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Le giornate della salute e del benessere: Innovazione e Ricerca

Milano, 30 Giugno - 1 Luglio



Glutathione: relazione con stress ossidativo ed ageing; strategie per migliorarne la biodisponibilità

Daniela Buonocore, Ph.D.

Università degli Studi di Pavia

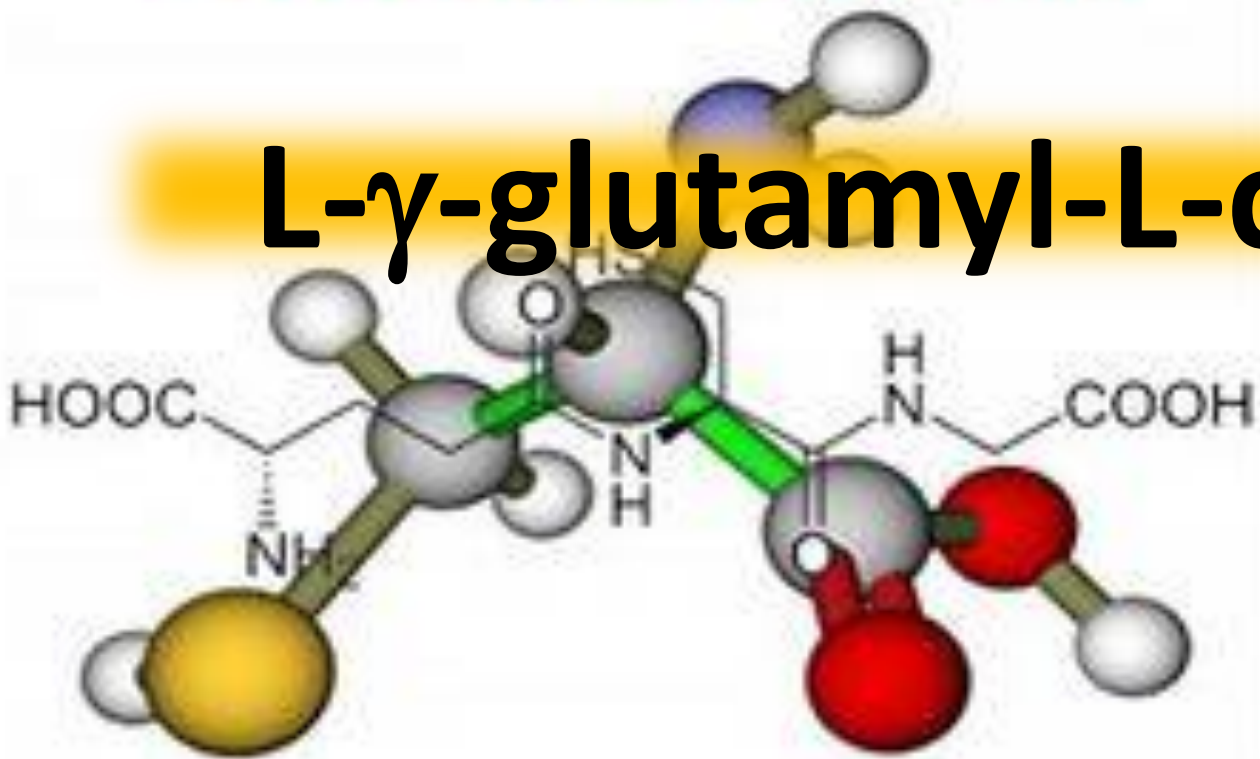
Dipartimento di Biologia e Biotecnologie «L. Spallanzani»

Laboratorio di Farmacobiocchimica, Nutrizione e Nutraceutica



The Master Antioxidant

L- γ -glutamyl-L-cysteinyl-glycine

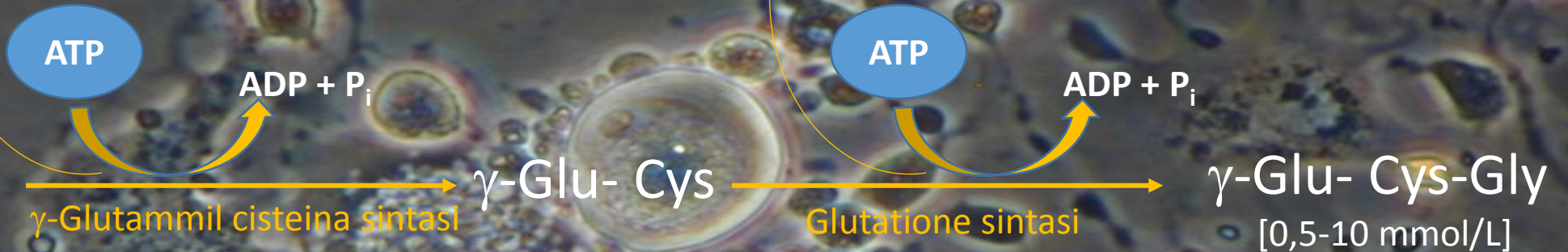


«GLUTATHIONE»

Cisteina

Glicina

Glutammato



Glutatione ridotto

GSH

$\gamma\text{-Glu-Cys-Gly}$

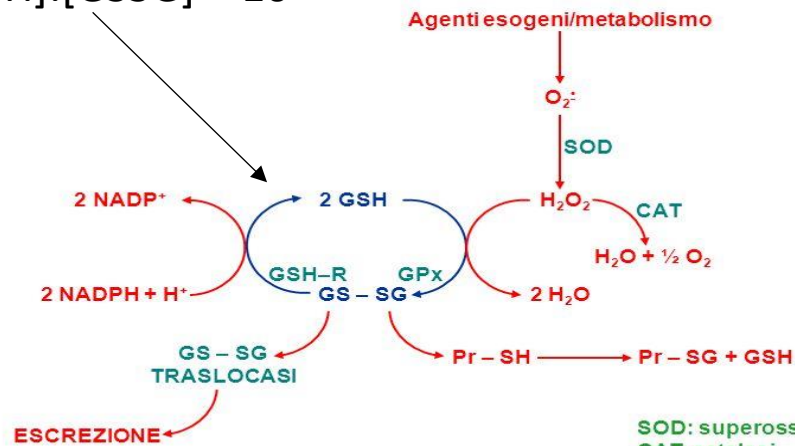
$\gamma\text{-Glu-Cys-Gly}$

Glutatione ossidato

GSSG

Ciclo del glutatione

[GSH]:[GSSG] > 10



SOD: superossidodismutasi
 CAT: catalasi
 GPx: glutatione perossidasi
 GSH-R: glutatione riduttasi

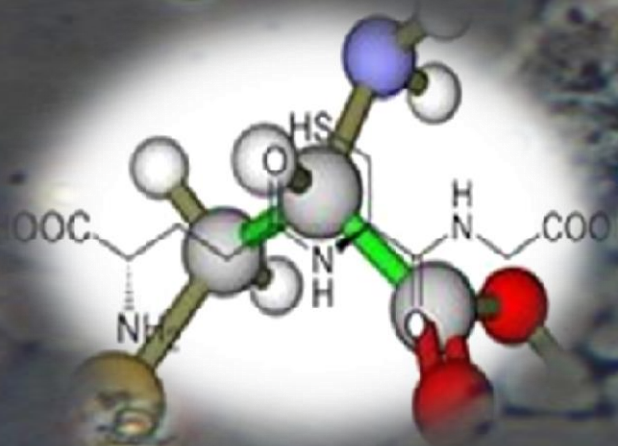
• Gruppi sulfidrilici delle prot nello stato ridotto

• Ferro del gruppo eme allo stato ferroso (Fe^{2+})

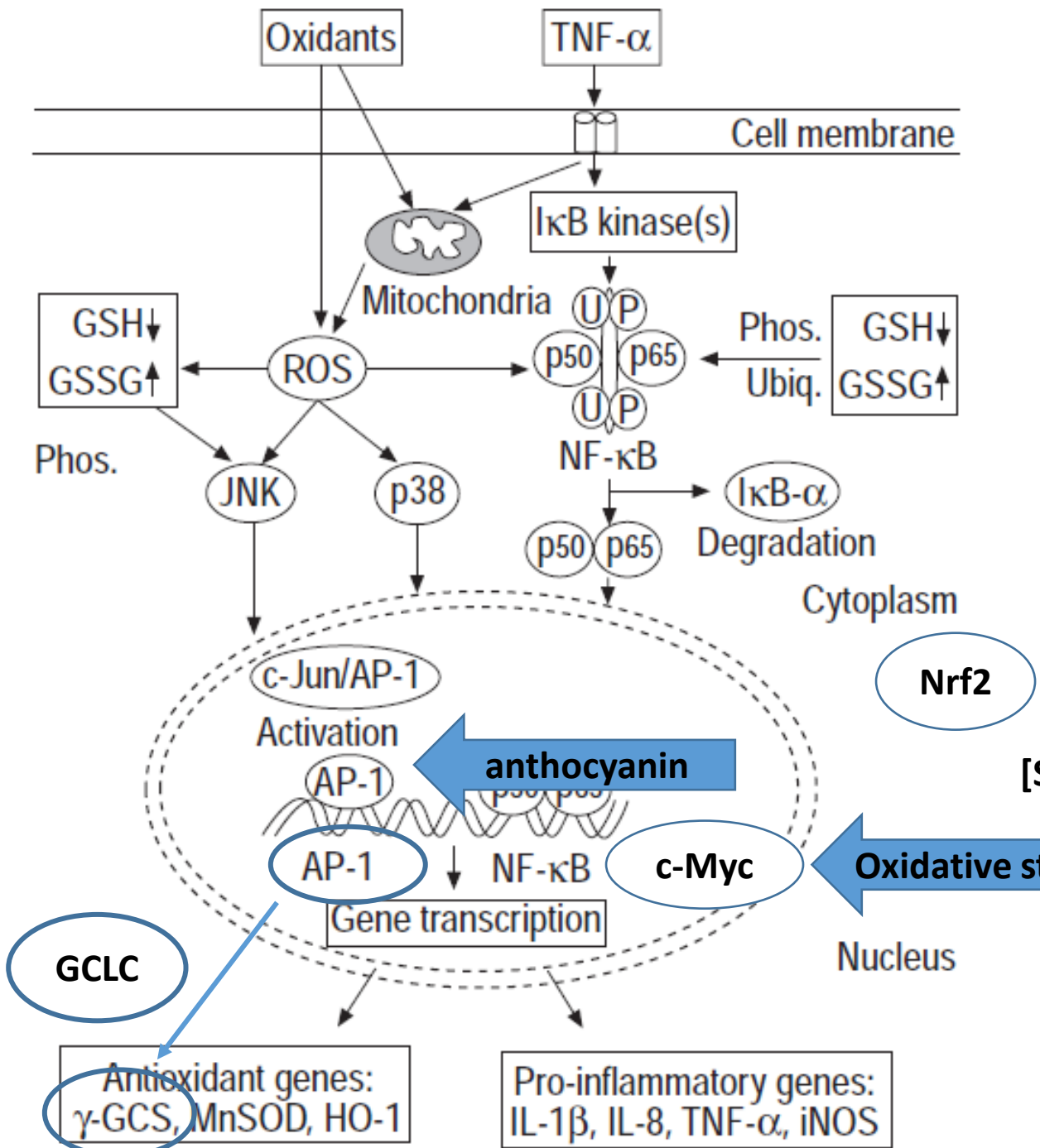
• Agente riducente della glutaredossina

COFATTORE DI GLUTATIONE-S-TRANSFERASI, DETOX DI XENOBIOTICI

IMMUNO MODULAZIONE E RISPOSTE INFIAMMATORIE



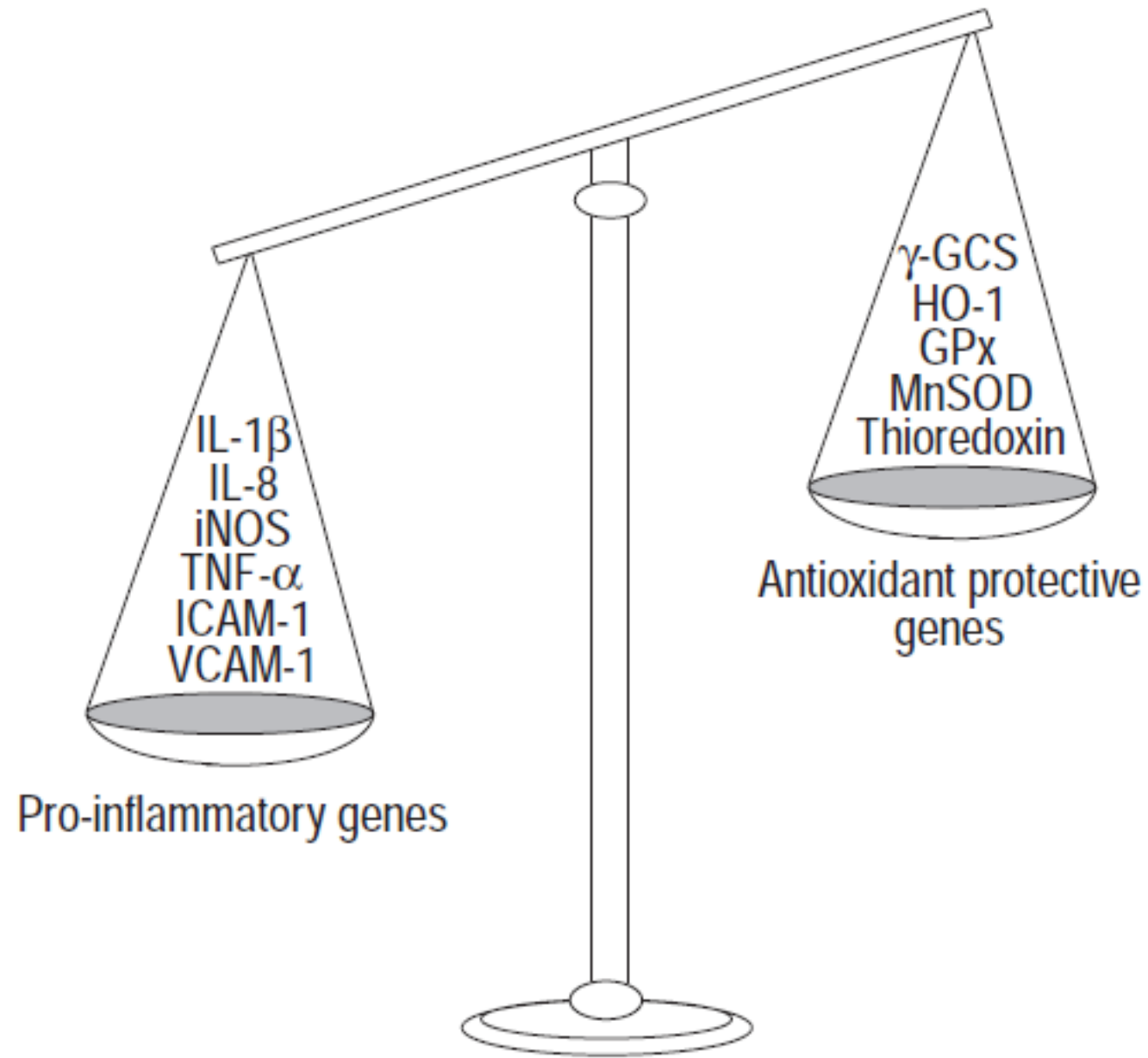
- ✓ TRASDUZIONE DI SEGNALI REDOX
- ✓ REGOLAZIONE DELLA PROLIFERAZIONE CELLULARE
- ✓ ESPRESSIONE GENICA
- ✓ METABOLISMO DI NO
- ✓ RIMODELLAMENTO DELLA MATRICE EXTRACELLULARE (ECM)
- ✓ APOPTOSI
- ✓ RESPIRAZIONE MITOCONDRIALE
- ✓ GLUTATIONILAZIONE DELLE PROTEINE

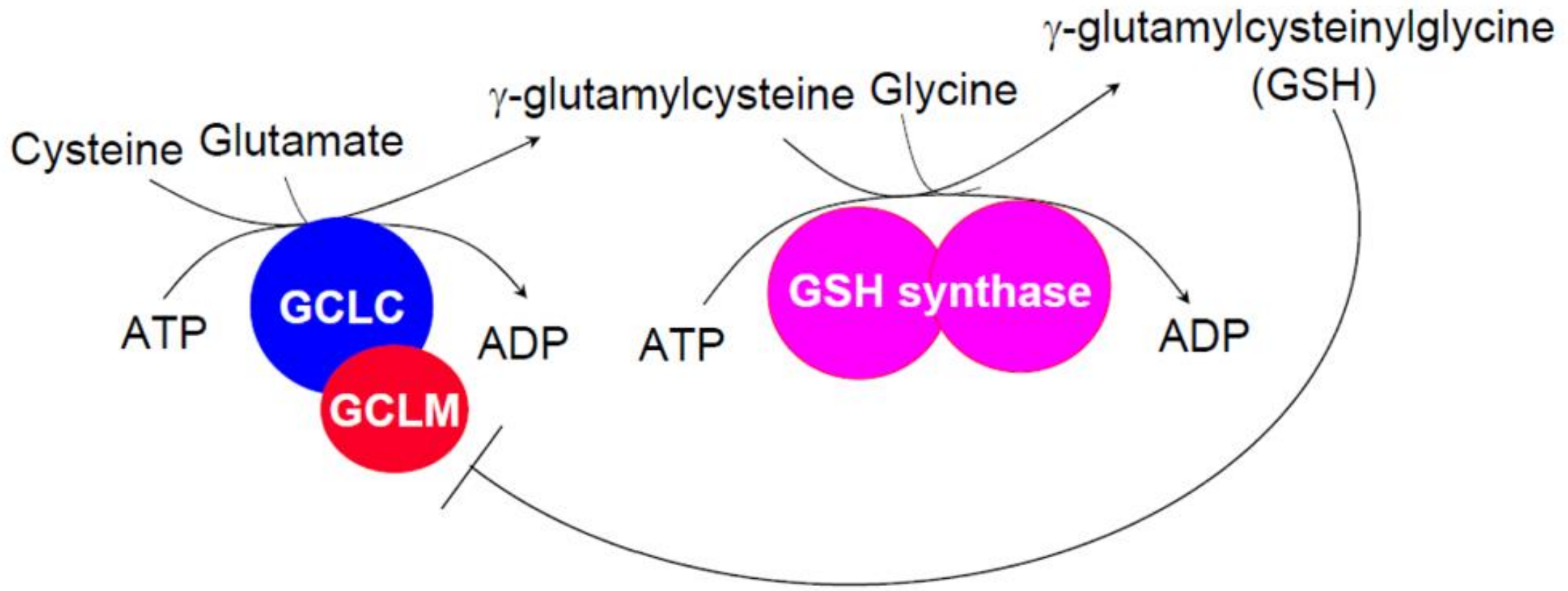


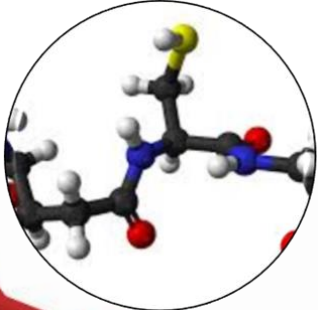
Intracellular redox state (GSH/GSSG) of the cell may play a key role in the regulation and potentiation of the inflammatory responses in lung cells

[Shelly C. Lu. *Biochim Biophys Acta* 2013; 1830(5): 3143–3153]

[Rahman I, MacNee W. *Eur Respir J* 2000; 16: 534±554]

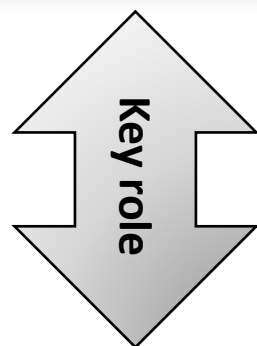
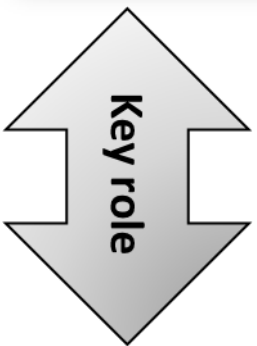
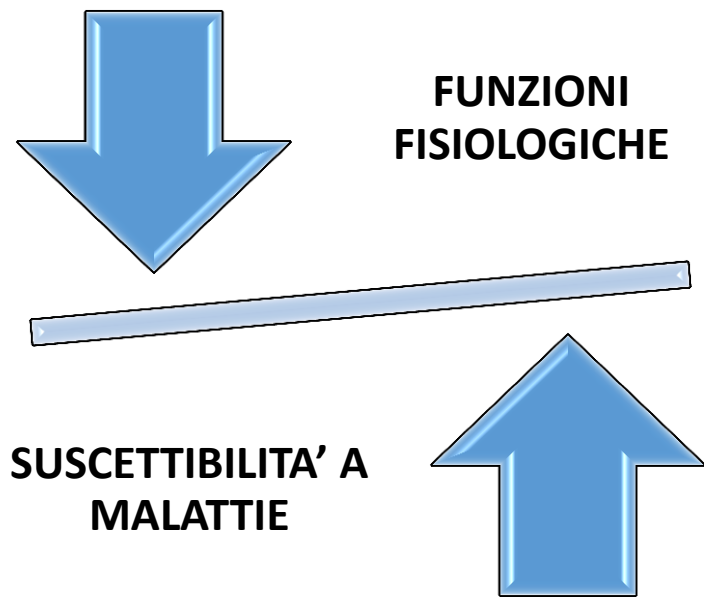






DECREASE

Stress Ossidativo



- Alzheimer
- Parkinson
- Malattie epatiche
- Fibrosi cistica
- kwashiorkor
- Anemia falciforme
- AIDS
- HIV
- Cancro
- Cardiovascolari
- Diabete

Patogenesi
di malattie

Ageing



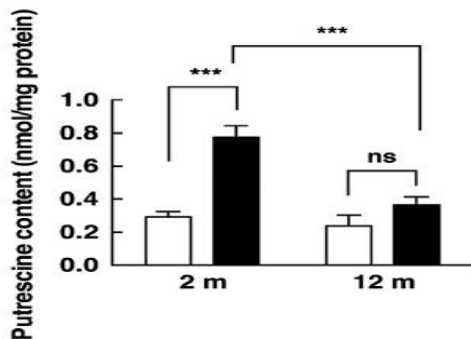
Aggravation of brain infarction through an increase in acrolein production and a decrease in glutathione with aging



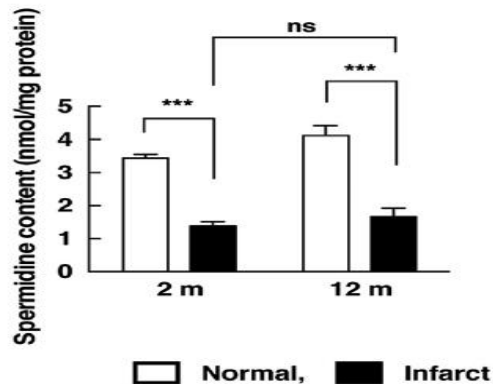
Takeshi Uemura ^a, Kenta Watanabe ^b, Misaki Ishibashi ^b, Ryotaro Saiki ^a, Kyoshiro Kuni ^b, Kazuhiro Nishimura ^b, Toshihiko Toida ^b, Keiko Kashiwagi ^c, Kazuei Igarashi ^{a, b, *}

A. Polyamine contents

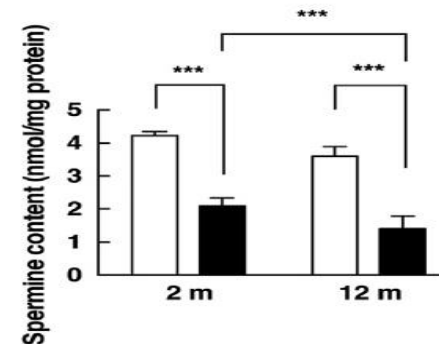
Putrescine



Spermidine



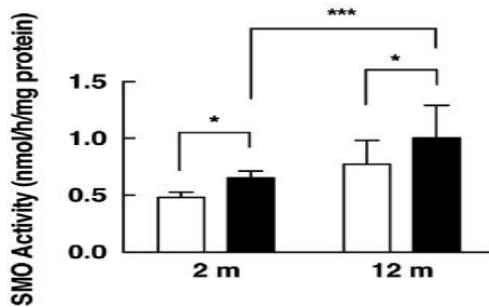
Spermine



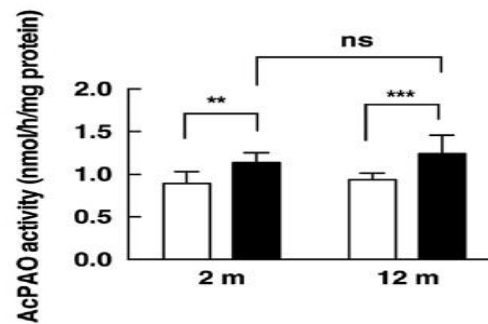
□ Normal, ■ Infarct

B. Polyamine metabolizing enzyme activities

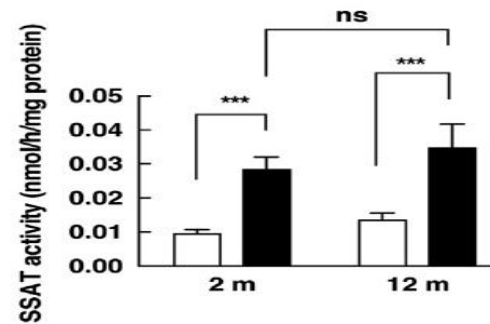
SMO



AcPAO



SSAT



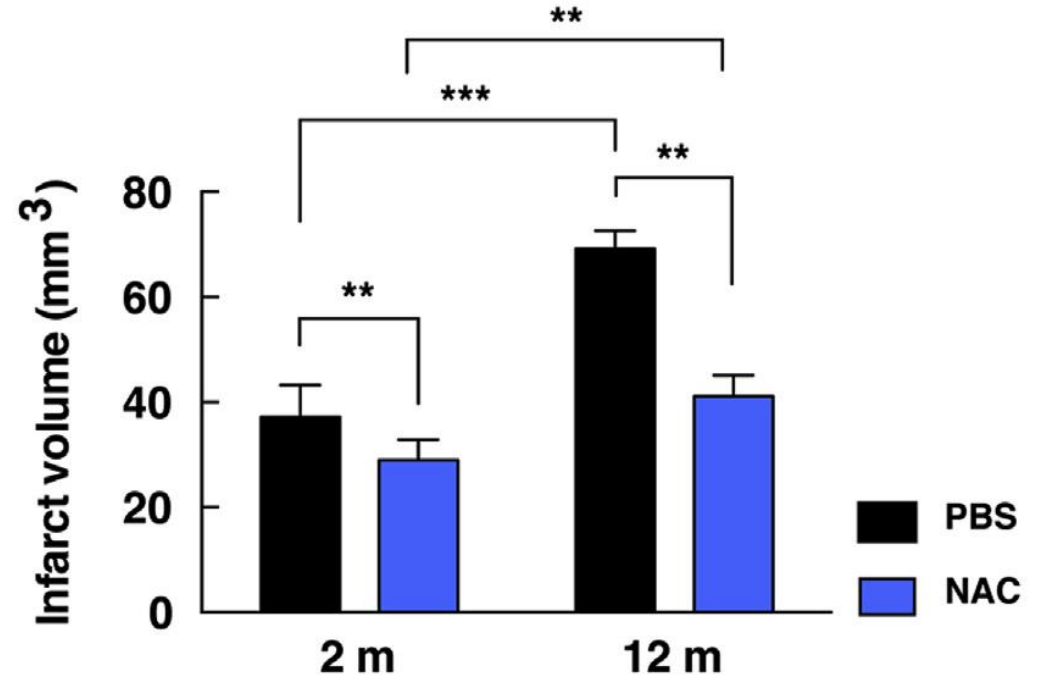
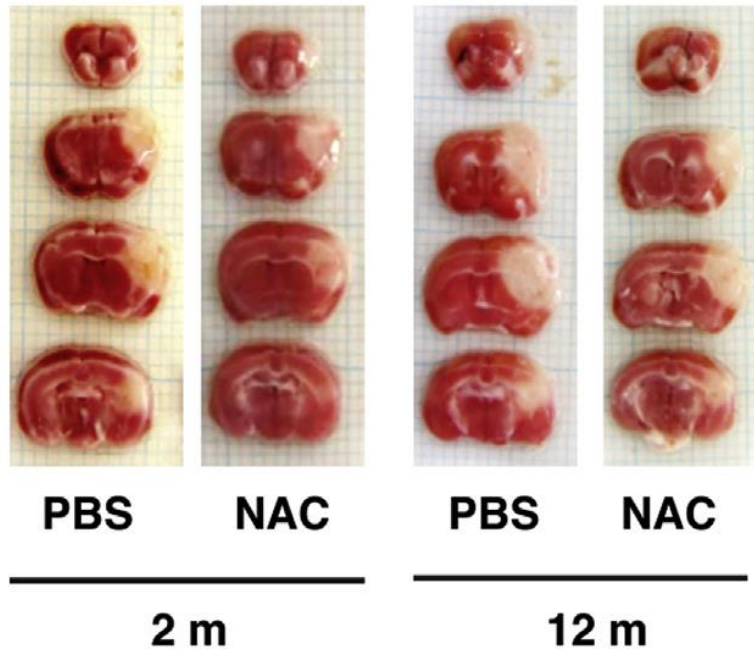


Aggravation of brain infarction through an increase in acrolein production and a decrease in glutathione with aging



Takeshi Uemura ^a, Kenta Watanabe ^b, Misaki Ishibashi ^b, Ryotaro Saiki ^a, Kyoshiro Kuni ^b, Kazuhiro Nishimura ^b, Toshihiko Toida ^b, Keiko Kashiwagi ^c, Kazuei Igarashi ^{a, b, *}

C. Effect of NAC on infarct volume





Aggravation of brain infarction through an increase in acrolein production and a decrease in glutathione with aging



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- Acroleina è maggiormente coinvolta nel danno ai tessuti in diverse malattie (ictus, insufficienza renale, Alzheimer, etc.)
 - L'aggravarsi dell'ictus in età avanzata è dovuto ad aumento di acroleina e diminuzione di GSH
 - GSH è coinvolto nella riduzione della porzione di cervello infartuato
 - N-acetylcysteine è un potente *scavenger* di acroleina più dei ROS

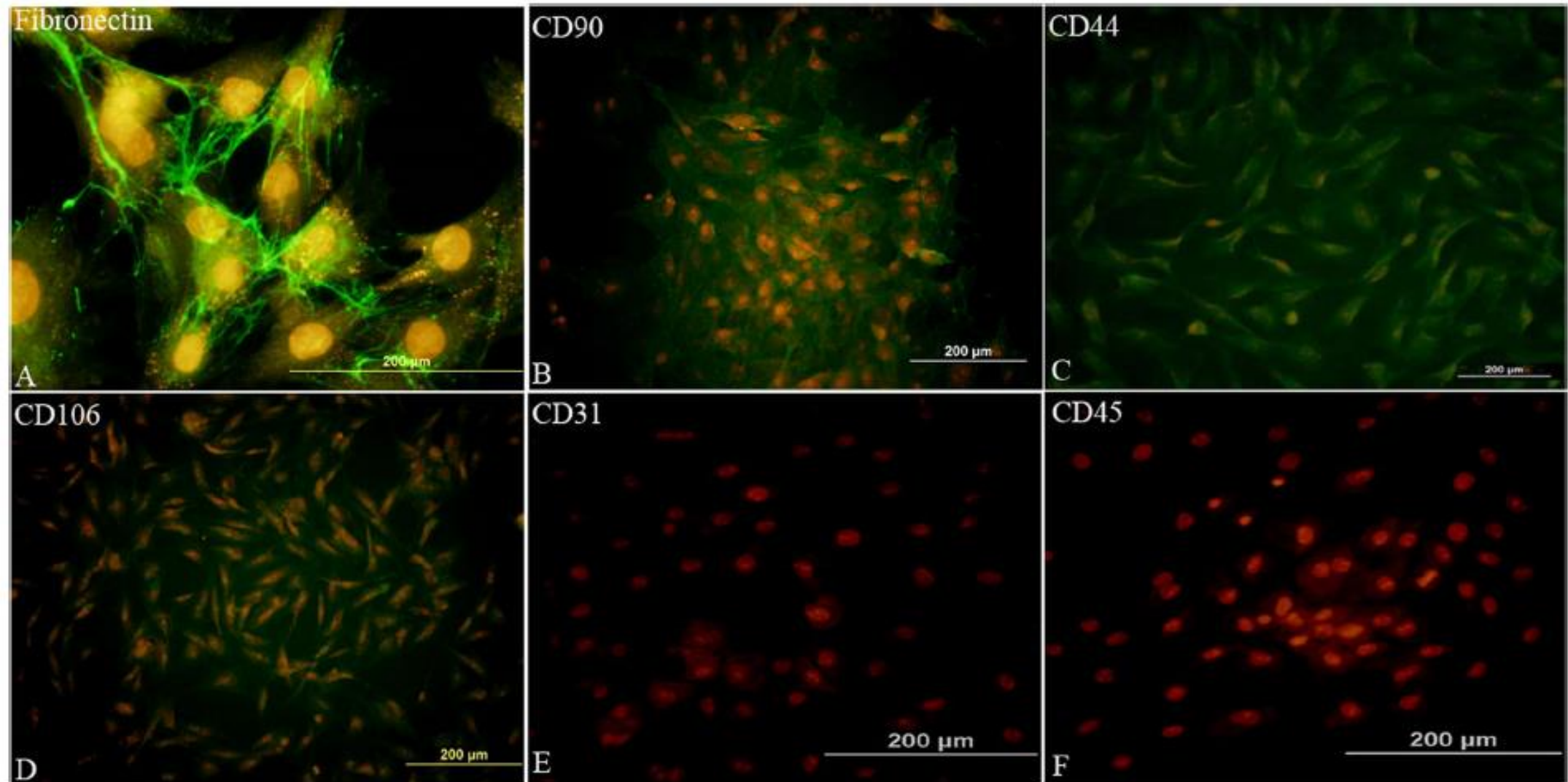
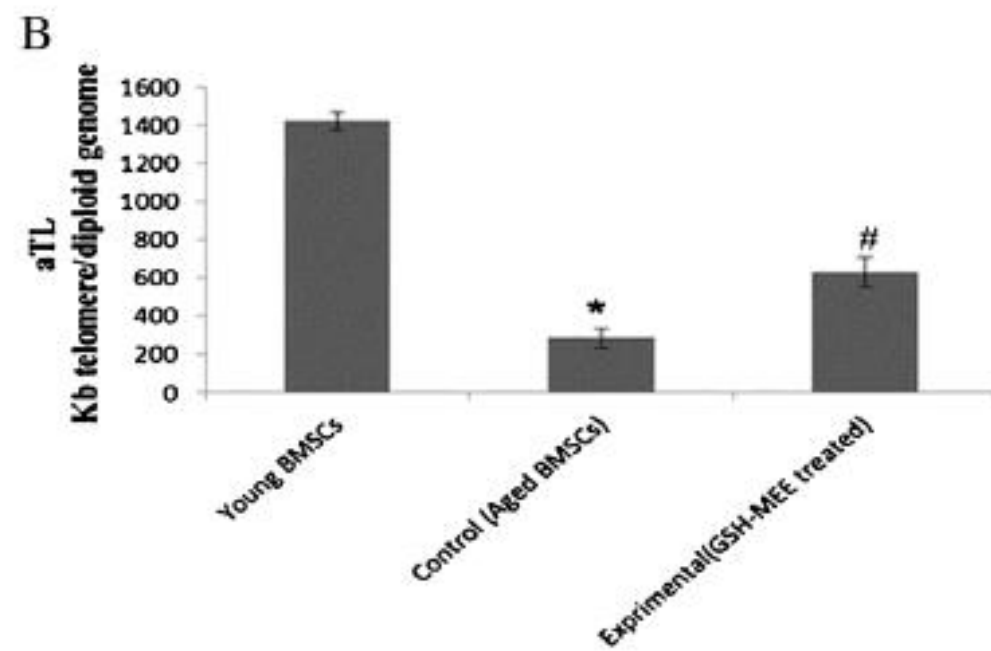
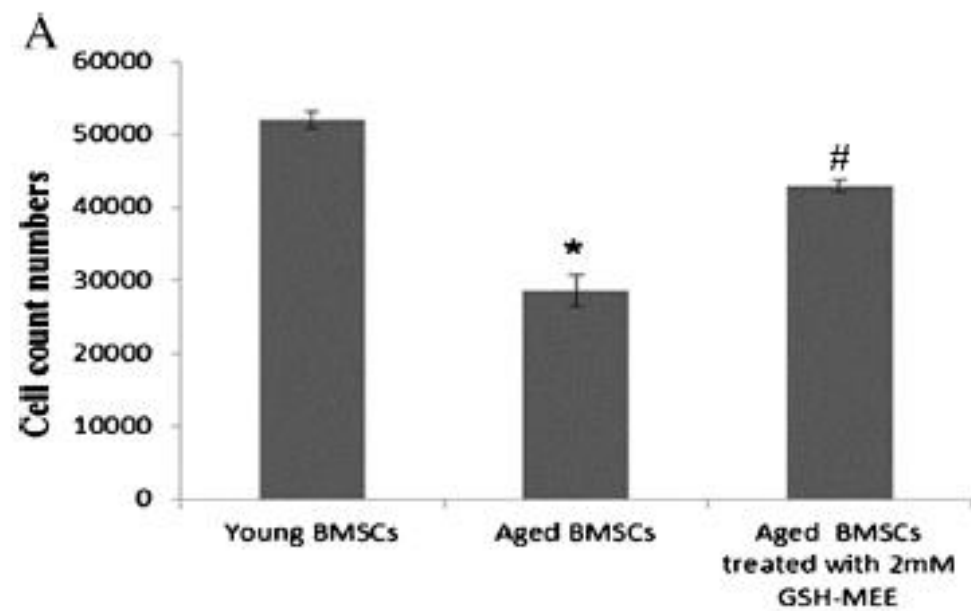
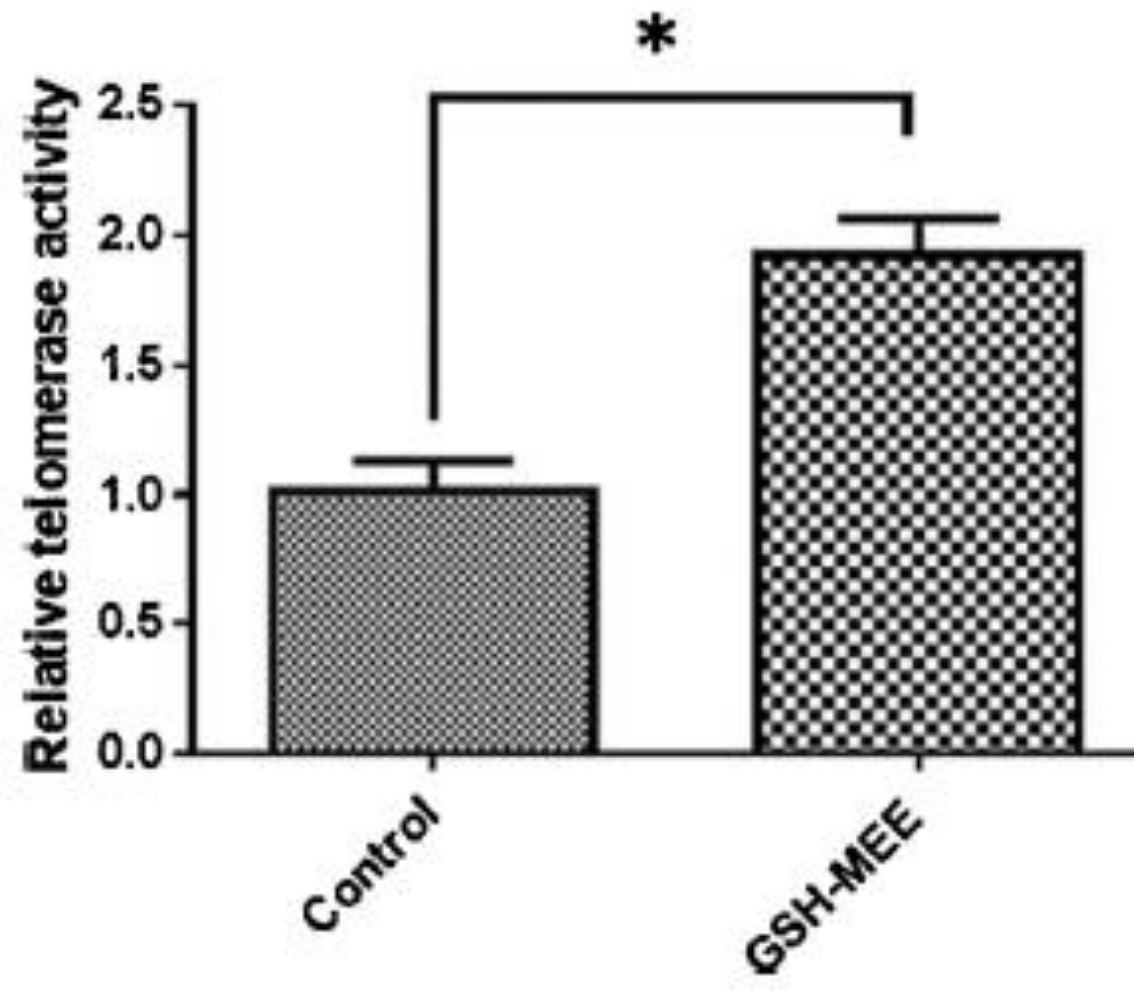
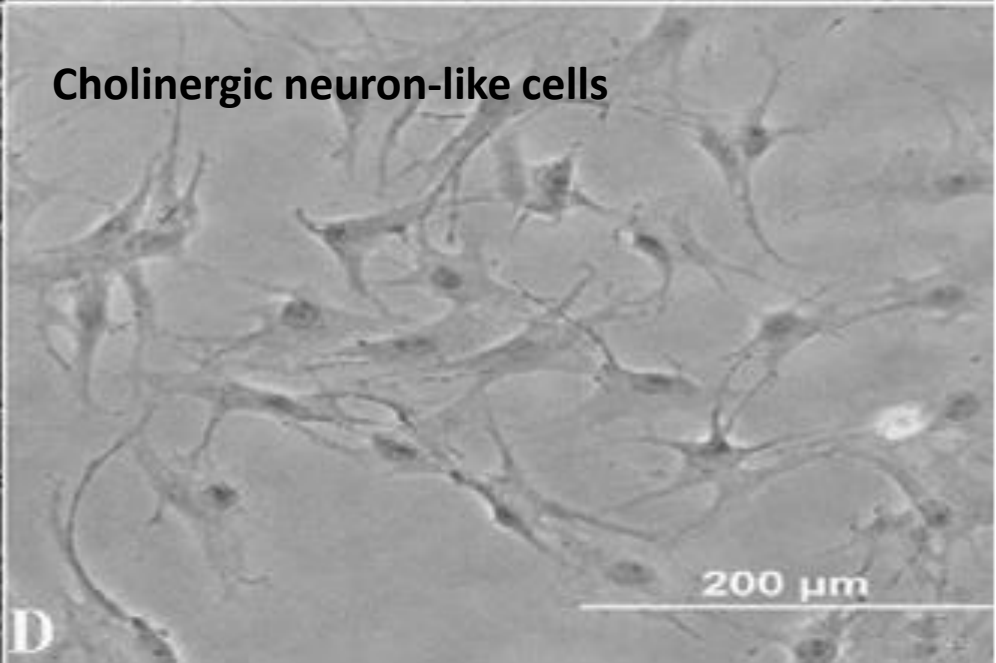
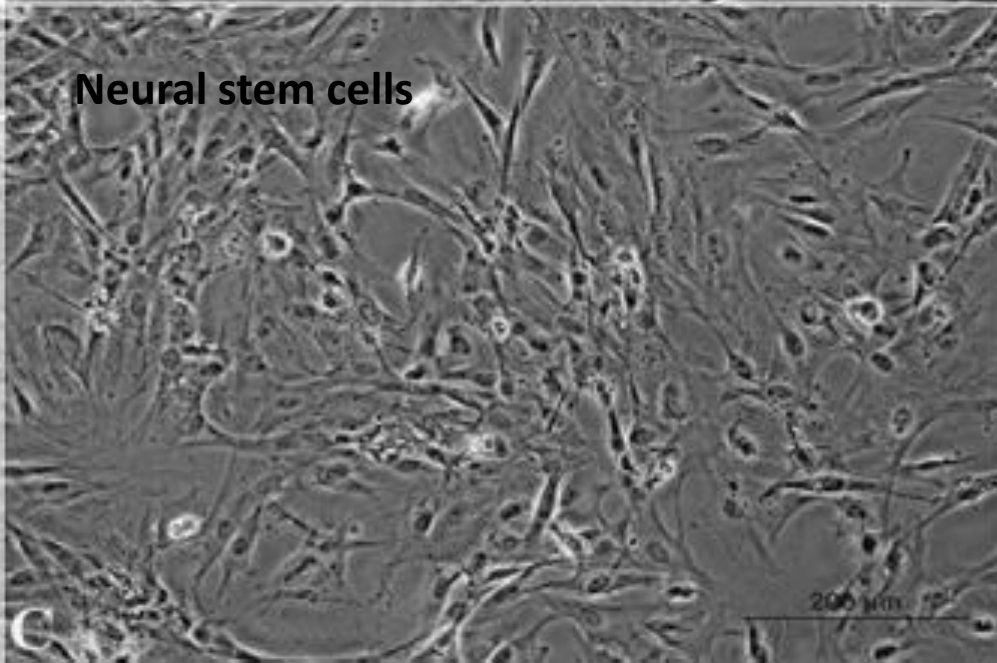
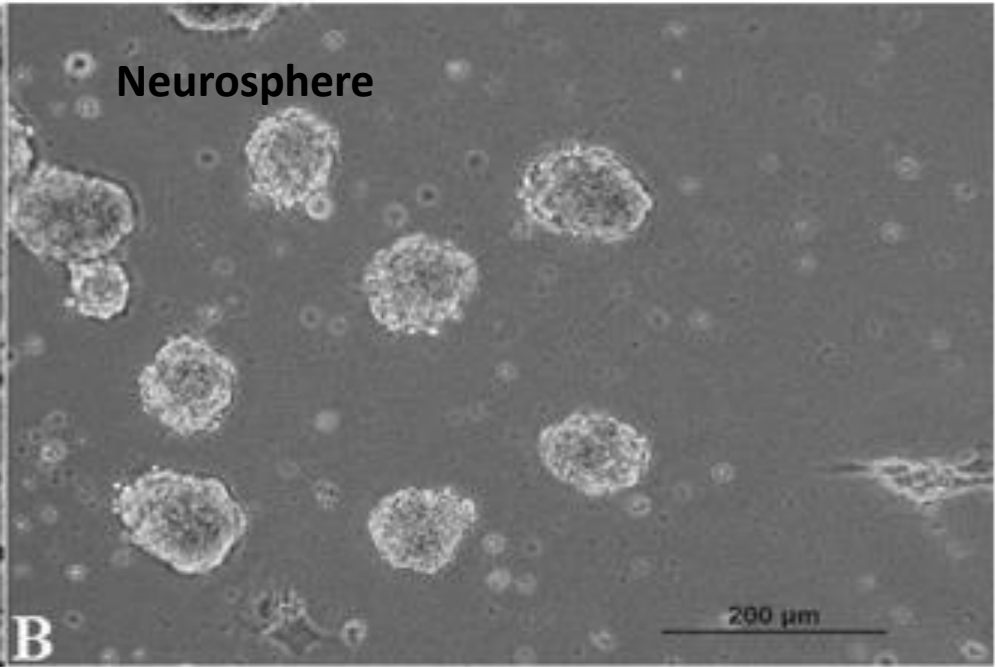
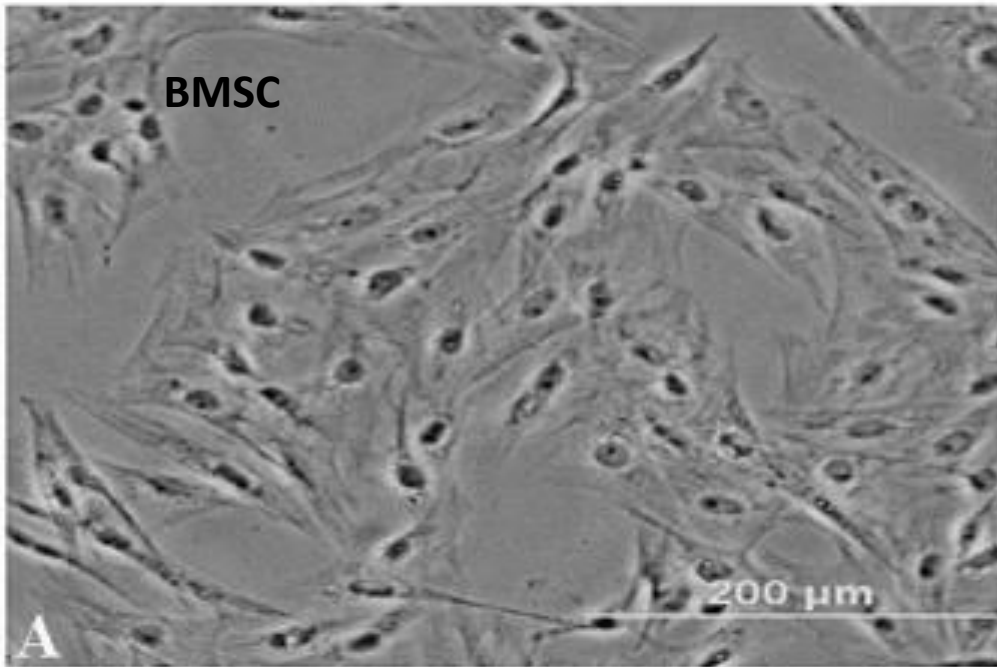


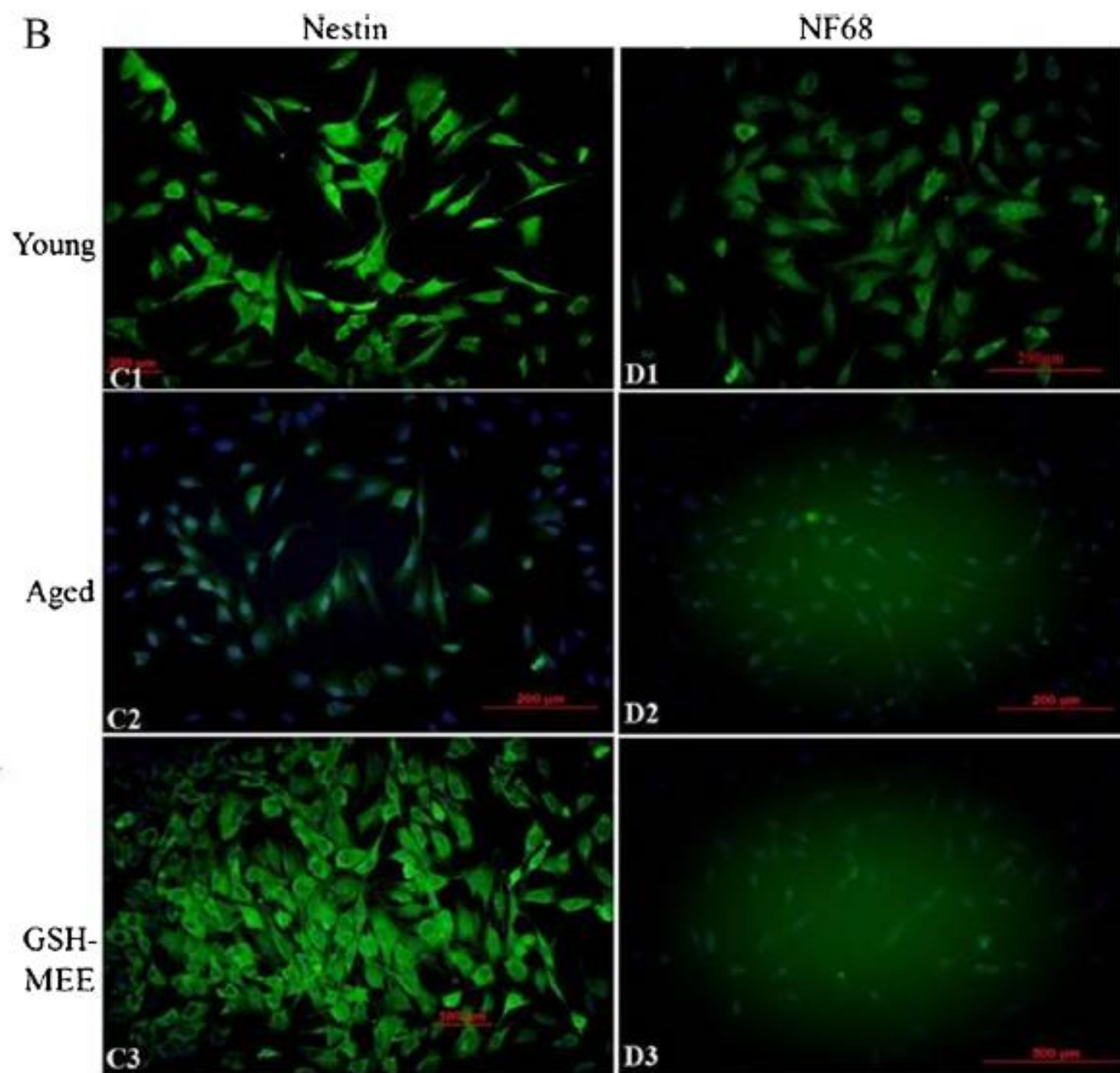
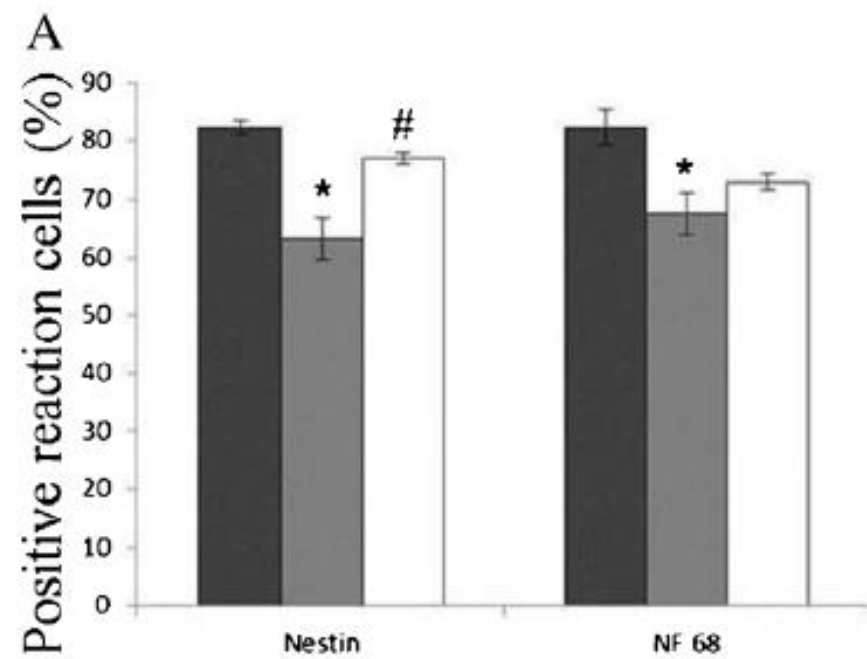
Figure 1. Represents the immunostaining of BMSCs at the third passage of (A) Fibronectin, (B) CD90, (C) CD44, (D) CD106, (E) CD31, and (F) CD45, respectively. The primary antibodies for these markers were labeled BMSCs and incubated with secondary antibodies conjugated with

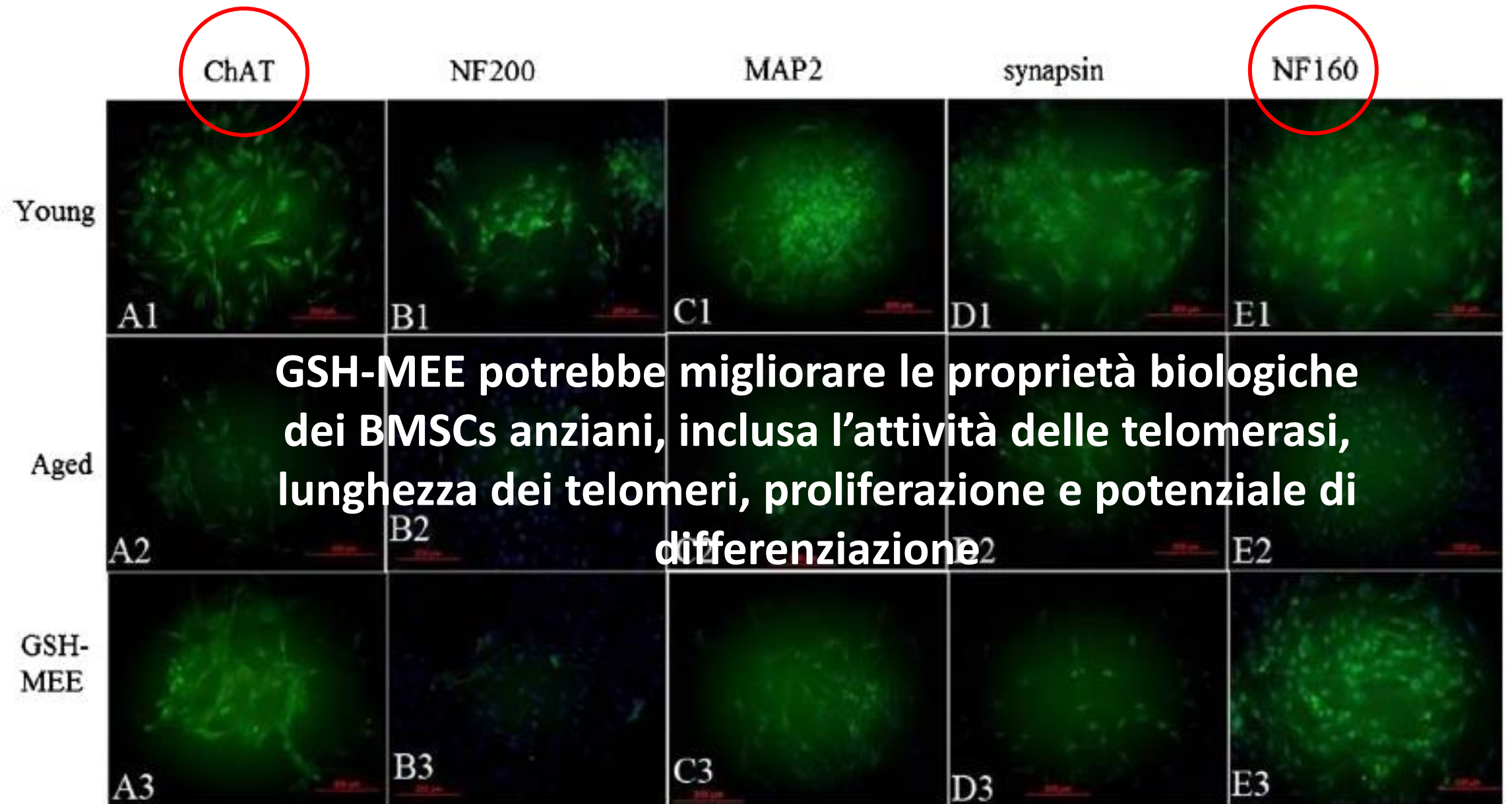
FITC. Cells with green staining cytoplasm were positive. The nuclei were stained with propidium iodide; these are illustrated in *yellow* or *orange*. (scale bar = 200 μm , all).









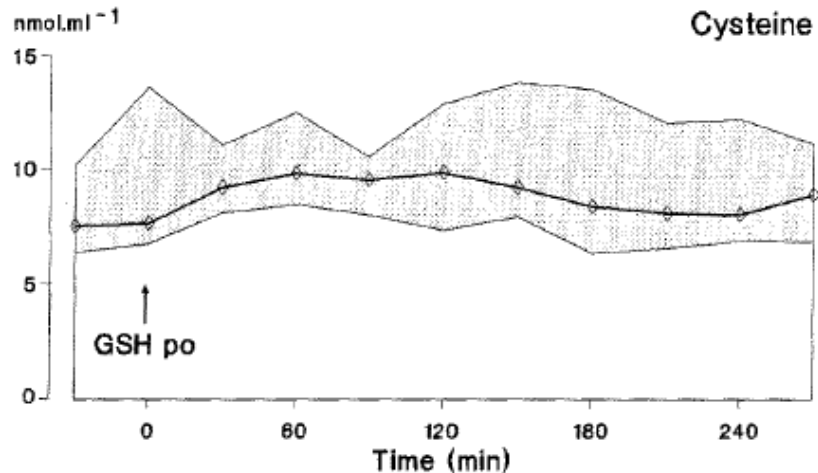
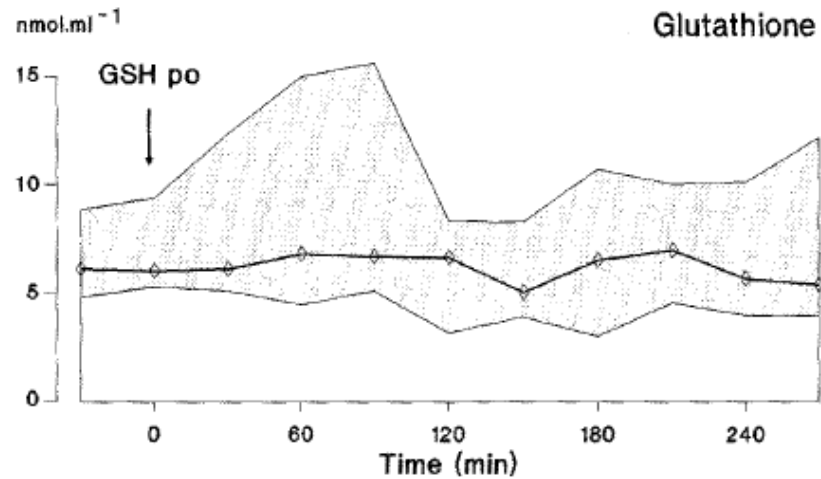


The systemic availability of oral glutathione

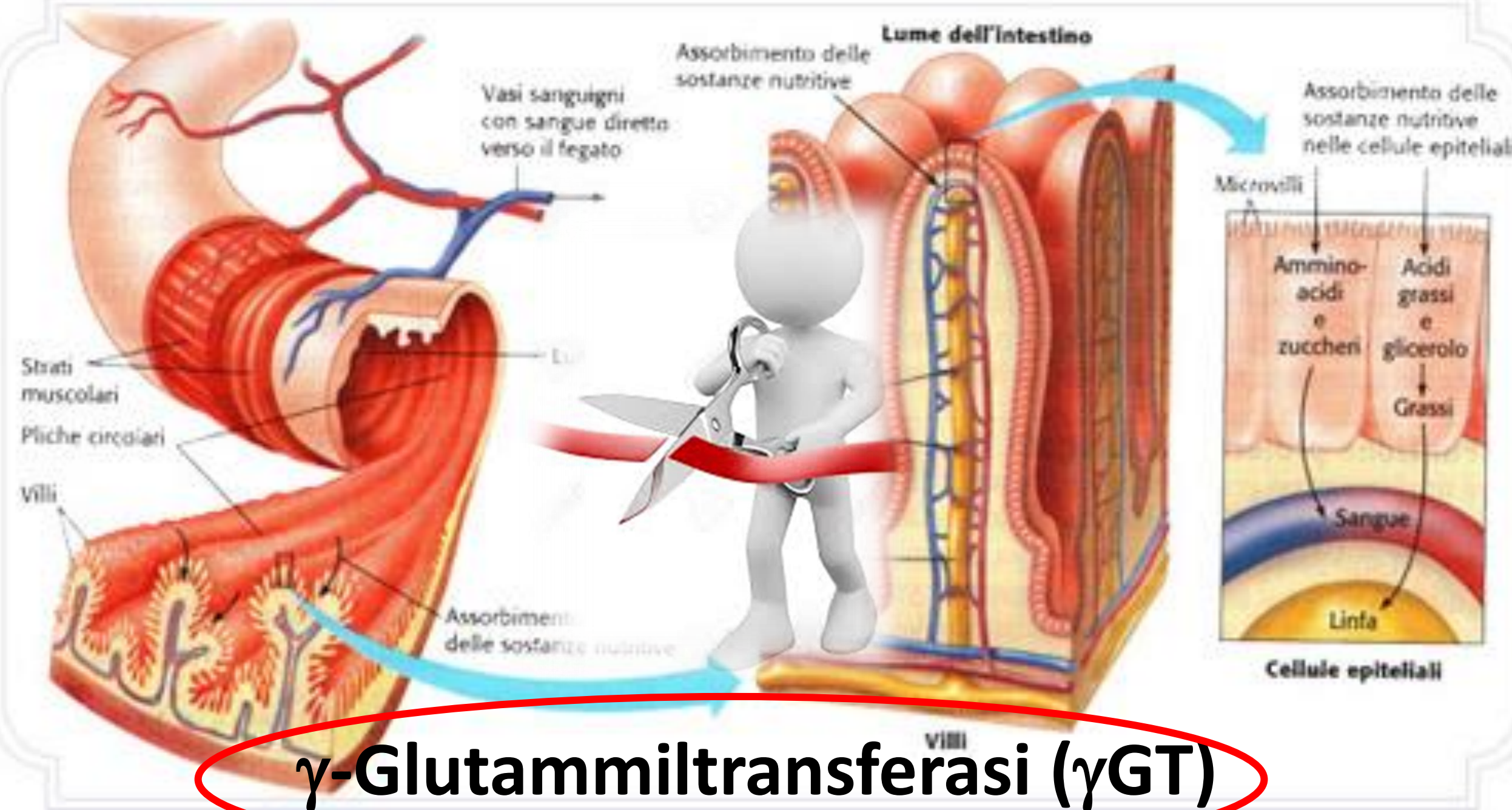
A. Witschi, S. Reddy, B. Stofer, and B. H. Lauterburg

European Journal of **Clinical
Pharmacology**

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Plasma concentrations of unbound glutathione (top) and unbound cysteine (bottom) in seven healthy volunteers after the oral administration of 0.15 mmol/kg/~ glutathione.

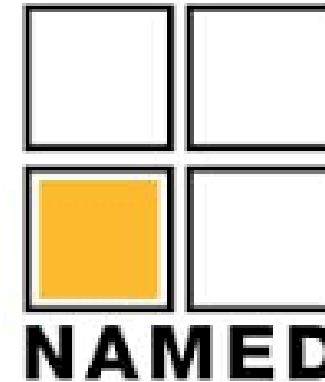




It is needed to design antioxidant therapeutic strategies for the treatment of various conditions

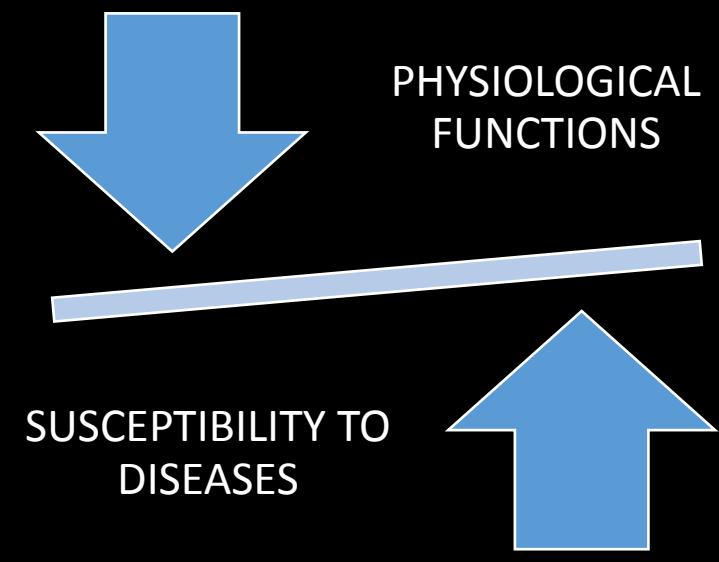
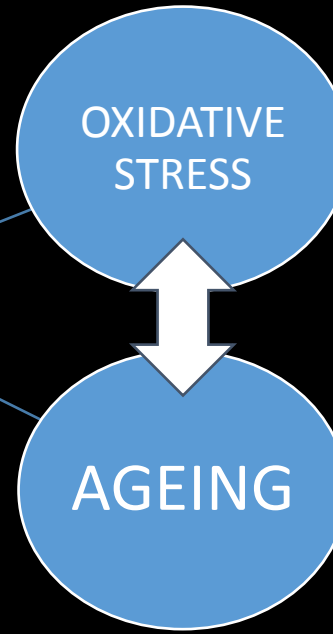
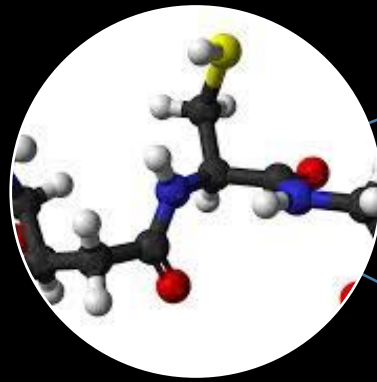


LABORATORIO DI FARMACOBIOCHIMICA NUTRIZIONE E NUTRACEUTICA



COLLABORARE E INNOVARE

GLUTATHIONE



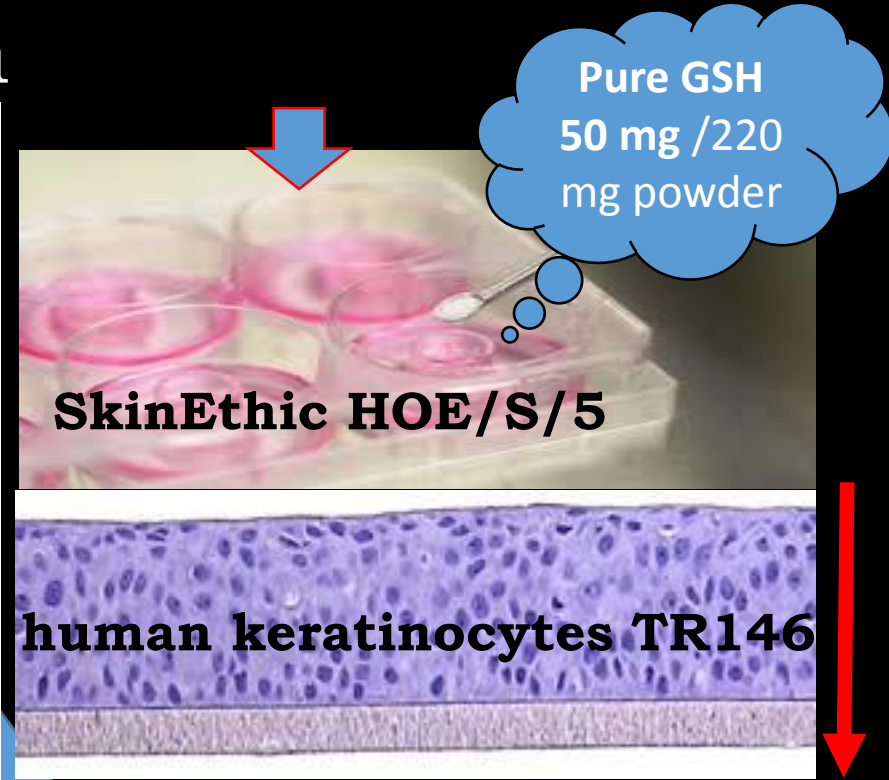
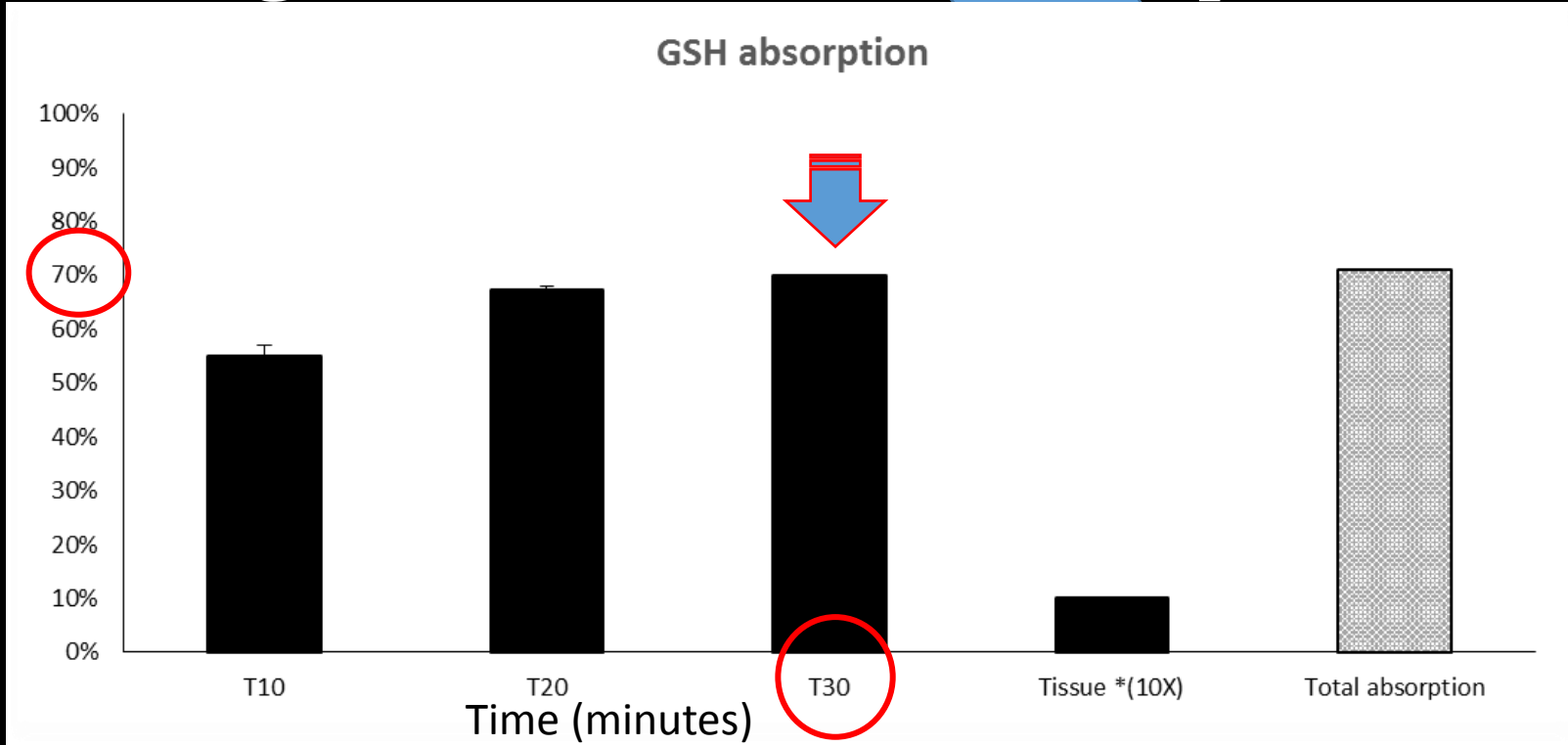
Aim: to evaluate improvement of GSH systemic availability testing an **orobuccal fast-slow** release formulation tablet

dissolving and releasing immediately GSH upon contact with the oral mucosa bypassing the intestinal degradation



differentiated release of selected ingredients

In vitro: orobuccal fast-slow GSH release formulation through reconstructed oral epithelium



Glutathione dose by HPLC

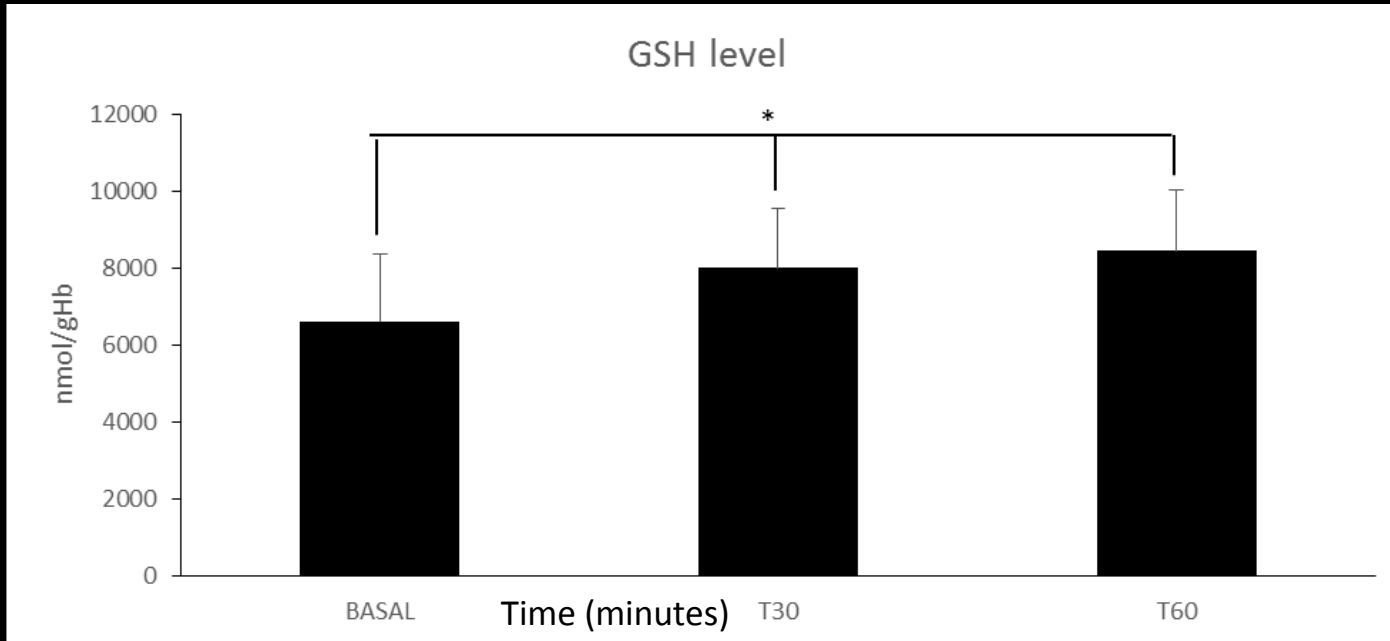
MTT toxicity test

in vitro data obtained from the MTT irritation test performed on the HOE tissue for the evaluation of tissue viability

	OD 540	TISSUE VIABILITY	CLASSIFICATION
UNTREATED TISSUE	1.486	100%	
TREATED TISSUE	1.476	99.33%	NI

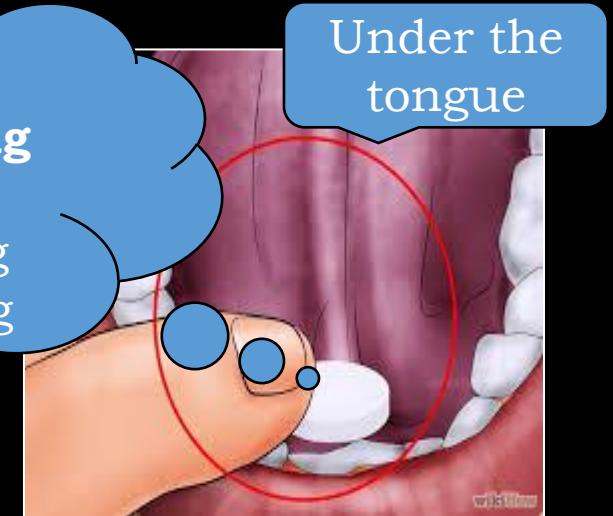
to carry the glutathione for
dependent absorption through
the oral mucosa

In vivo: GSH systemic bioavailability using an optimized orobuccal fast-slow release formulation tablet



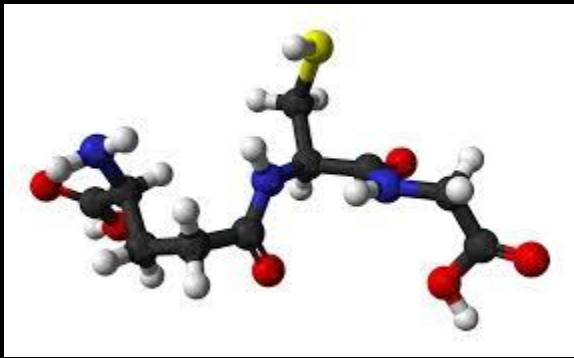
15 healthy volunteers (f, m), w 60 ± 5 Kg, 20-40 year-old

1 tablet:
Pure GSH 250 mg
L-cystine 50 mg
Vitamin C 40 mg
Selenium 55 mcg

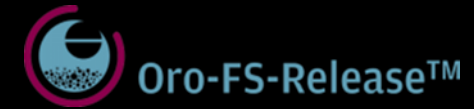


alkylating agent N-ethylmaleimide (NEM) [Giustarini et al. *Nature Protocols* 2013; 8(9): 1660–1669]

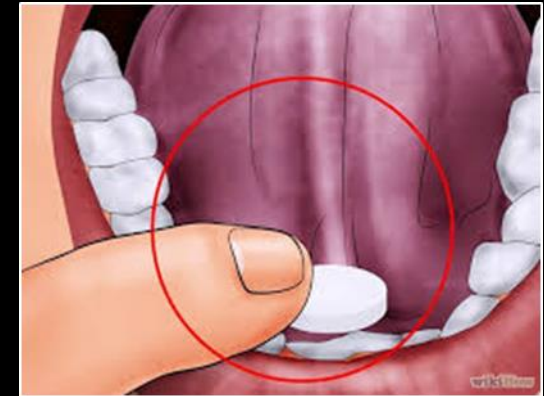
fast absorption rate of GSH through the *in vivo* oral mucosa



✓the intake of GSH, formulated through optimized orobuccal fast-slow release tablets, gave positive results in raising GSH blood concentration



✓probably going to strengthen all *in vivo* by-products and processes that involve this important tripeptide



Orobuccal fast-slow GSH release tablet-**Glutaredox**[®]- is a new, innovative, efficient and functional dosage form

Hindawi Publishing Corporation
Oxidative Medicine and Cellular Longevity
Article ID 594191

Research Article

Bioavailability Study of an Innovative Orobuccal Formulation of Glutathione

**Daniela Buonocore,¹ Matteo Grosini,¹ Silvana Giardina,²
Angela Michelotti,² Mariaelena Carrabetta,¹ Antonio Seneci,¹ Manuela Verri,³
Maurizia Dossena,³ and Fulvio Marzatico¹**





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Laura Cattaneo
Alice Ascani
Alberto Zurma

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Food Supplements & Medical Devices
MILANO



*Memory of
Professor Fulvio Marzatico*





Thank you for attention

Daniela Buonocore

Laboratorio di Farmacobiochimica,
Nutrizione e Nutraceutica

farmbio@unipv.it

daniela.buonocore@unipv.it