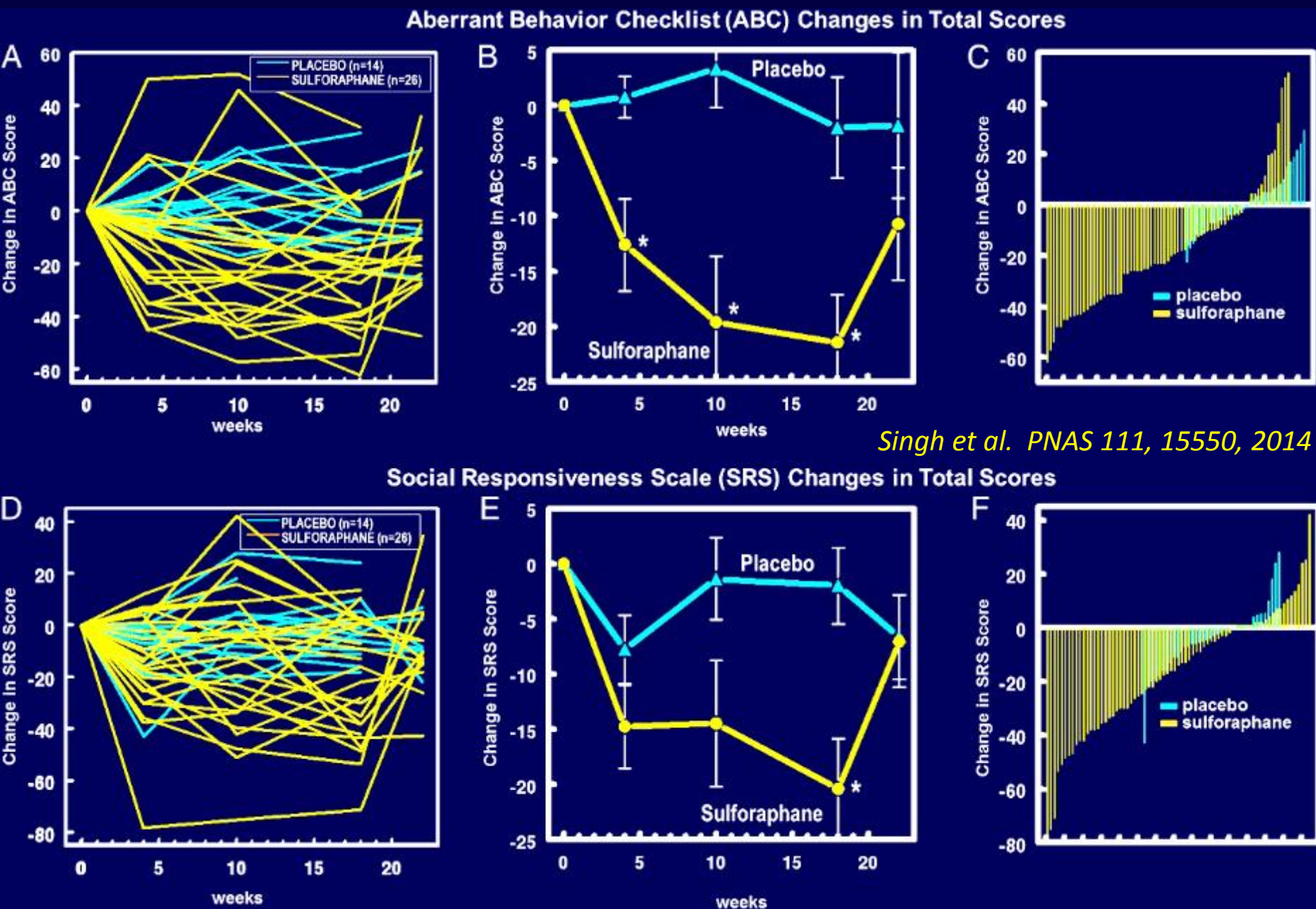
Rikkert MGMO, J Alzheimer's Dis 44, , 471, 2015

A black and white photograph of two men in business suits. The man on the left is leaning over a desk, looking intently at a document. The man on the right is sitting at the desk, looking up at the first man. The background is blurred, suggesting an office setting.

AUTISMO
1/68 nascite
X 2 dopo cesareo

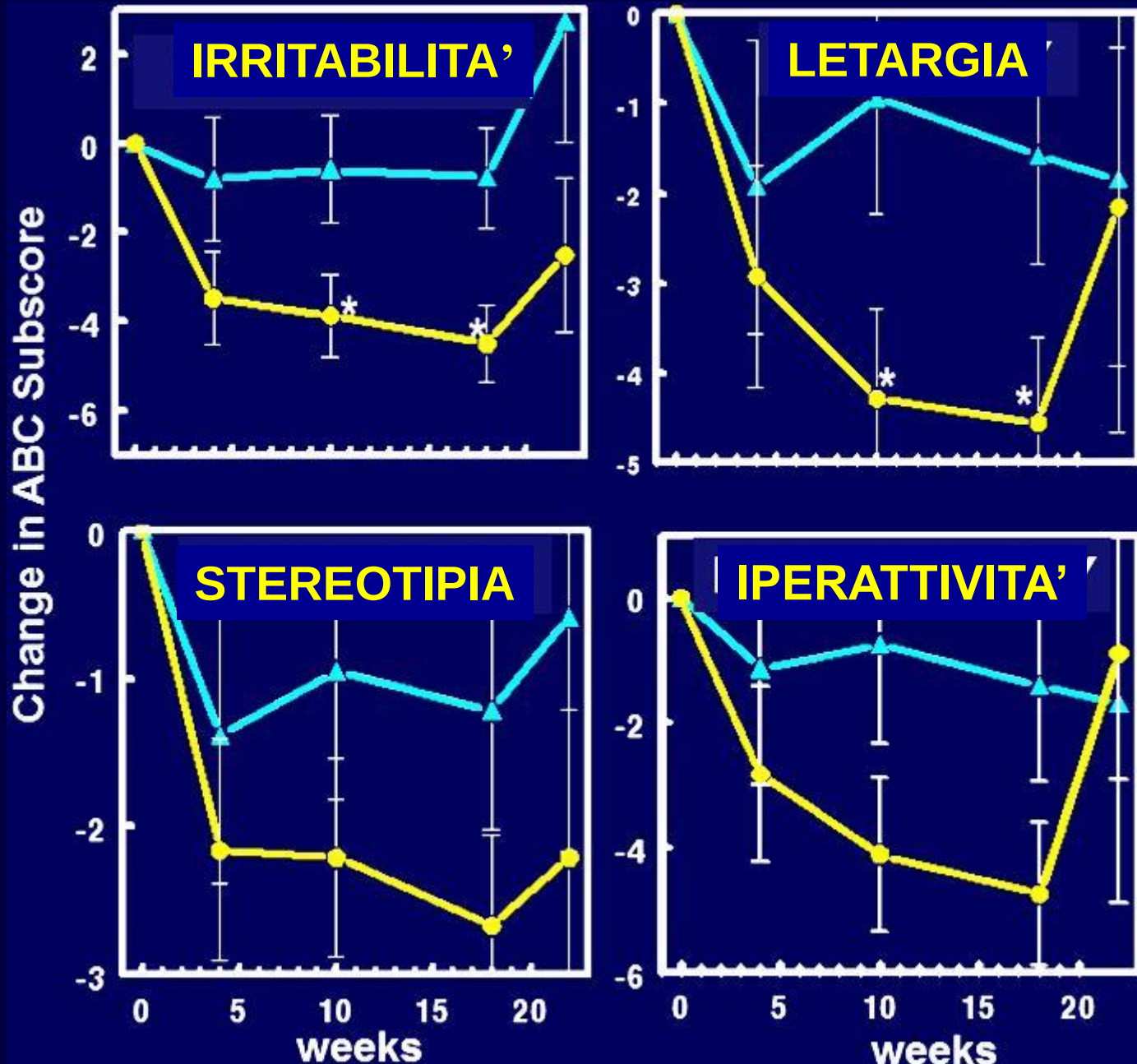


ATTIVITA' DEL SULFORAFANO (460-690 mg/die) SU COMPORTAMENTO/SOCIALIZZAZIONE



SULFORAFANO NELL'AUTISMO: ABC SOTTOPUNTEGGI

Singh et al. PNAS 111, 15550, 2014





super smart
BROCCOLI
SULFORAPHANE
GLUCOSINOLATE

Food supplement
Supplément nutritionnel
Nahrungsergänzung

60

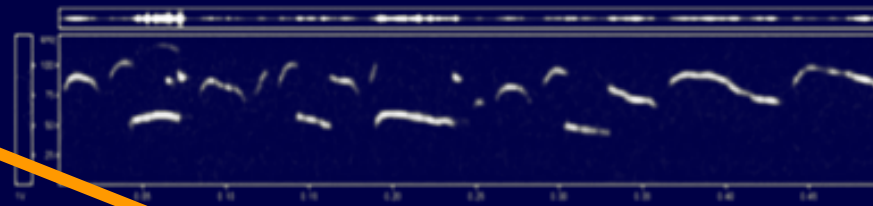
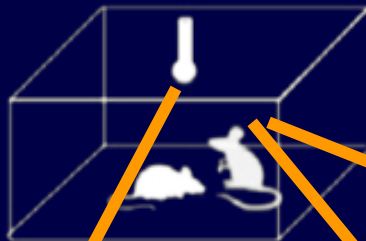
Vegetarian Capsules
Gélules Végétariennes
Händliche Cellulosekapseln

300 mg

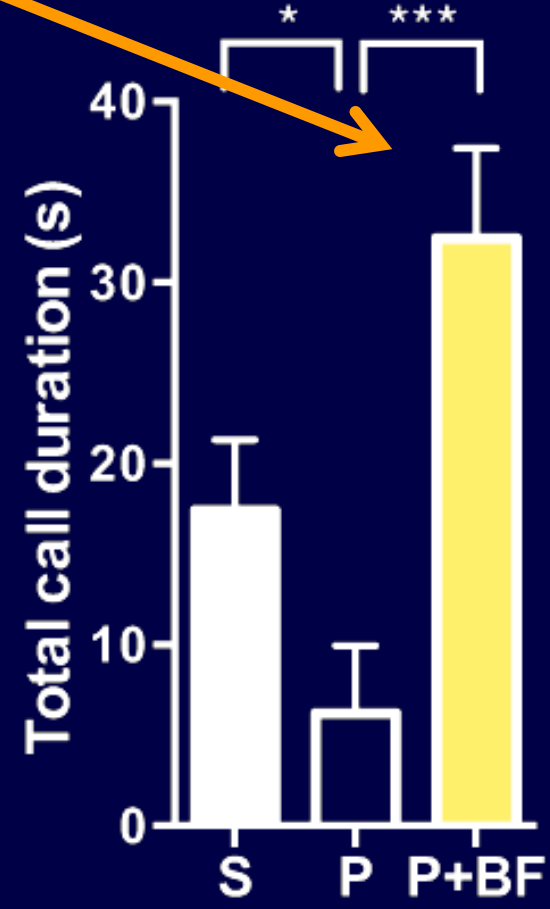
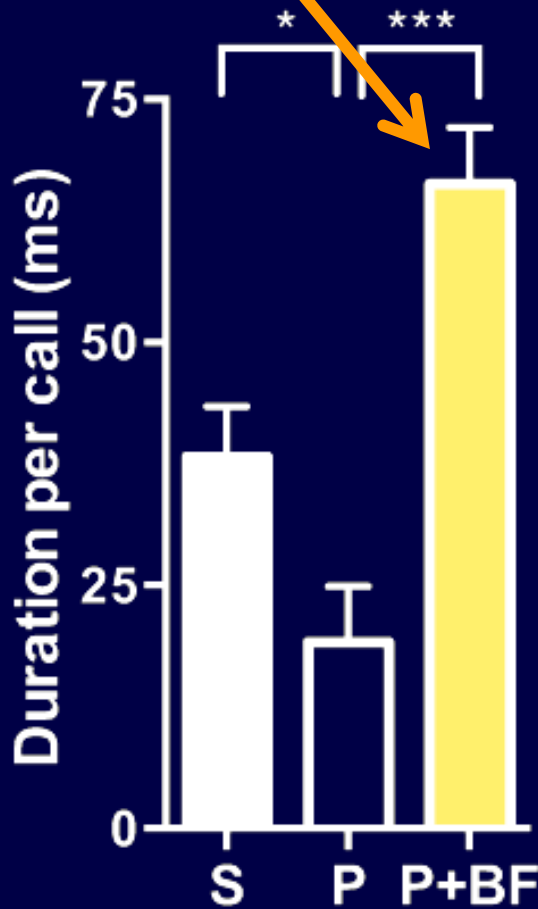
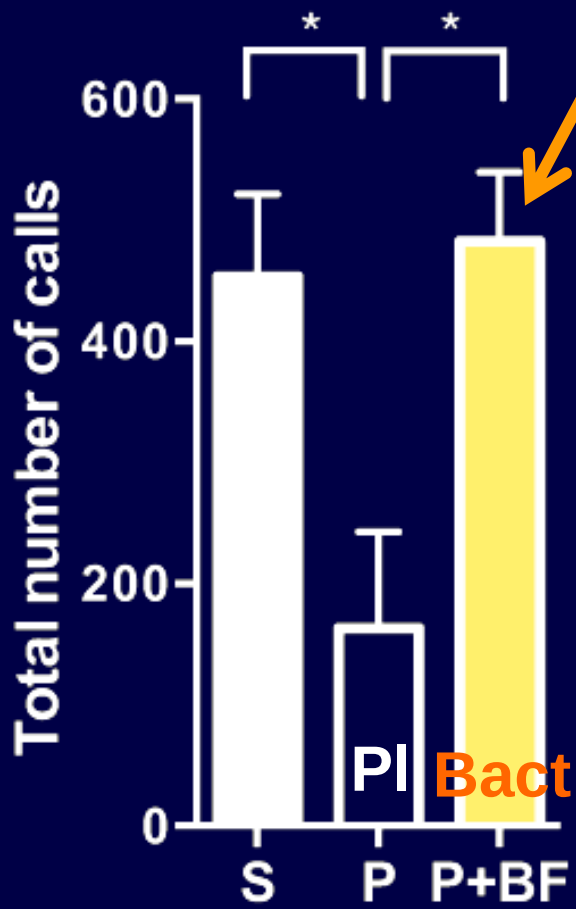
Recommendation:
dry. Each capsule
extract. Prostate
This product is
balanced diet. It
heat and health
create a healthy
program. Includes
Cannabis oil
just. Capsules
Prostate
Ca product is a
one alternative
young adults. Caps
Flavonoids. Caps
protection of
alcohol or is
Bach's or is
to get. Hand
distributed per
Duke 7. J. J. J.
Smart Co. U.S. P.O.
Grand Duchy

PROBIOTICO CON B. FRAGILIS MIGLIORA LA COMUNICAZIONE NEL TOPO MIA

Communication:
Ultrasonic vocalizations

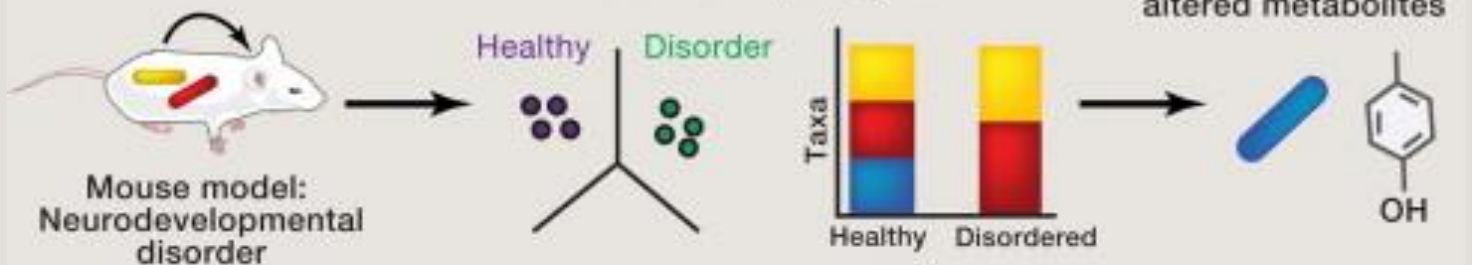


D

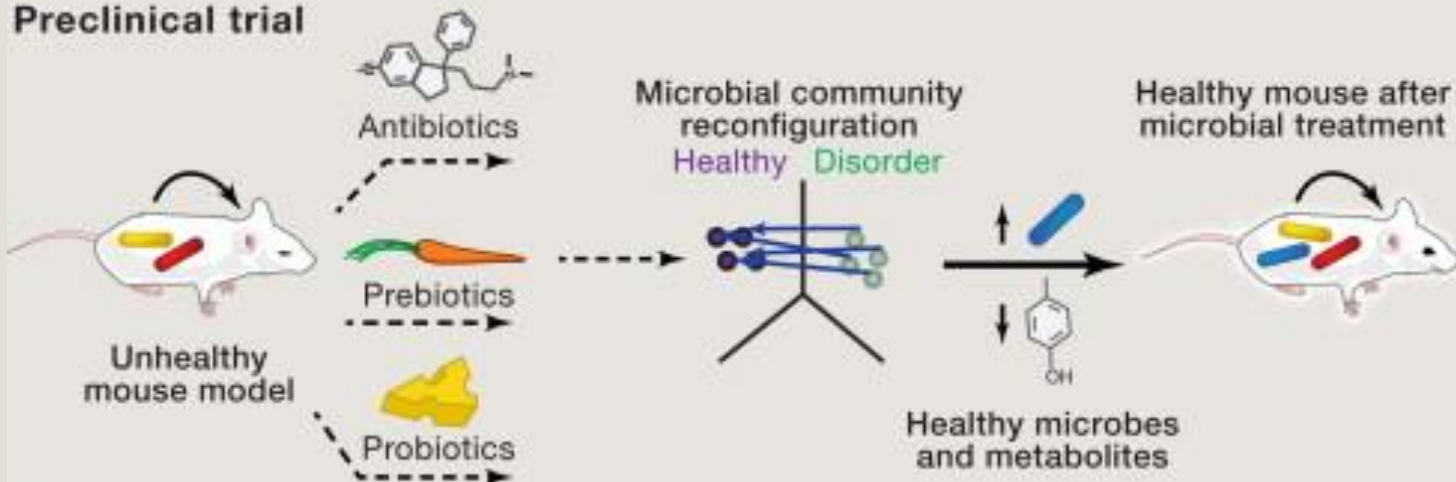


(Hsiao et al, Cell 155, 1451, 2013)

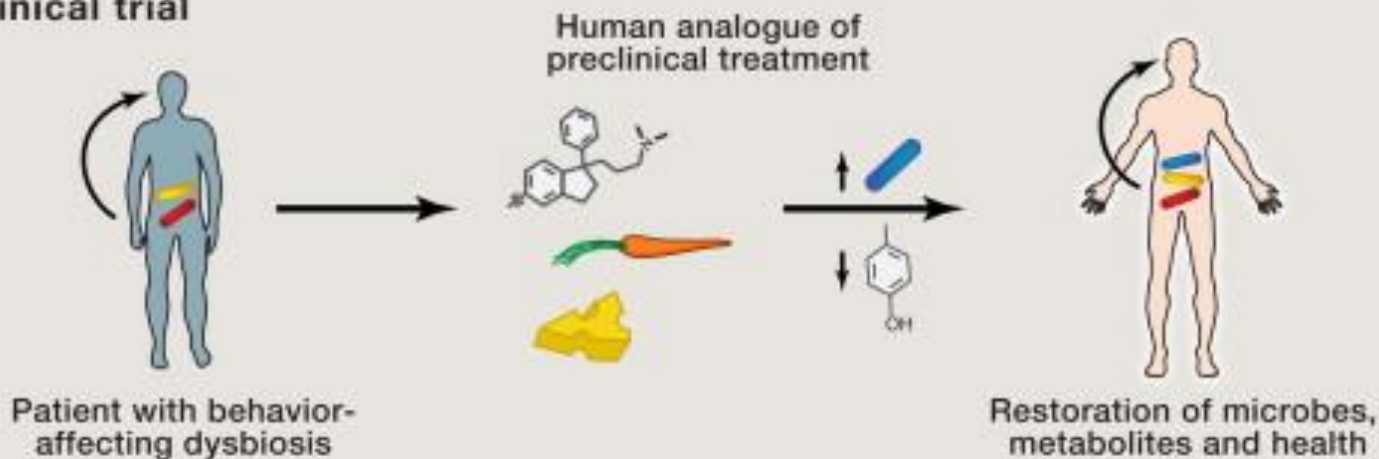
Laboratory



Preclinical trial



Clinical trial

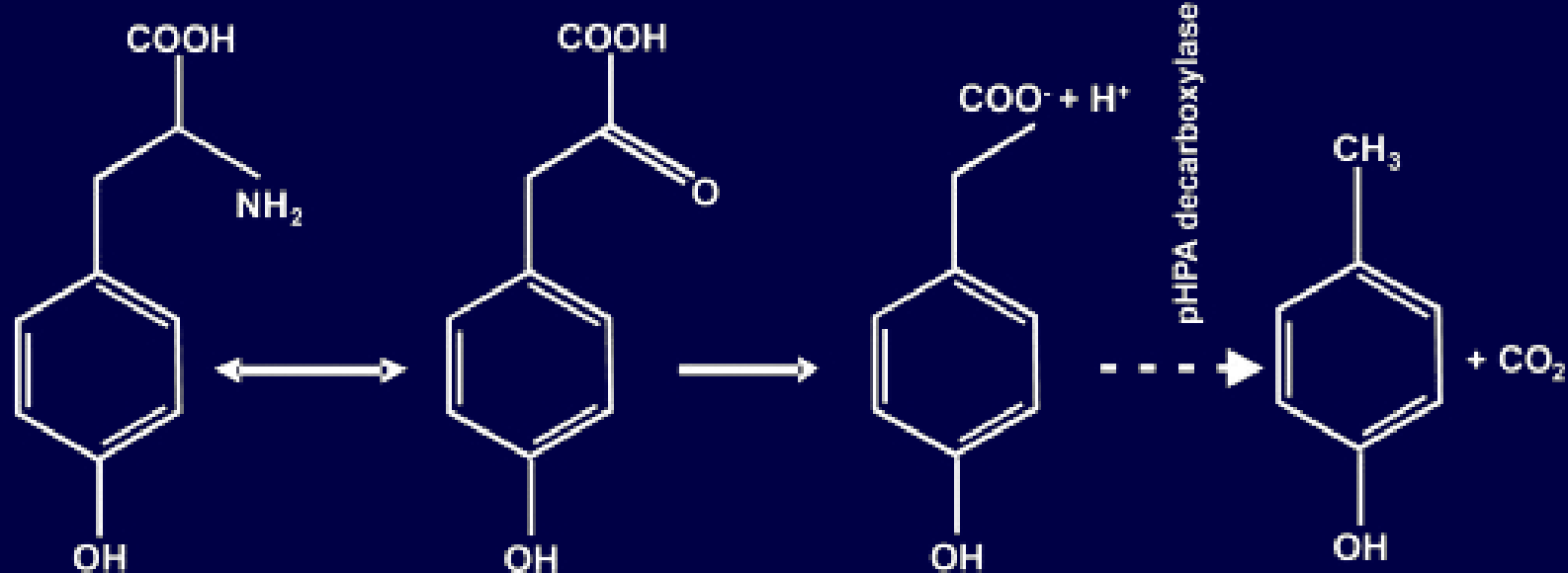


AUTISMO-ASSE PROBIOTA- INTESTINO-CERVELLO

Obiettivo

- migliorare l'integrità della barriera intestinale
- la tossina uremica 4-etilfenilsolfato (4EPS) è un marcatore lineare di autismo ed è il metabolita più alterato
(>40 volte il normale)

(Gilbert et al. Cell 155, 1446, 2013)

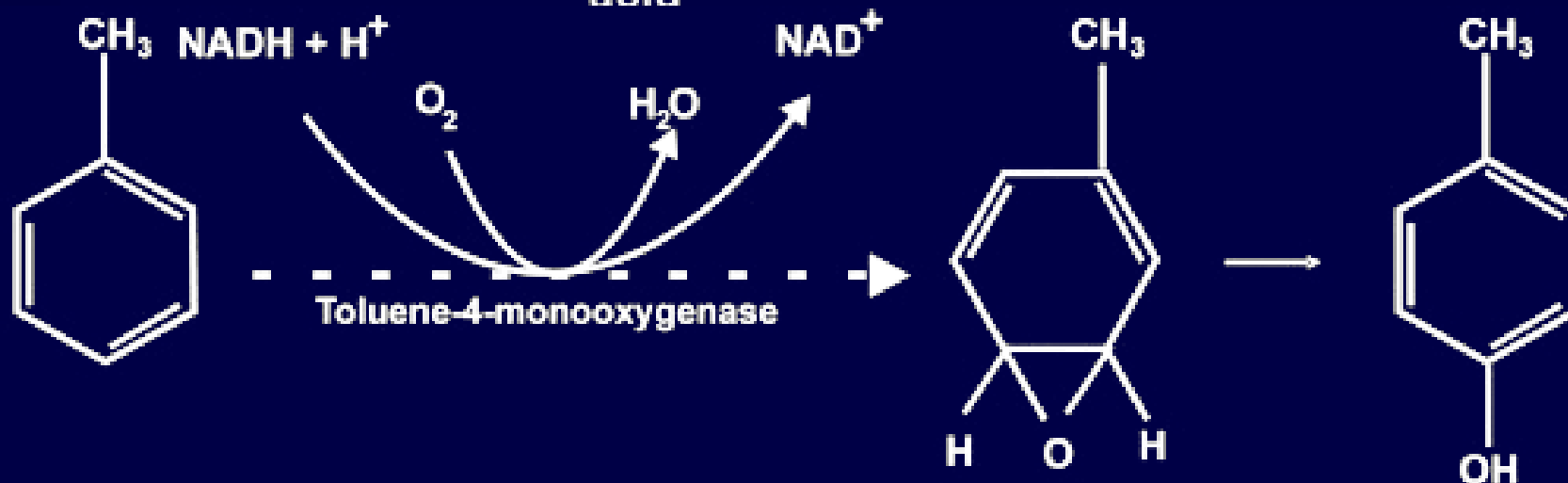


L-Tyrosine

p-hydroxy-phenylpyruvic acid

p-hydroxy-phenylacetate

p-Cresol

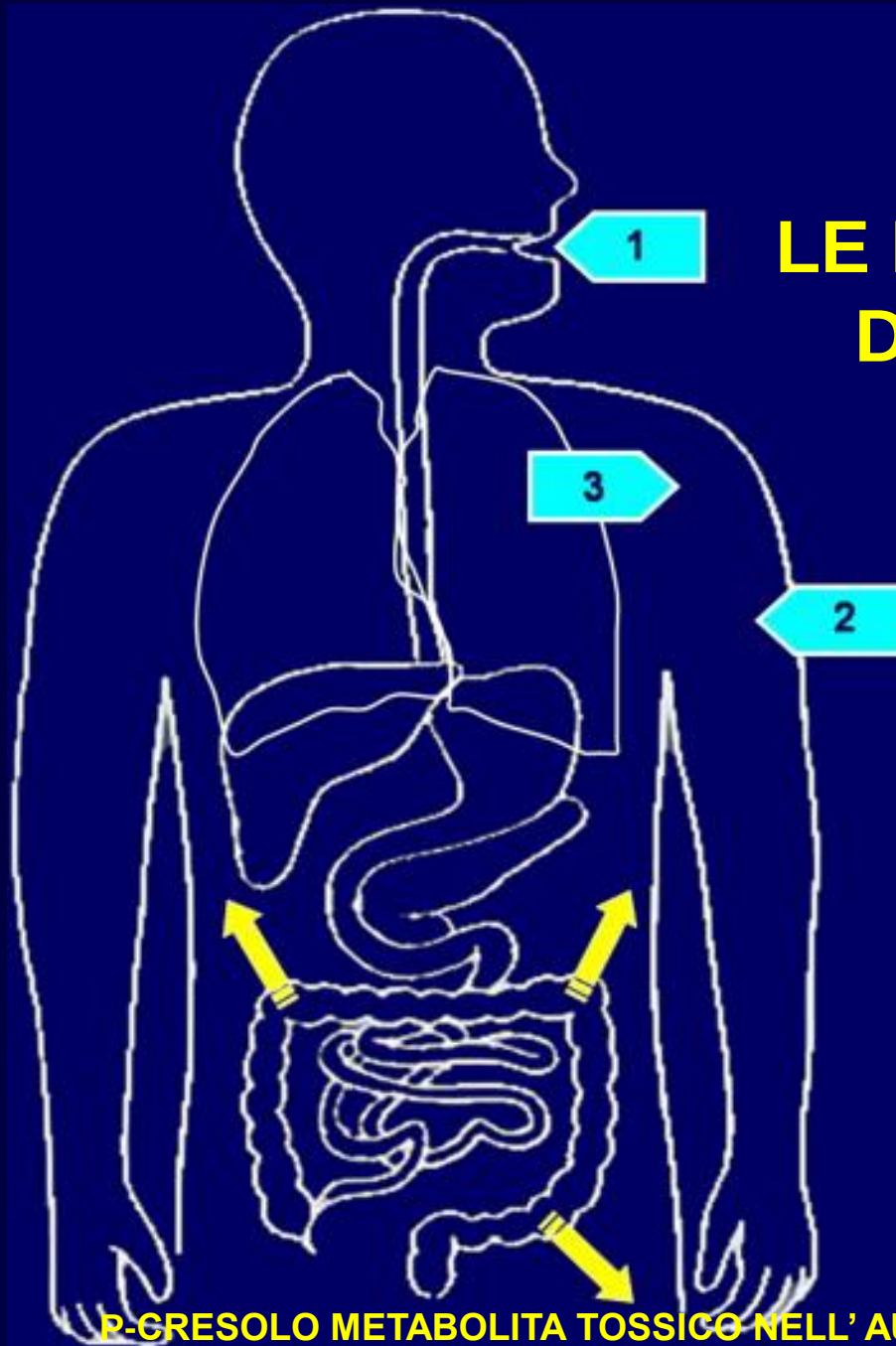


Toluene

P-CRESOLO METABOLITA TOSSICO NELL' AUTISMO
(Persico, Napolioni, Neurotoxicol. Toxicol. 36, 82, 2012)

p-Cresol

LE DIVERSE ORIGINI DEL P-CRESOLO



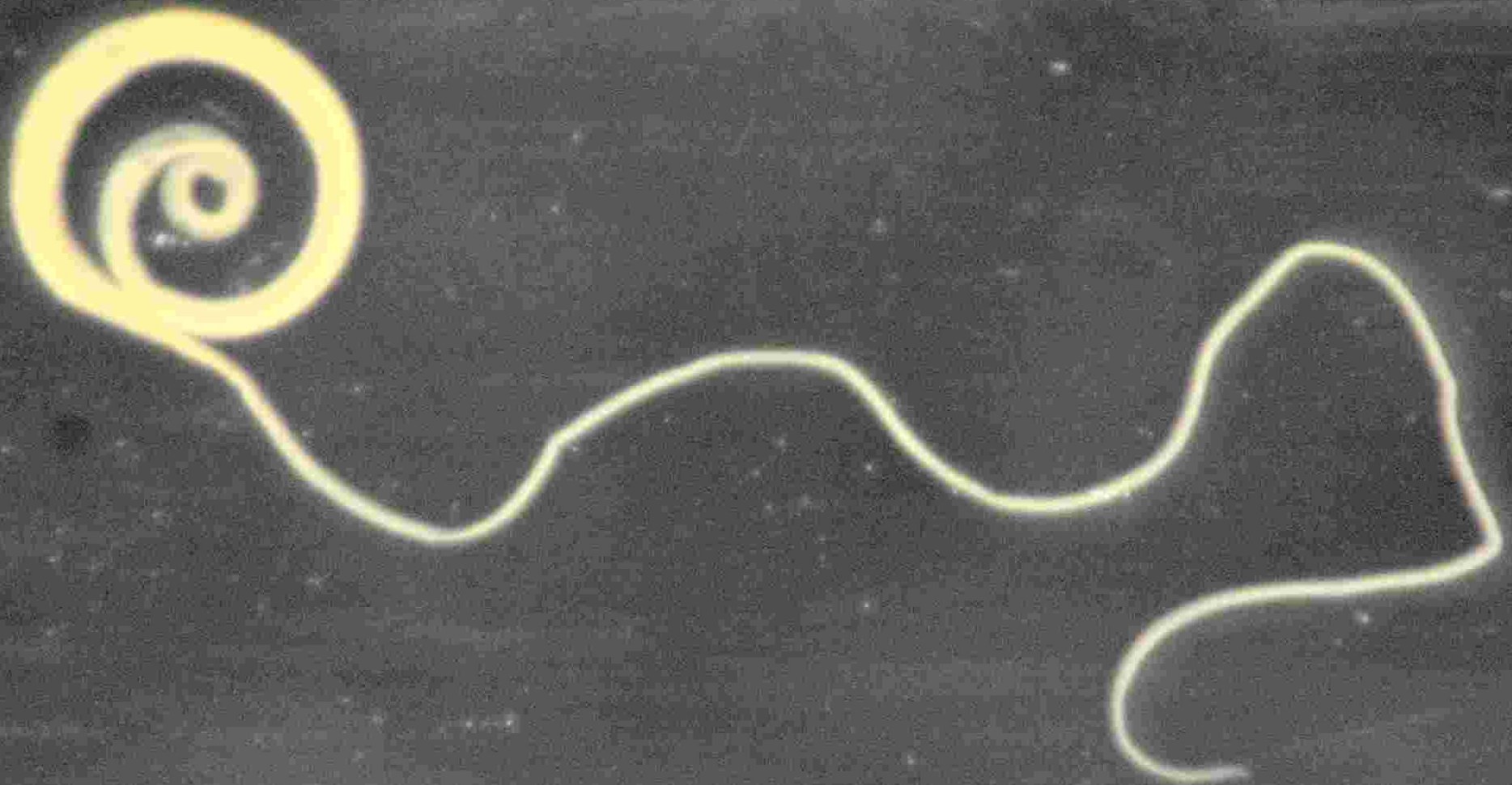
P-CRESOLO METABOLITA TOSSICO NELL' AUTISMO
(Persico, Napolioni, *Neurotoxicol. Toxicol.* 36, 82, 2012)

MICROBIOTA E L'ASSE INTESTINO CERVELLO NELL'AUTISMO

*Tramite una ridotta permeabilità della
barriera intestinale*

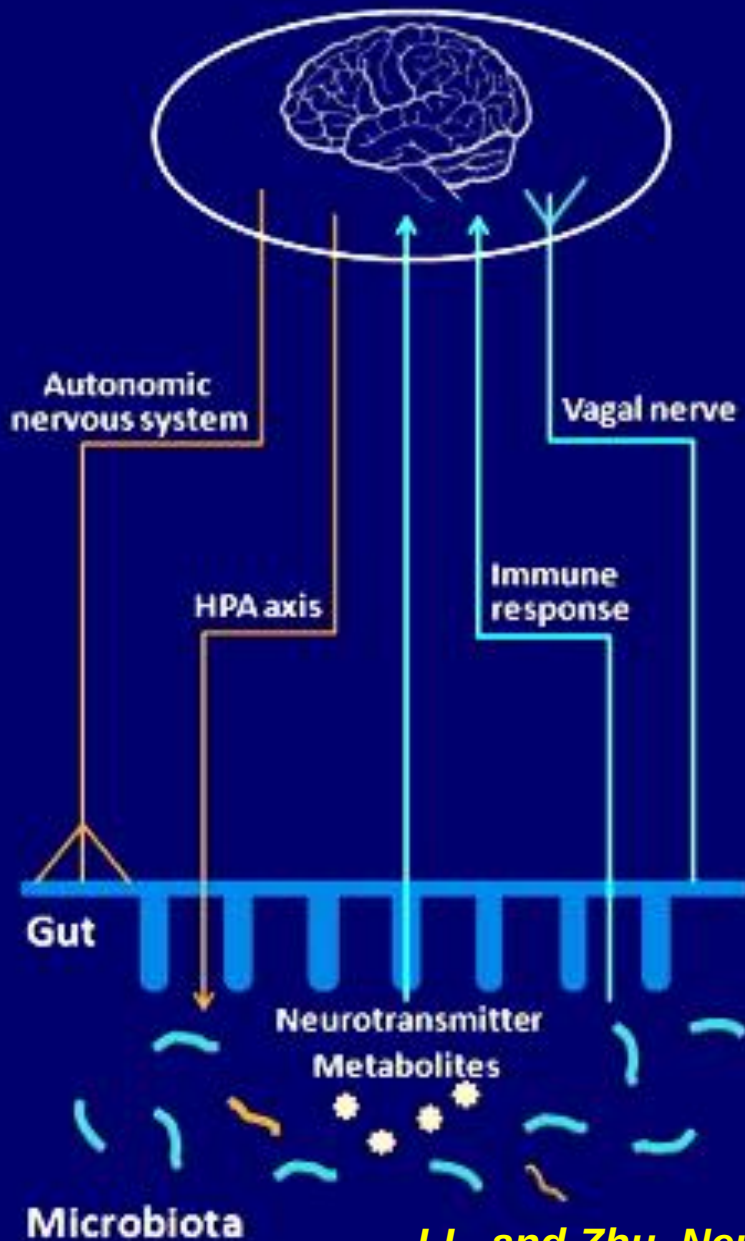
- L'asse microbiota-intestino-cervello agisce tramite meccanismi neuroendocrini, neuroimmuni e autonomici
- Modulatori dell'asse: probiotici o diete speciali possono essere una strategia

Trichuris suis (ova)

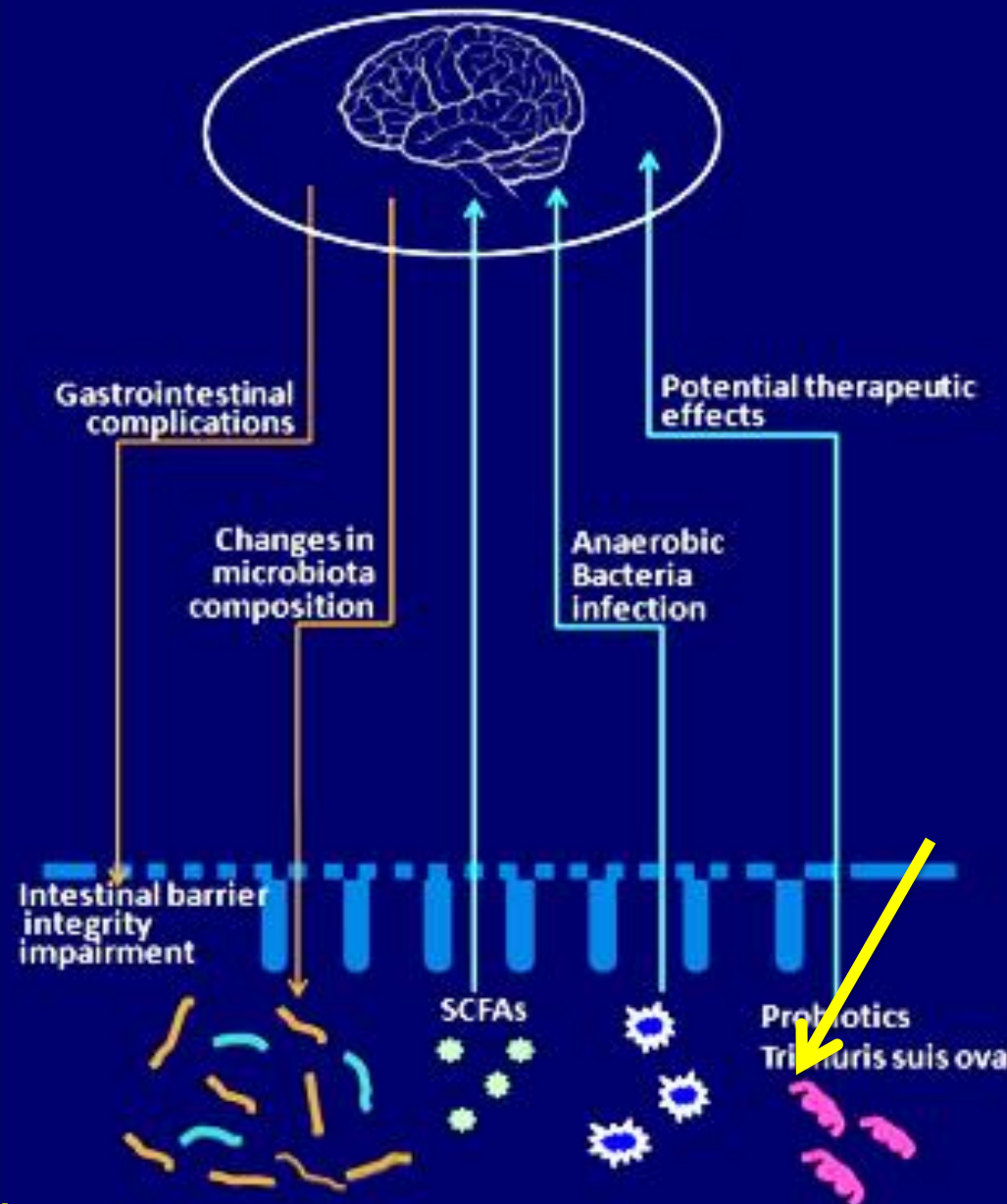


TSO NELL'AUTISMO - IL MECCANISMO

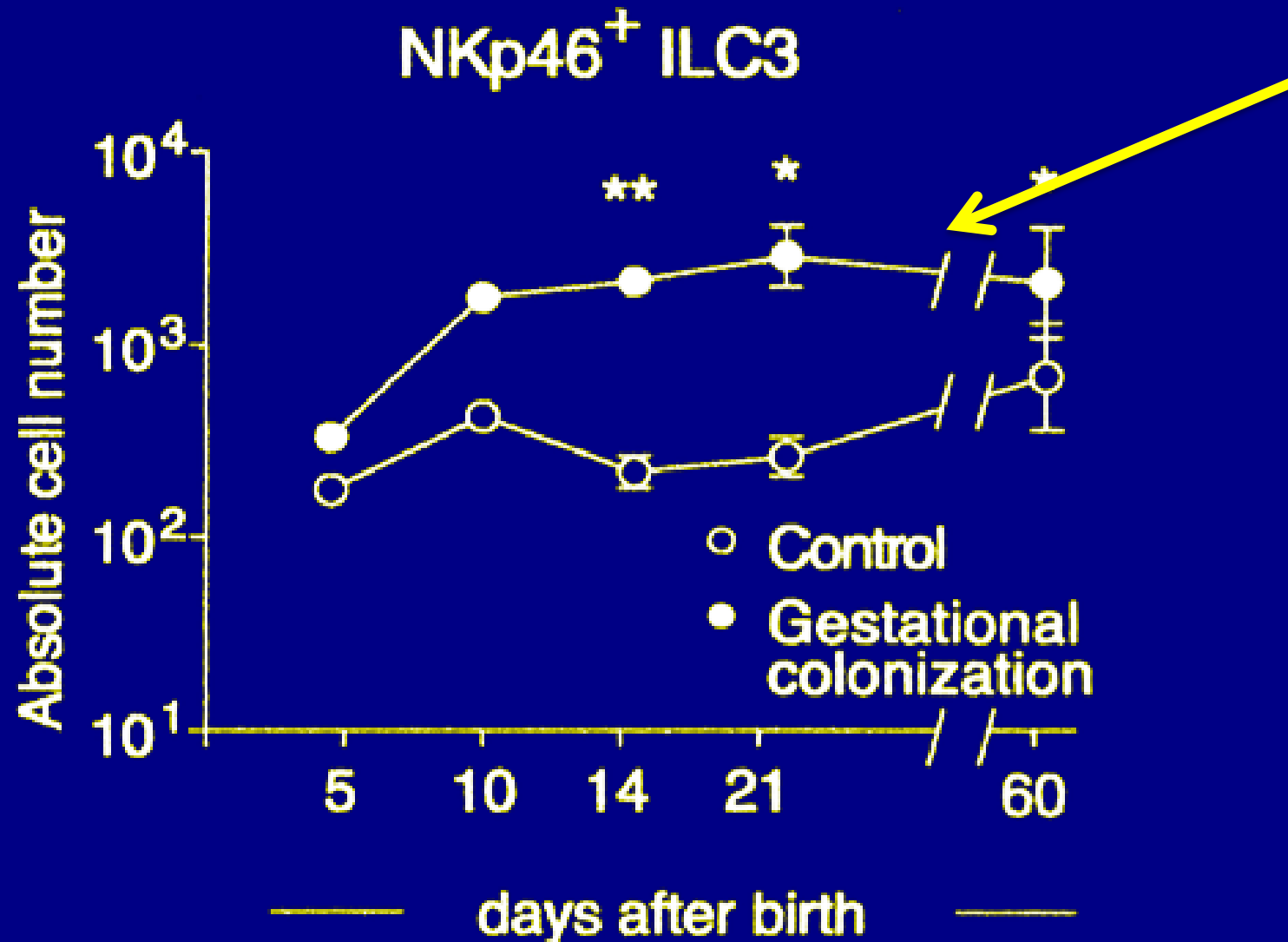
Microbiota-gut-brain axis



Autism spectrum disorder



PRECOCE MATURITA' IMMUNITARIA IN NEONATO DI MADRE ESPOSTA A E.COLI GESTAZIONALE



de Agüero et al, Science 351, 1296, 2016

OBBIETTIVI DEI PROBIOTICI NELL'AUTISMO

Limitare accesso di sostanze tossiche a livello centrale nel neonato a rischio di autismo:

- **Bacteroides fragilis**
- **Impedire l'accesso di p-cresolo e 4-EPS**
(Persico e Napolioni, Neurotoxicol Teratol, 36, 82, 2013)
- **Trichuris suis Ova (TSO): Attività immunomodulatoria e blocco della mucosa intestinale; possibile terapia?**
(Siniscalco e Antonucci, Medical Hypoth. 81, 1, 2013)

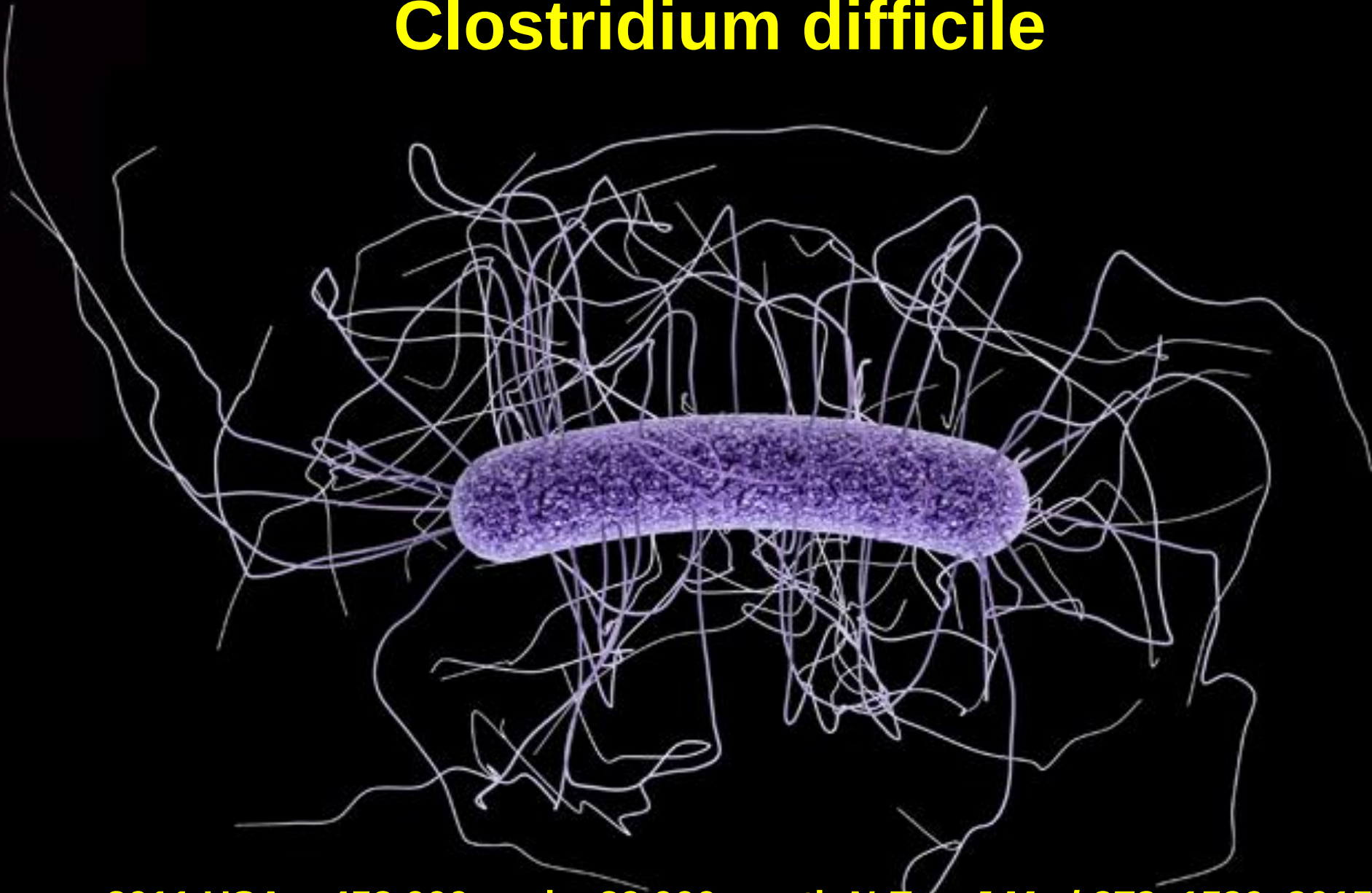
TSO - RIDUZIONE DI SINTOMI E RITORNO DOPO IL TRATTAMENTO

2.500 uova ogni due settimane in doppia cecità
in *autistici allergici* per 28 settimane.
Miglioramento in alcuni fino ad oltre 5 anni
Efficacia anche aumentando la temperatura
corporea

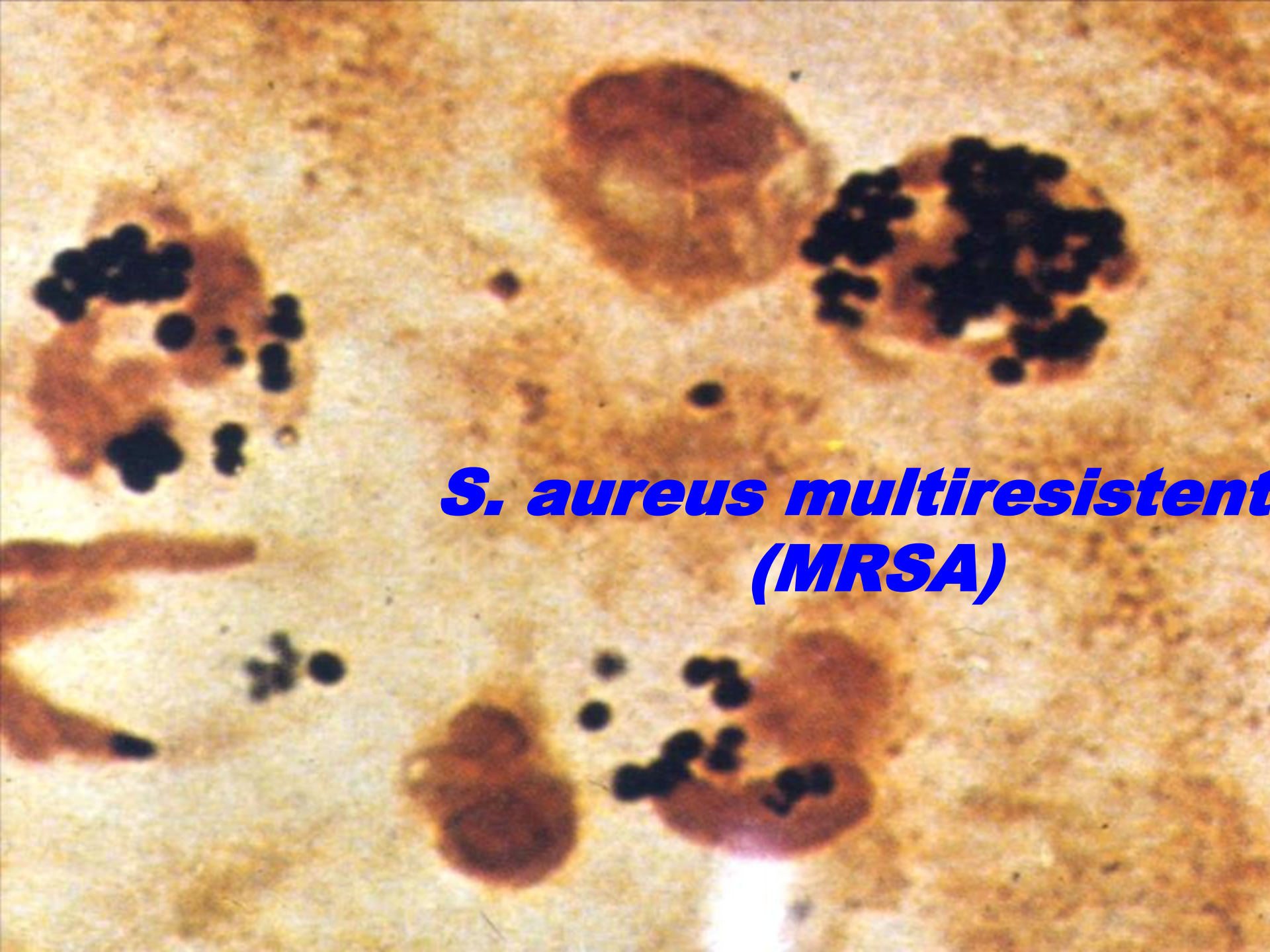
Friedrich JAMA 312, 474, 2014

Obiettivi attuali: identificare autistici con
fenomeni allergici che sembrano di più
rispondenti
(bassa incidenza nei paesi sotto-sviluppati)

Clostridium difficile



2011 USA : 453.000 casi – 29.000 morti, *N Eng J Med* 372, 1539, 2015
Previsti 10 milioni di morti in Europa nel 2050

A microscopic image showing several colonies of MRSA (Methicillin-resistant *Staphylococcus aureus*) on a culture medium. The colonies are characterized by dark, dense clusters of bacteria, some of which are surrounded by a lighter, more diffuse area of growth. The background is a light, textured surface, likely the agar medium. The text "*S. aureus* multiresistent (MRSA)" is overlaid in blue, bold, italicized font in the center-right of the image.

***S. aureus* multiresistent
(MRSA)**

ANTIBIOTICO RESISTENZA: BATTERIO CONTRO BATTERIO

Obiettivo: ripristinare una microflora non adatta alla crescita di *Enterococcus vancomicina* resistente (VRE) e *Clostridium*

Approcci:

- Trapianto fecale
- Trattamento con ceppi batterici che impediscono la colonizzazione di VRE o *Clostridium*

Barnesiella genus – anaerobi commensali riducono la colonizzazione di VRE

(Ubeda et al., Infect Imm 81: 965, 2013)

TRAPIANTO FECALE?



*Material fresco o congelato porta ad uguale beneficio
Lee et al, JAMA 315, 142, 2016*

TRAPIANTO FECALE: PROBLEMI

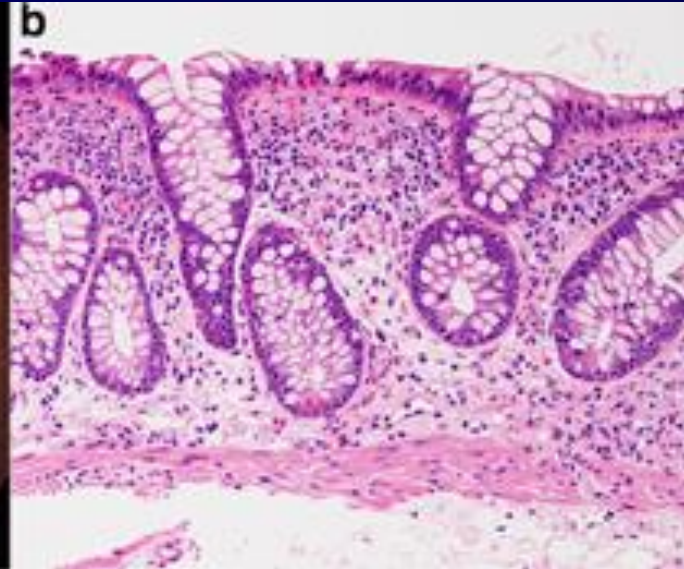
LA TOLLERANZA LOCALE

Episodi di colite

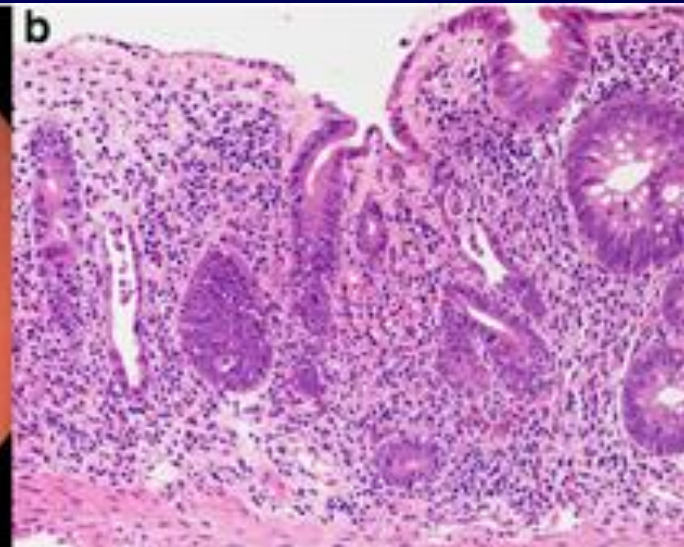
- colonizzazione con germi (non CDI) in presenza di terapia cortisonica o antibiotica
- può portare a colite cronica che richiede trattamento cortisonico locale (budesonide)

(Tariq et al. Am J Gastroenterol 111, 751, 2016)

COLITE POST TRAPIANTO FECALE



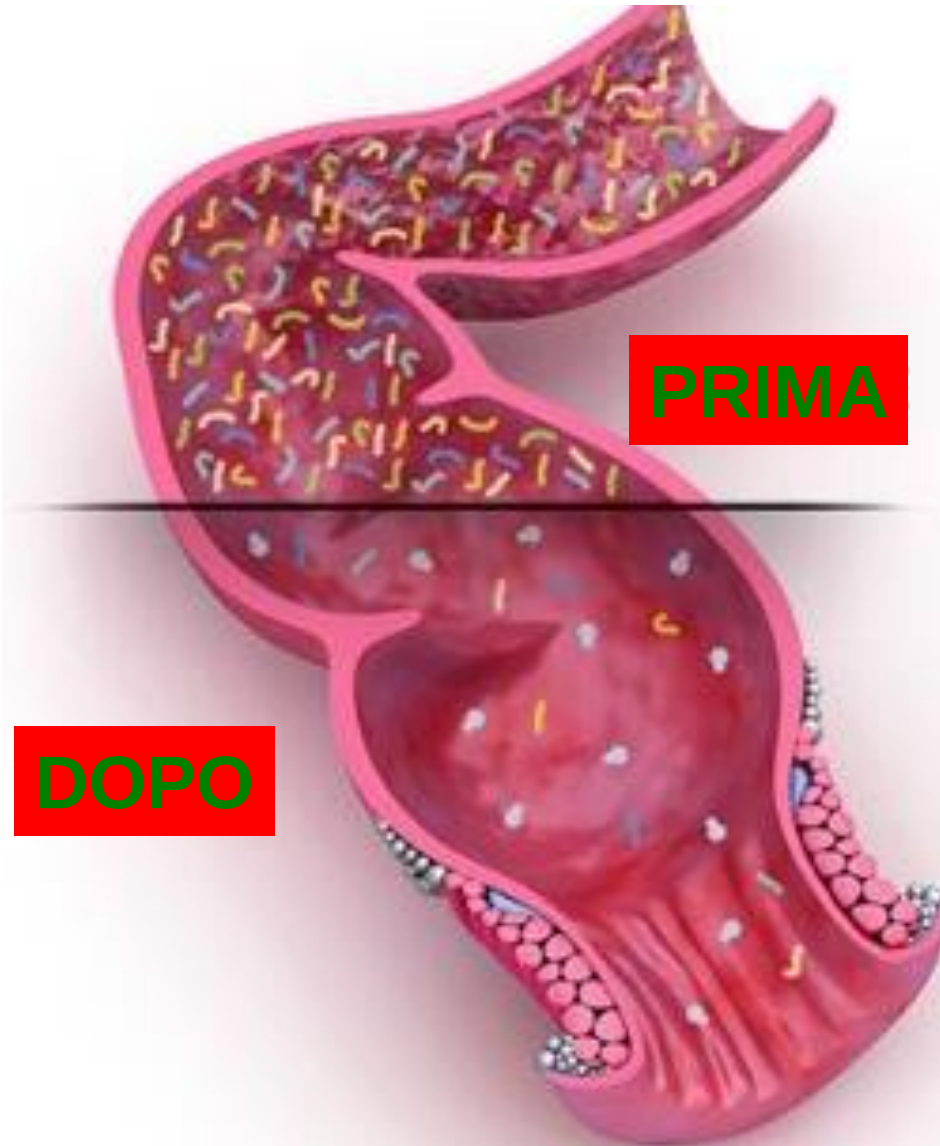
TP



**POST
TP**

(Tariq et al. Am J Gastroenterol 111, 751, 2016)

LA DIARREA DA ANTIBIOTICI



PREVENZIONE DEL RISCHIO DI DIARREA DA ANTIBIOTICI

La diarrea da antibiotici (5-35%) aumenta il rischio di colonizzazione da CD e Klebsiella

Ouwenhand et al, Ann Med 48, 246, 2016

Meta-analisi: riduzione del rischio con probiotici del 60%: L. rhamnosus, S. cerevisiae var Boulardii

Mc Farland et al. Am J Gastroenterol 101, 812, 2006

Migliori dati con S. cerevisiae var. boulardii: -50% dopo antibiotici per infezioni o H. pylori *Szajewska,*

Kolodzil, Alim. Pharmacol. Ther. 42, 793, 2015

Saccharomyces boulardii

Diarrea da antibiotici

Da 18.7 a 8.5% (-53%)

Nei bambini da 20.9 a 8,8% (-57%)

Diarrea da Clostridio

Bambini -75%

Non negli adulti



INTESTINAL MICROBIOTA CONTAINING BARNESIELLA
(Caballero et al. Ann Rev Immunology, 33: 227-256, 2015)

COME AUMENTARE LA BARNESIELLA INTESTINALE?

Supplementazione con 2- e 3-fucosil-lattosio (componenti del latte umano)

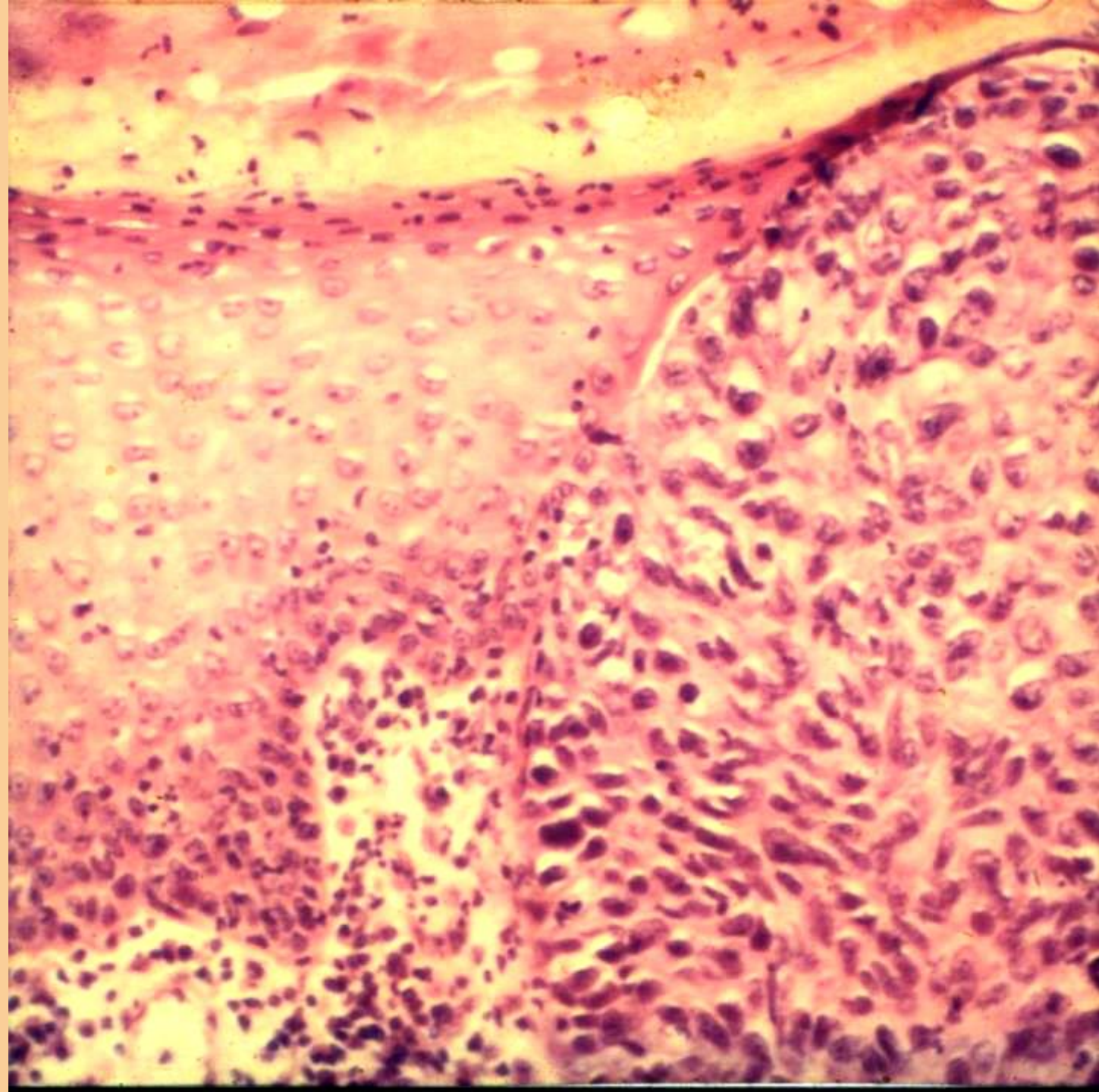
Nel topo

6 settimane di 2-FL, 3-FL nell'acqua da bere (3.3 μ /l) aumentano del 60% la Barnesiella intestinale.

Bambino: Maggiore resistenza a colite. Importante per bambini con madri carenti di 2-FL nel latte (20% dei caucasici) (*Kunz et al, Annu Rev Nutr 20, 699,2000*)

Possibile sintesi di glucosillattosio con enzimi batterici ricombinanti

(*Wiss et al. Brit J Nutr 111: 1602, 2014*)



NUTRACEUTICI: IL CANCRO?

Nutraceutici efficaci per ridurre la
sintomatologia tossica da tumori o
chemioterapia

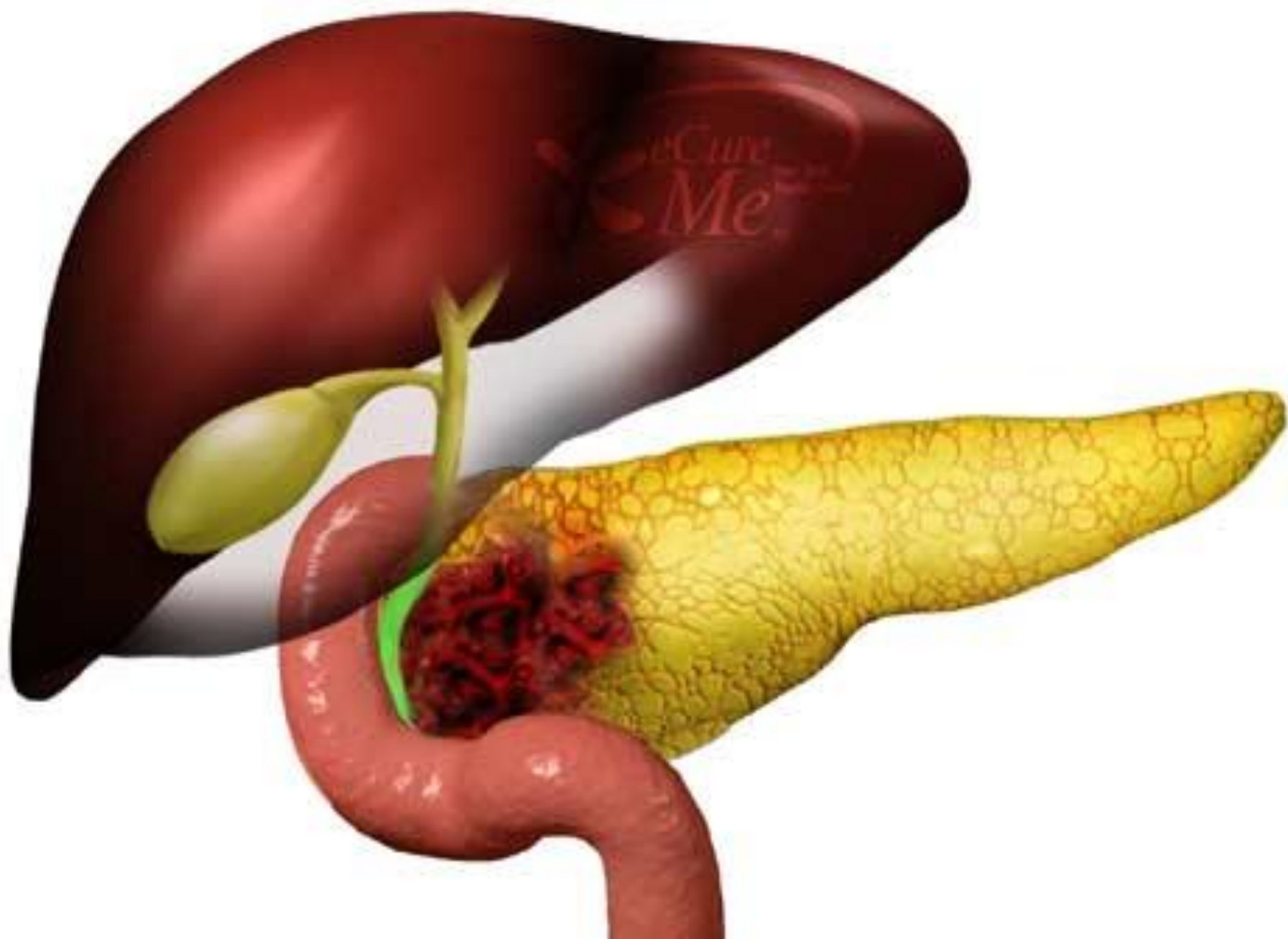
Es. curcumina lecitinata

(Belcaro et al. Phytother. Res 28, 444, 2014)

Attività diretta anticancro?

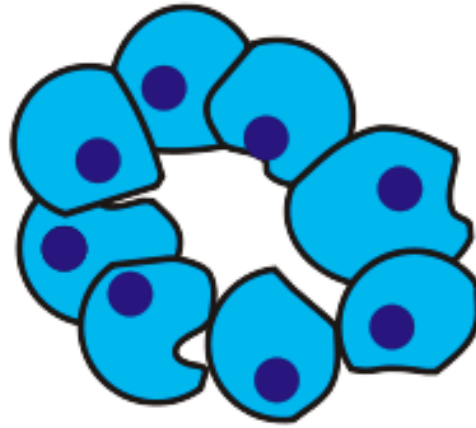
“activity against pancreatic cancer stem
cells”

(Sancho et al. Cell Metab. 22, 590, 2015)



Cancer stem cell
specific therapy

Tumor regression

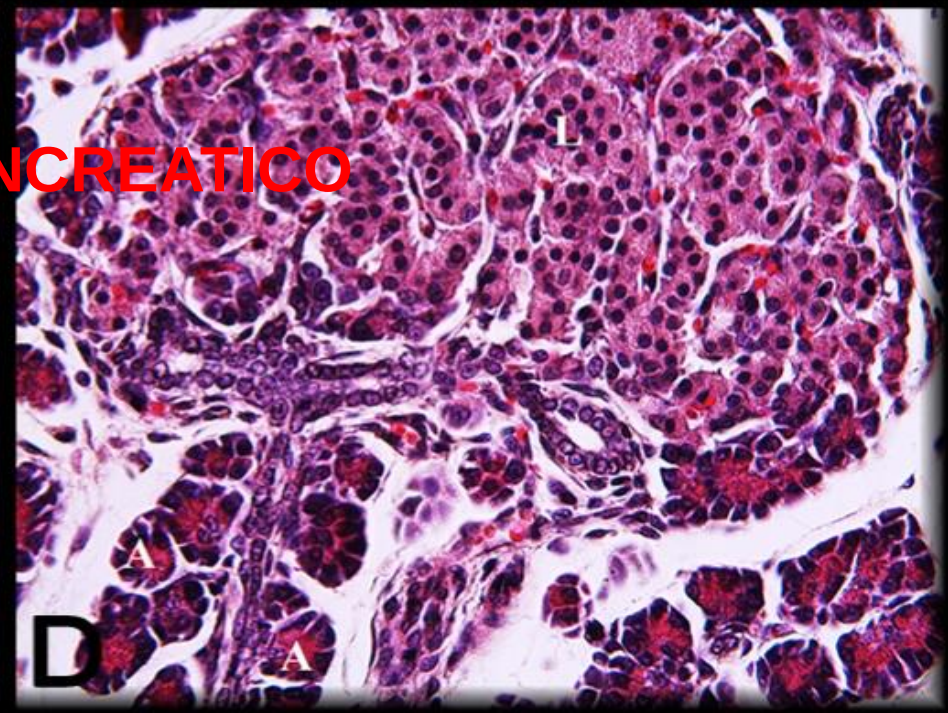
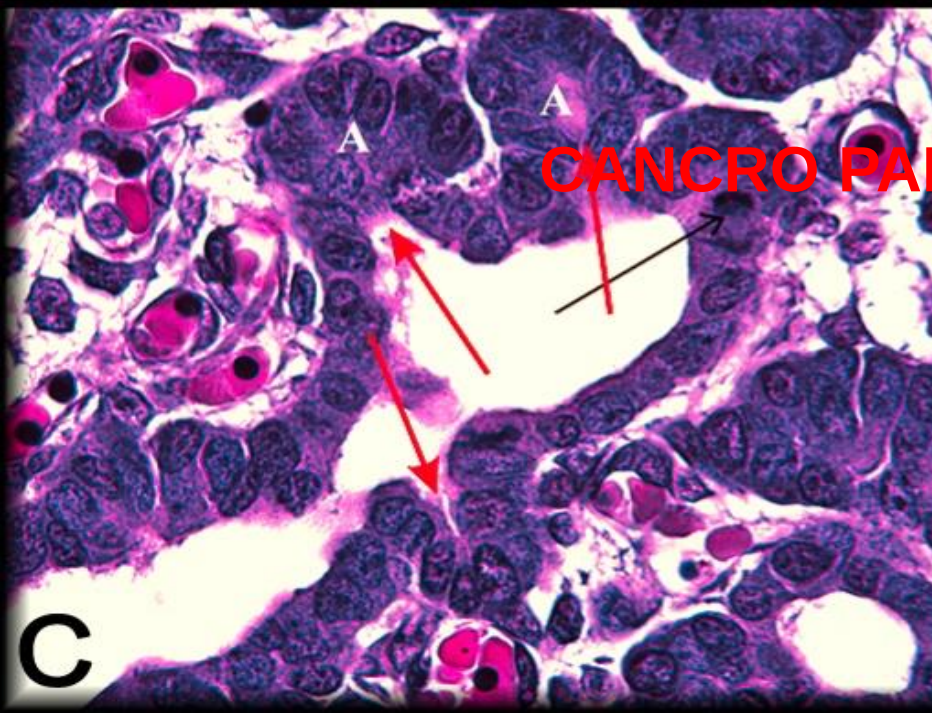
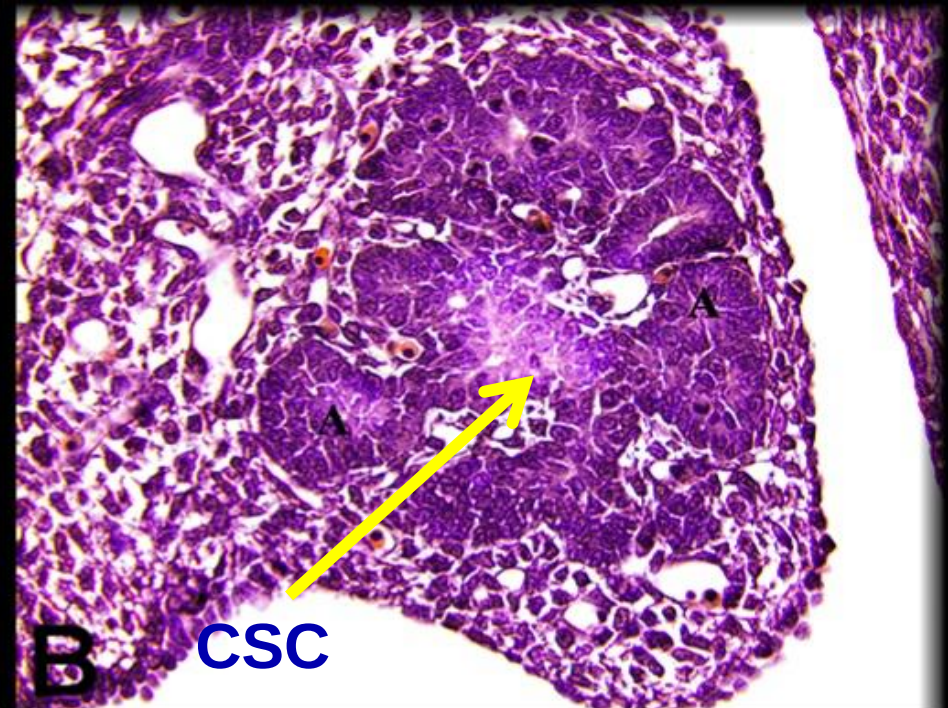
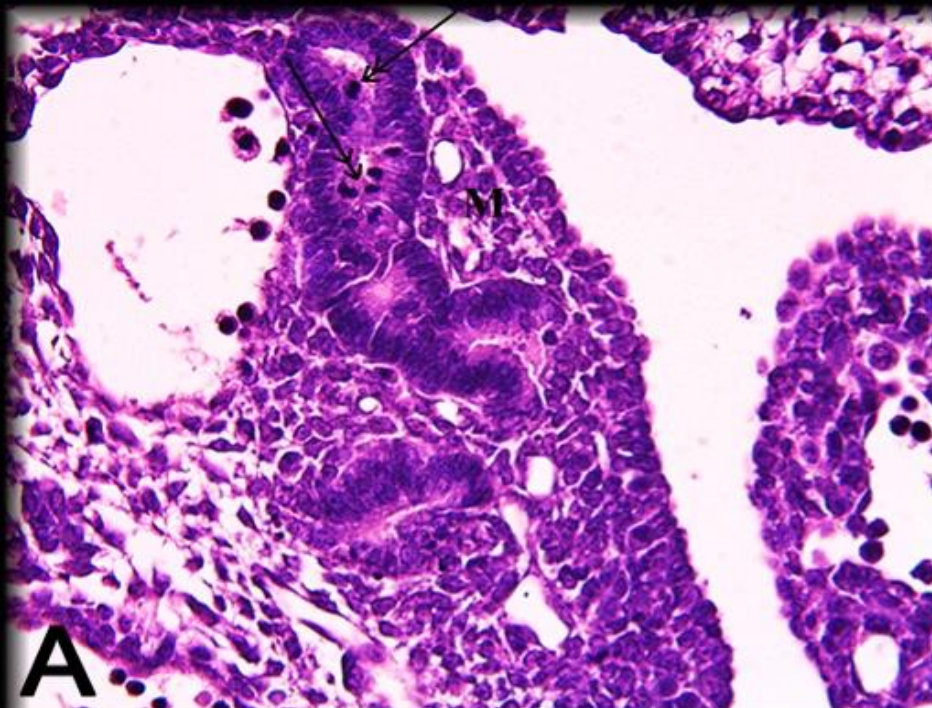


Conventional
cancer therapy

Tumor relapse



CELLULE STAMINALI E CANCRO



CANCRO PANCREATICO – PLASTICITA' DELLE CELLULE STAMINALI

Contiene una piccola quota di cellule staminali (*cancer stem cell* – CSC) fortemente oncogene e metastatizzanti. Può spiegare la gravità clinica.

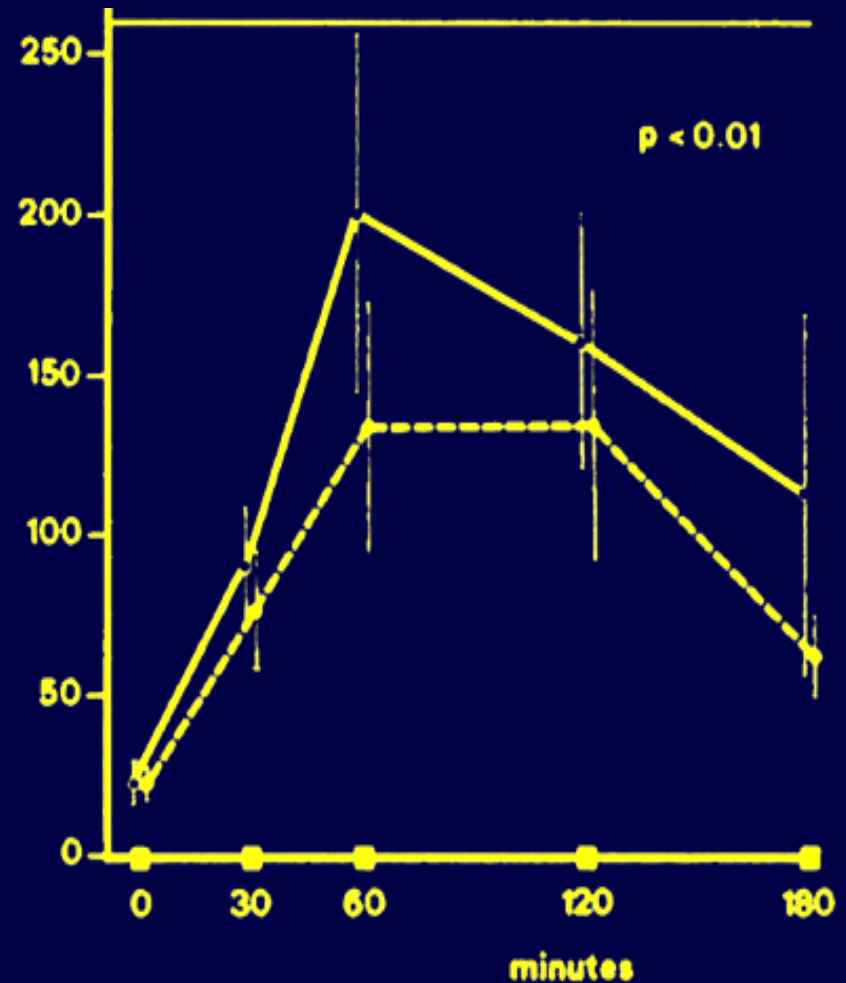
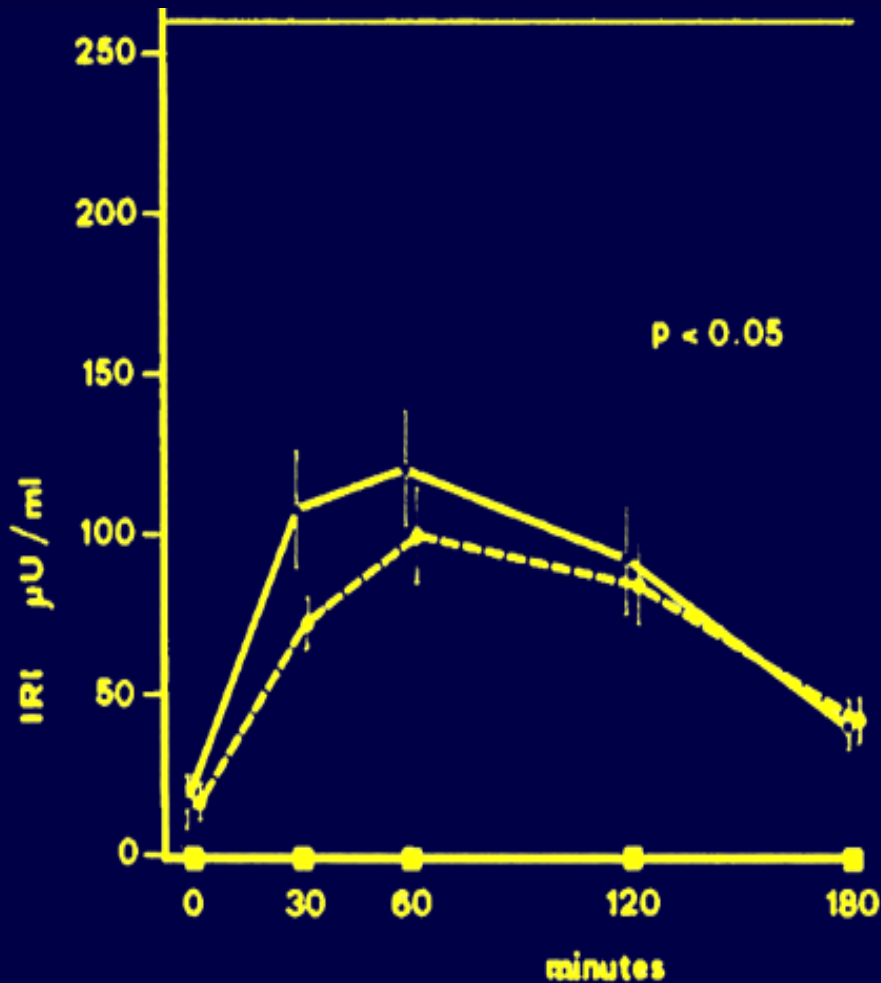
CSC non glicolitiche, fortemente dipendenti dal metabolismo ossidativo (OXPHOS), ridotta plasticità metabolica; antagonisti assai attivi sono gli inibitori mitocondriali, p. es. metformina o altri.



METFORMINA

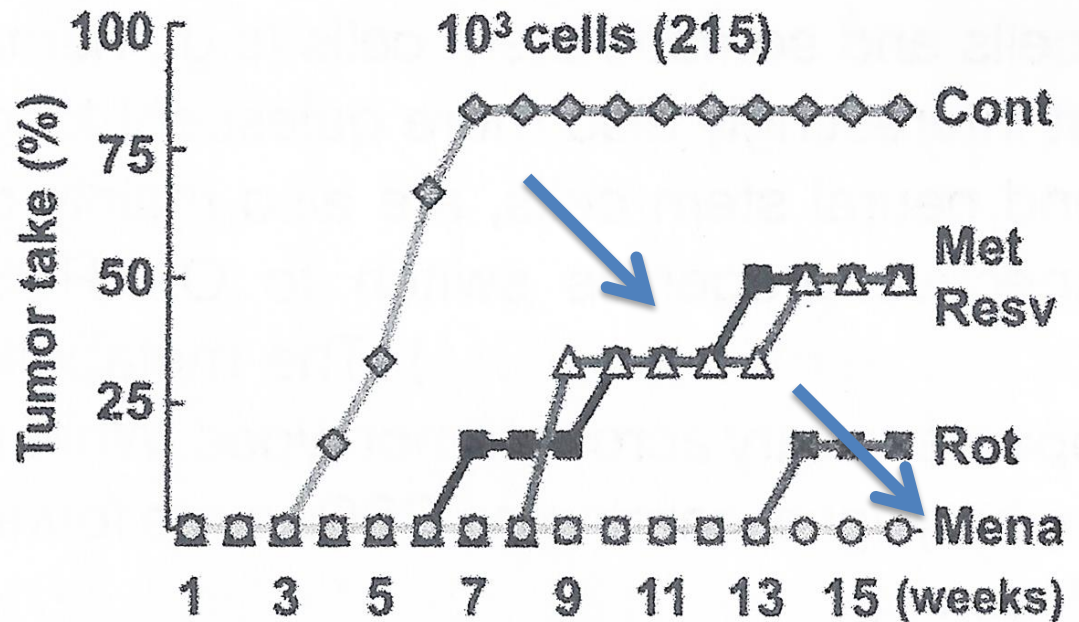
Metformin

lowers insulinemia

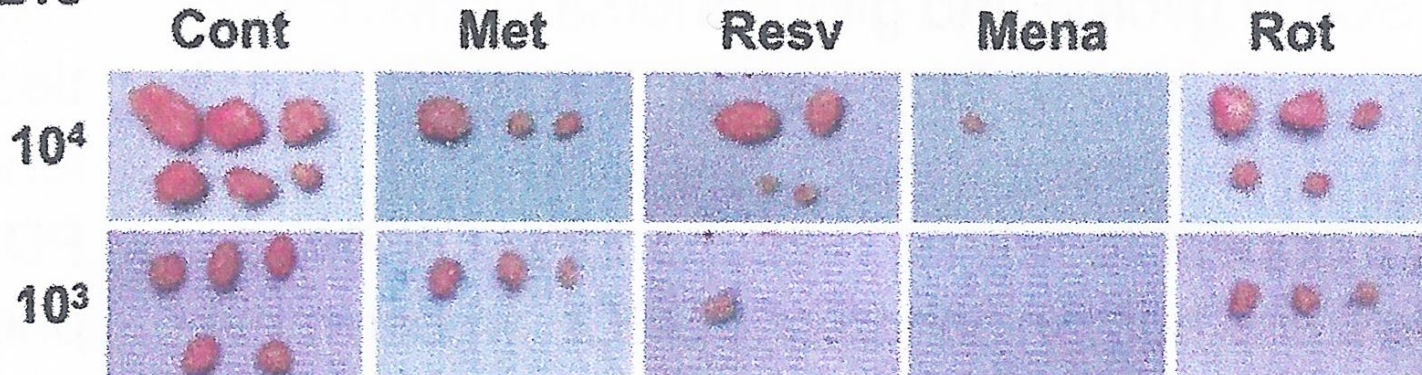


ATTIVITA' DI INIBITORI MITOCONDRIALI SU CA PANCREATICO

Cell #	215		354	
	10^4	10^3	10^4	10^3
Cont	6/6	5/6	5/6	5/6
Met	3/6	3/6	3/6	0/6
Resv	4/6	1/6	4/6	4/6
Mena	1/6	0/6	4/6	2/6
Rot	5/6	3/6	1/6	0/6



215

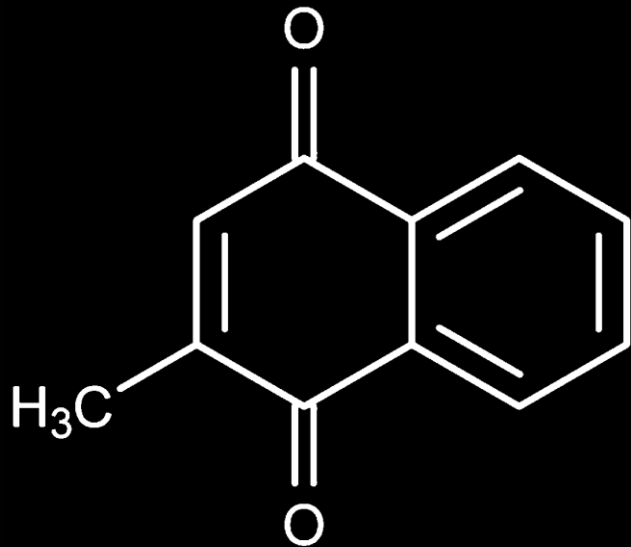


(Sancho et al. Cell Metab. 22, 590, 2015)

MENADIONE, ANALOGO DELLA VITAMINA K3

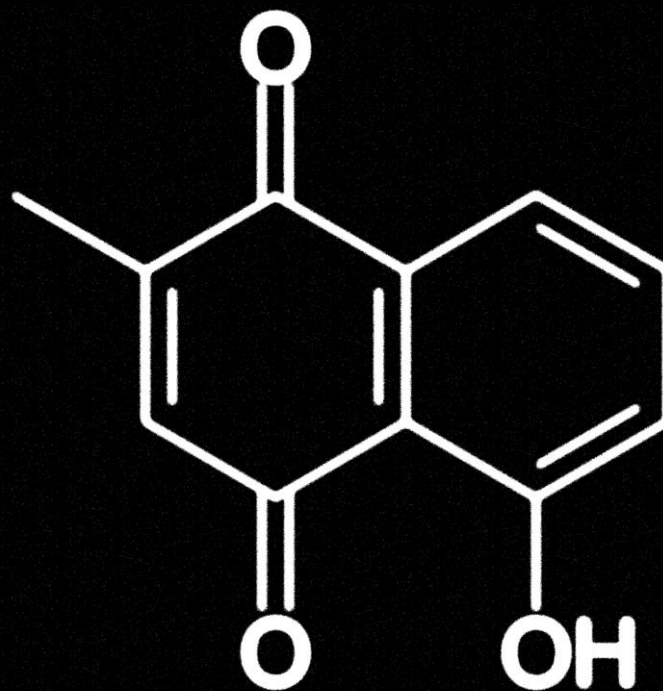
Menadione, naftochinone inibisce i meccanismi ossidativi mitocondriali e sopprime le cellule staminali del cancro pancreatico.

***Analogo nutraceutico:
Plumbagina***



MENADIONE

PLUMBAGINA



PLUMBAGINA ANALOGO ANTICANCRO DEL MENADIONE

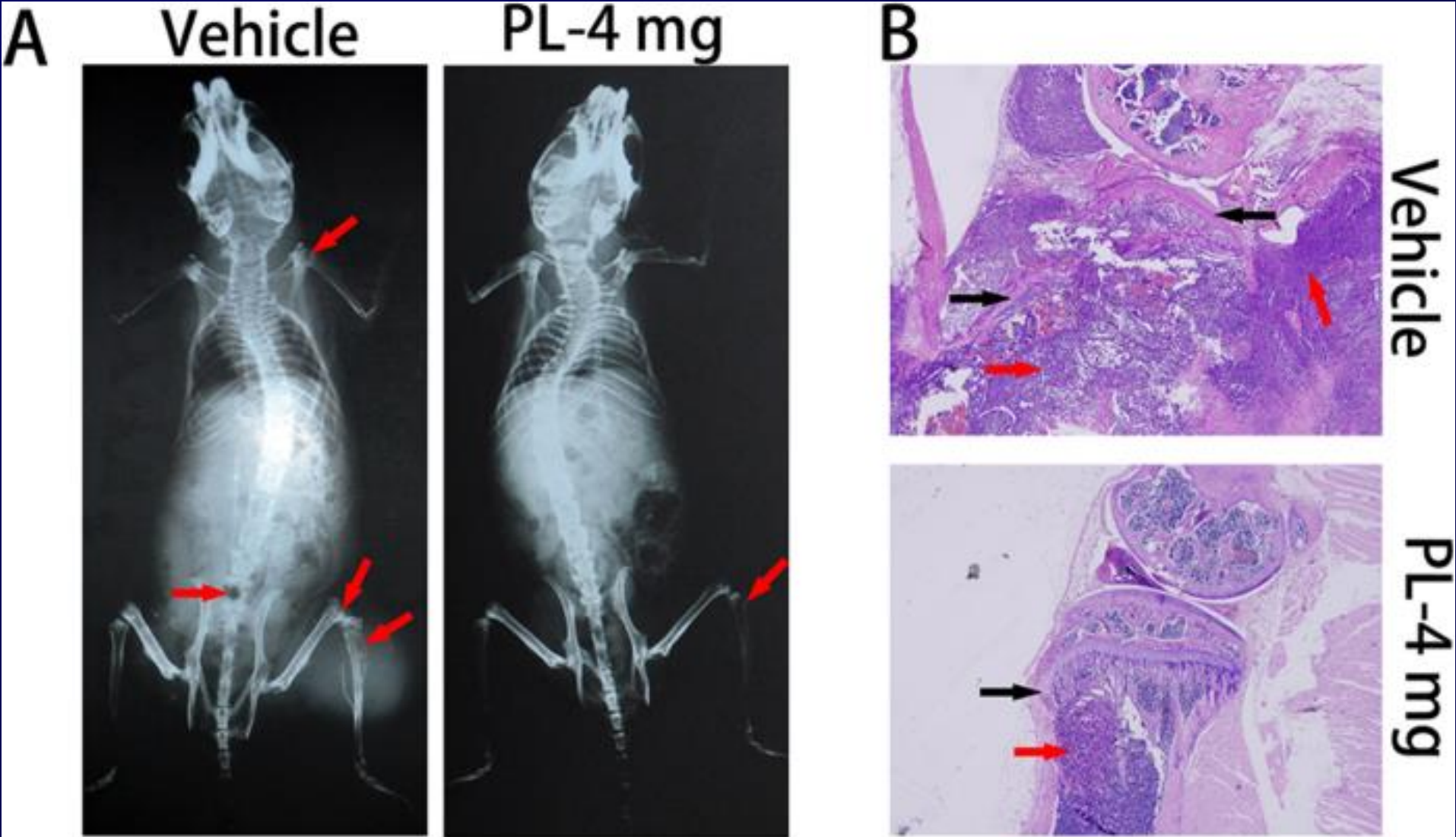
**Costituente della *Plumbago zeylanica*
stimolante di autofagia e apoptosi**

**Attiva accumulo di ROS in cellule di
carcinoma polmonare NSC**

**Potente attività in tumori prostatici,
mammari e in metastasi ossee**

(Balvan et al, PLOS One, 10: e0145016, 2015)

RIDOTTA INVASIVITA' DA PLUMBAGINA DELLE METASTASI OSTEOLITICHE DA CA. MAMMARIO



Yan et al, Bone Res 4, 362, 2013

TERAPIA CON NUTRACEUTICI NEL CANCRO

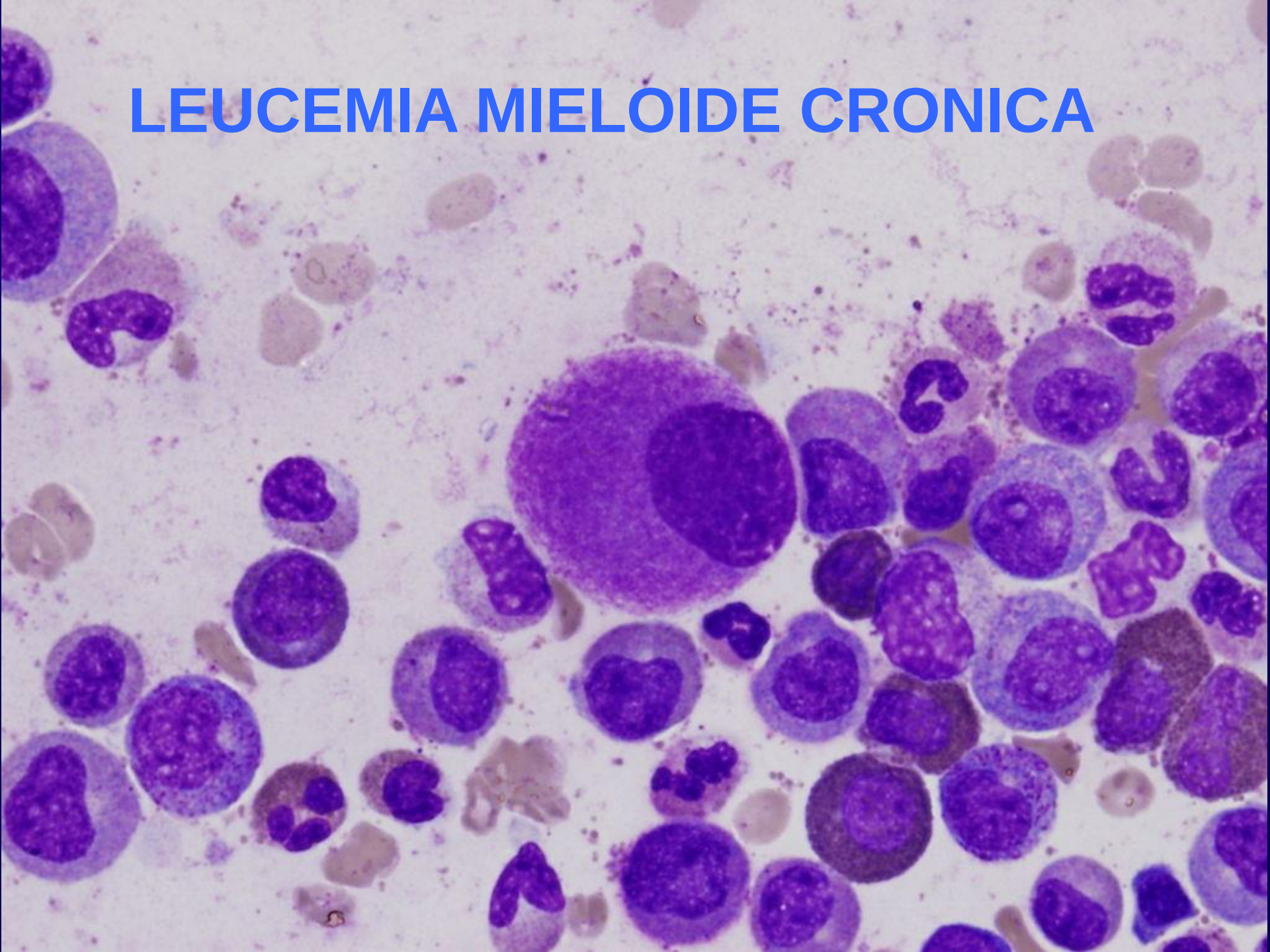
**Staminali con diverso metabolismo e
cinetica cellulare**

Presenza di recettori PGC-1 α e PPAR γ

- **Plumbagina inibisce l'attivazione di STAT3 da citokine**
- **Pioglitazone blocca attivazione di STAT5 tramite PPAR γ**

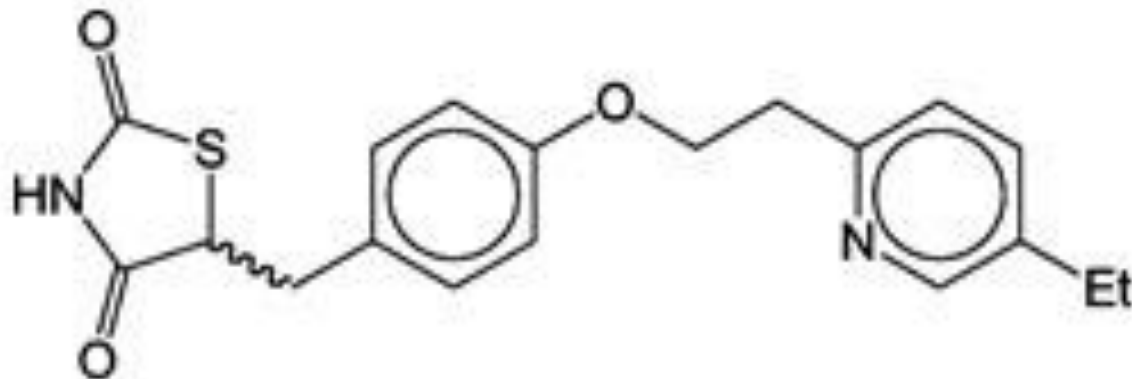
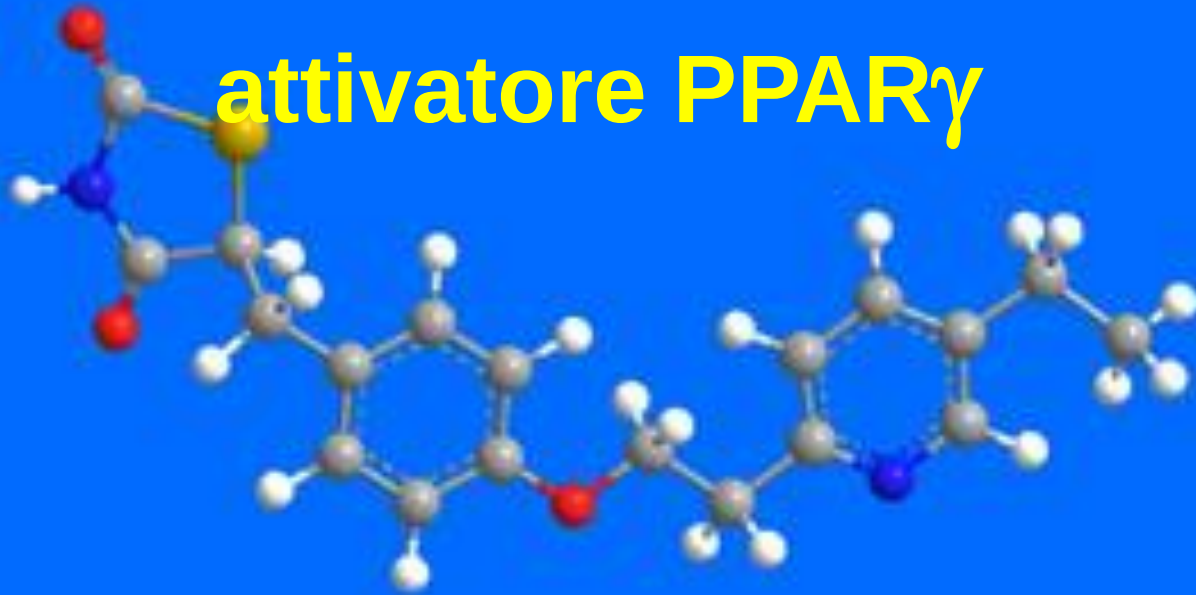
***Attività in cancro pancreatico,
carcinoma mammario metastatico e
leucemia mieloide cronica***

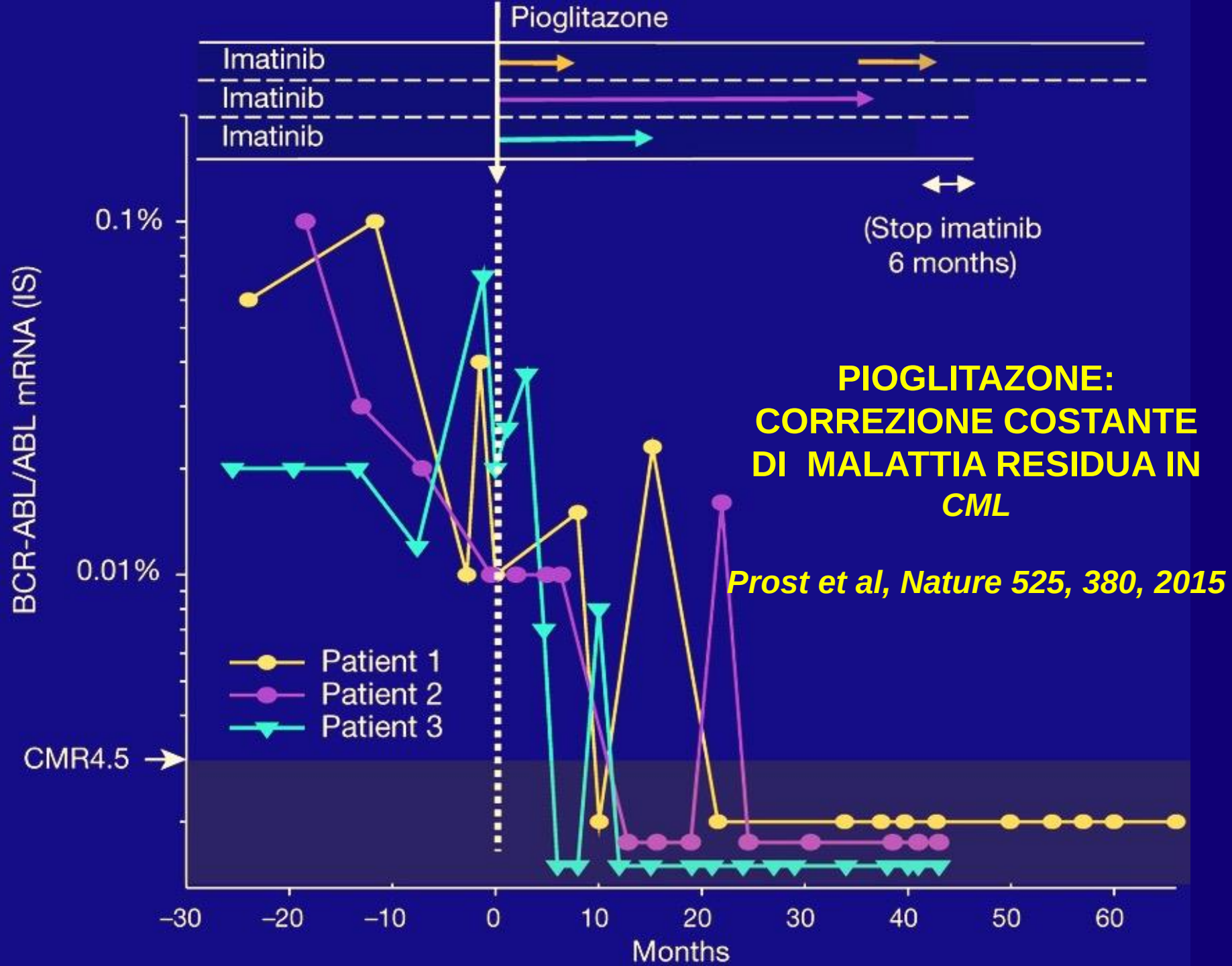
LEUCEMIA MIELOIDE CRONICA



PIOGLITAZONE

attivatore PPAR γ





LA NUTRACEUTICA MODERNA: LE NOVITA'

Alzheimer

metabolismo cerebrale, nuove
direttive nutraceutiche

Autismo

probiotici specifici
ridurre permeabilità intestinale a tossici cerebrali

Resistenze batteriche

trapianto fecale: efficacia e problemi
competizione batterio/batterio: cosa scegliere?

Cancro

tumori con cellule staminali: risposta a nutraceutici,
inibitori mitocondriali, altri meccanismi