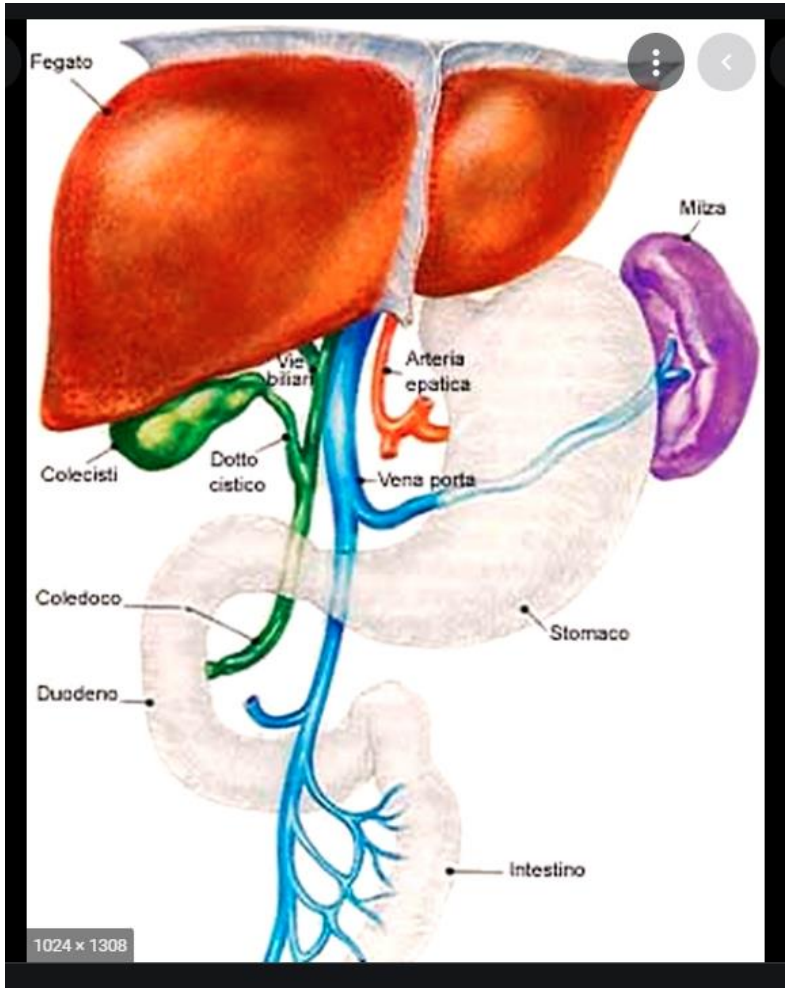
University of Genoa
Italy

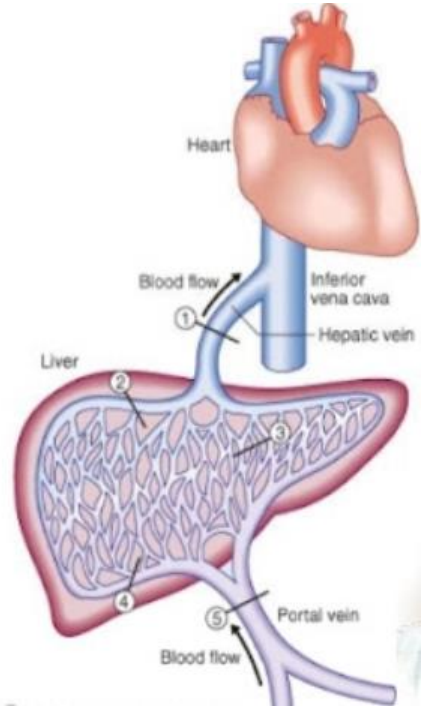
Il trattamento con olio ozonizzato per via orale. Un nuovo strumento per la prevenzione delle recidive e della progressione di malattie

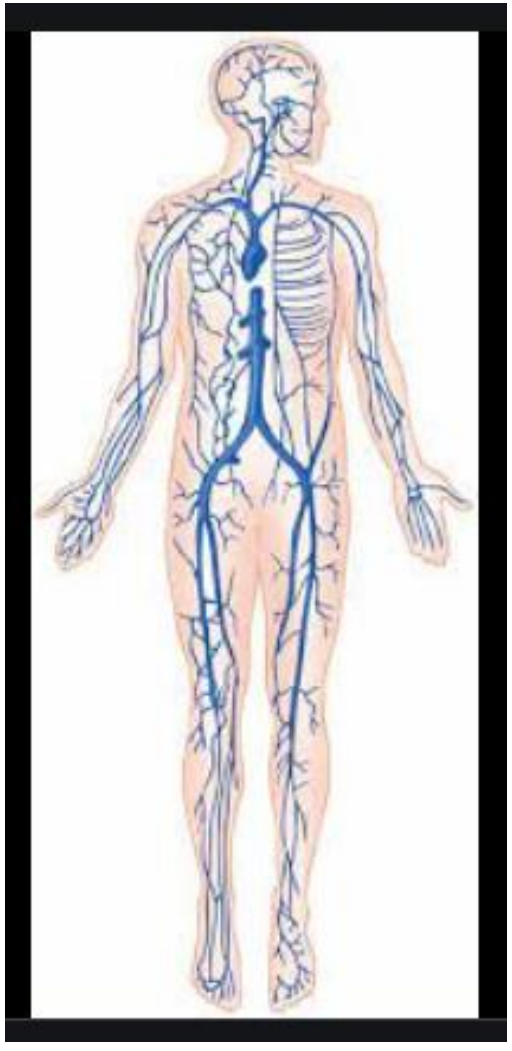
Izzotti A.

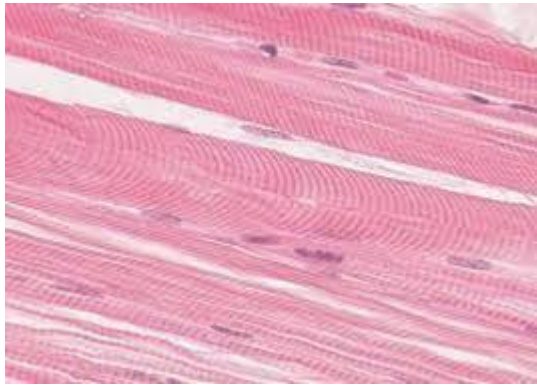
Full Professor, School of Medicine, University of Genoa
Director PhD School in Health Sciences and Cancer Prevention, University of Genoa, Italy

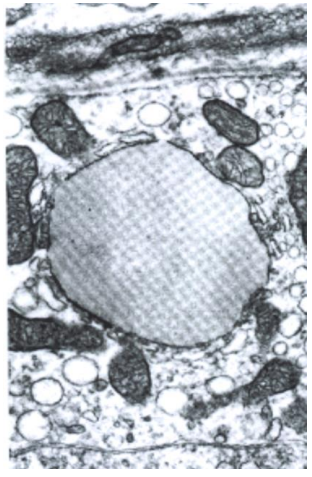
LIPID CARRIER
pharmacokinetic



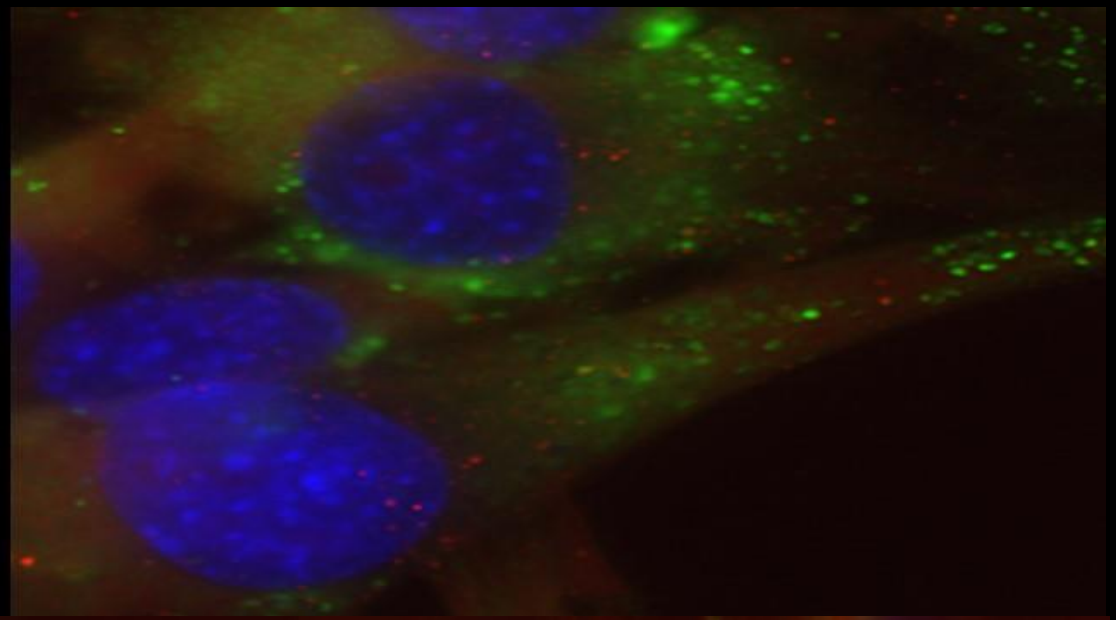


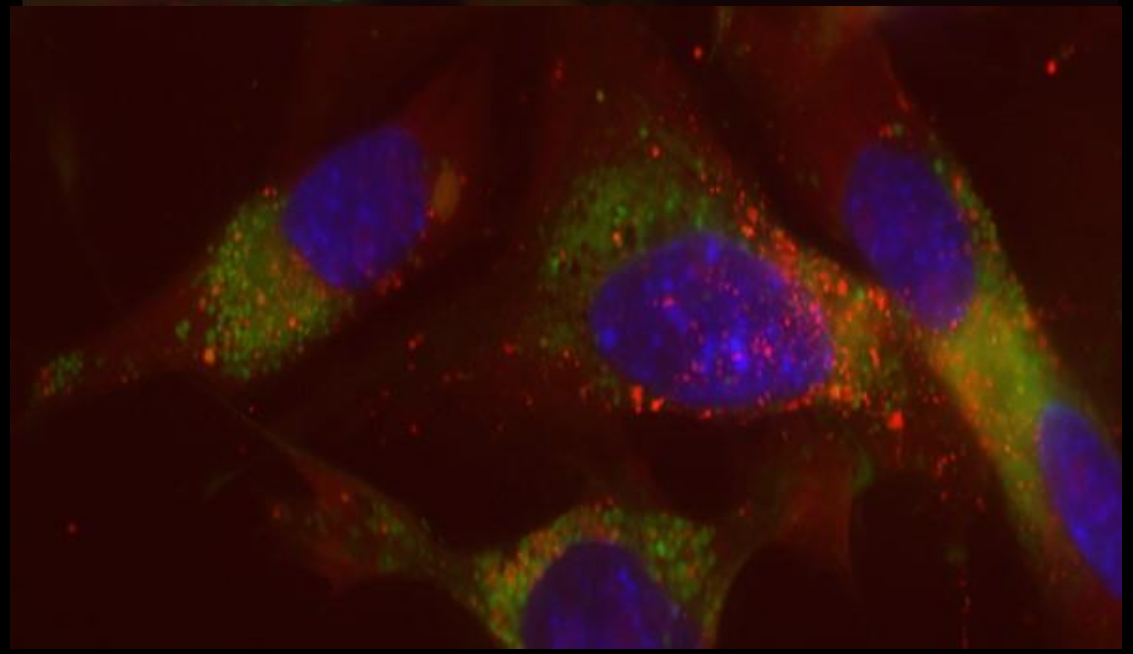


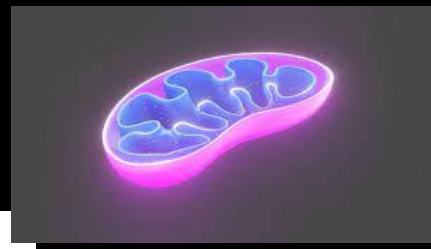




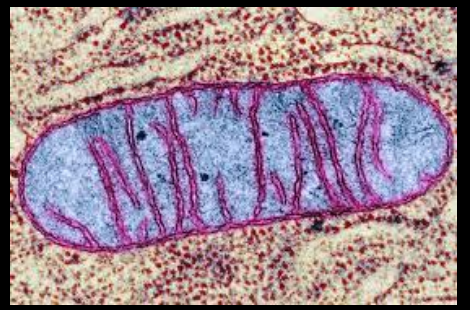
Intracellular delivery of ozonized lipid carrier in epithelial cells







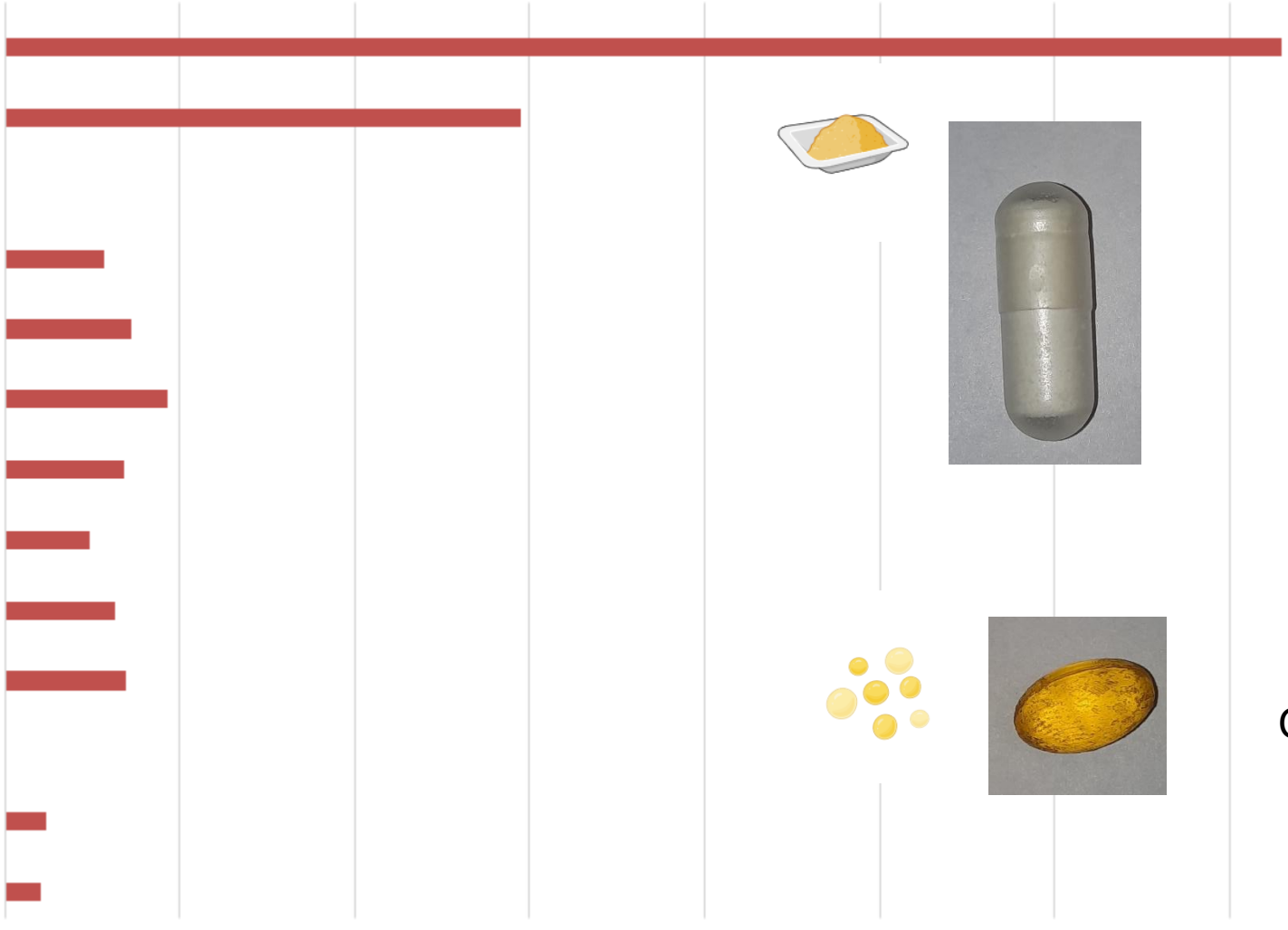
STANDARD PROCEDURE:
traditional extracellular approach with Gas, where ozone **cannot reach the cytoplasm**.



O3ZONE PROCEDURE:
the novelty and innovation of our technology ensure intracellular approach thanks to the ozone lipidic carrier. Confocal fluorescence microscopy with ozonized oil indicated in red (**reach the cytoplasm**)

OZONIZED OILS

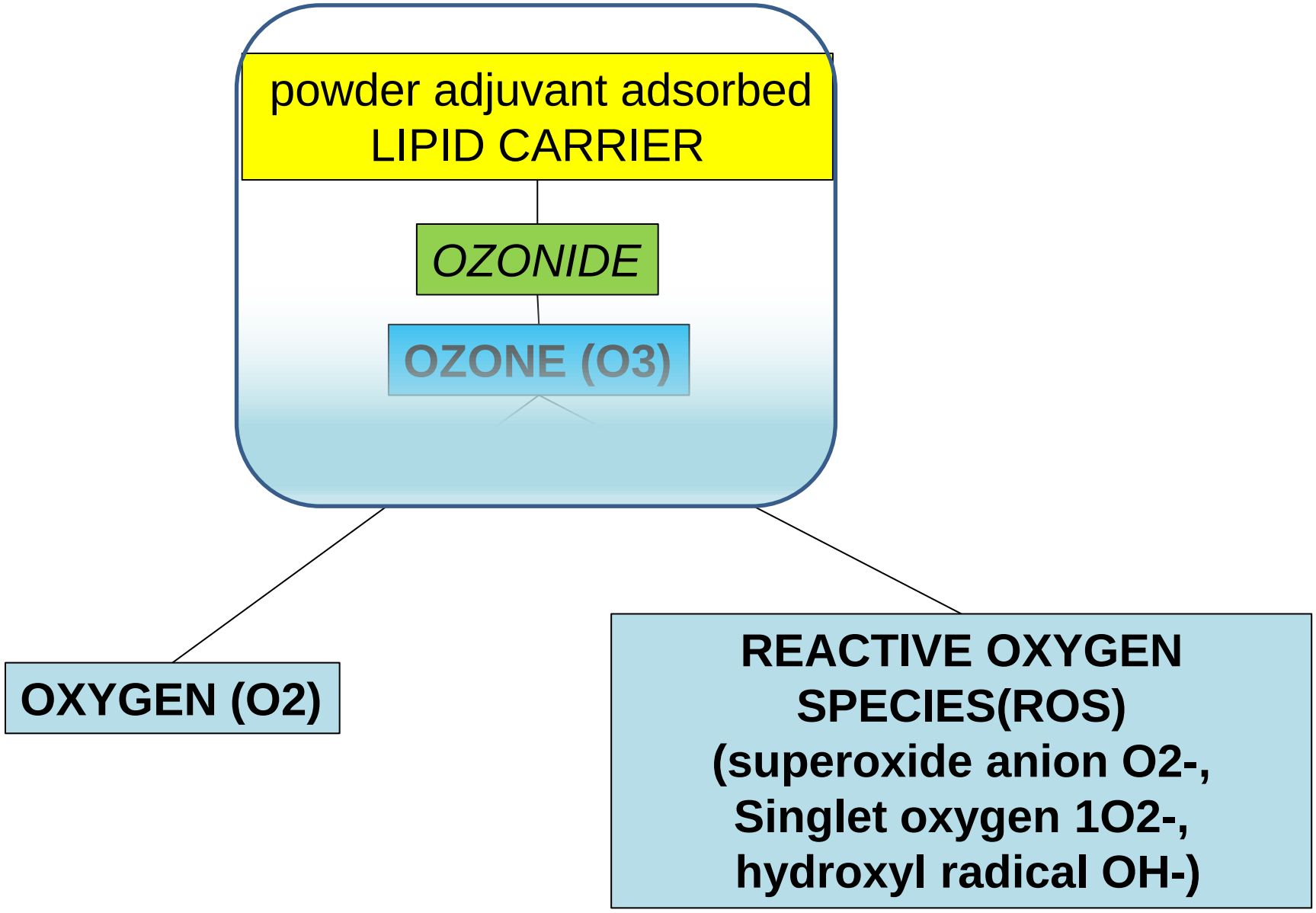
Comparative evaluation of ACTIVE-OXYGEN intracellular release



O3zone
Active oxygen
and oleic acid
in powder-adsorbed
gastroresistant pills

Ozonated oil ampoules

HIGH-OZONIDE OZONATED OIL



OXYGEN (O2)

Effetto di HOO su pO2 (4 days)

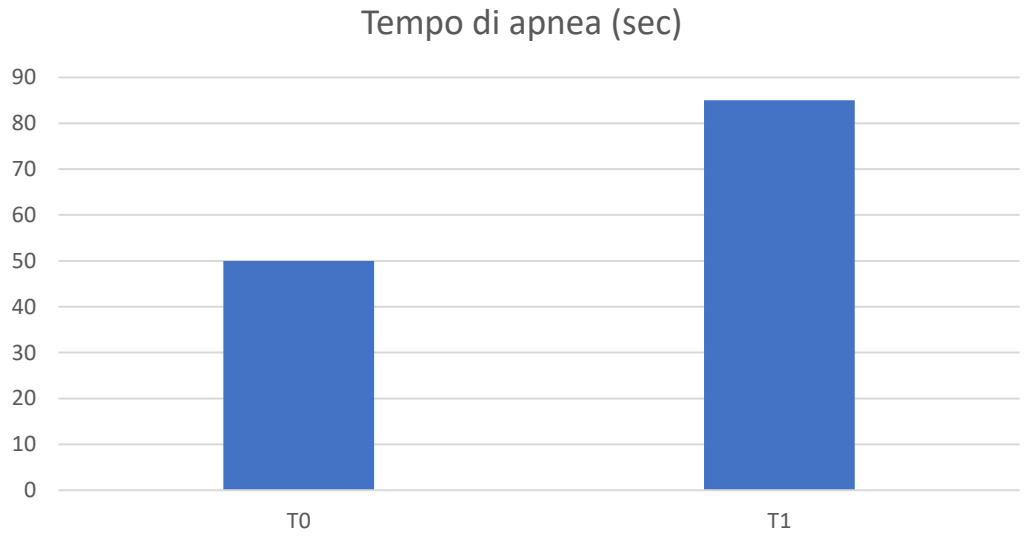
ERGOSPIROMETRIA

T0	test da sforzo PRE TRATTAMENTO				
	Vo2max ml/kg/min	vo2 (L/min)	Vo2 soglia ml/kg/min	Vo2 soglia (L/min)	% VO2max in soglia
subject 1	39.4	3.19	32.5	2.62	82
subject 2	36.6	2.42	30.6	2.07	86

T1	test da sforzo POST TRATTAMENTO				
	Vo2max ml/kg/min	vo2 (L/min)	Vo2 soglia ml/kg/min	Vo2 soglia (L/min)	% VO2max in soglia
subject 1	40.9	3.27	35.6	2.94	90
subject 2	38.9	2.63	33.4	2.07	86

Aumento del 10 % della soglia aerobica

TEMPO DI APNEA



Aumento del 58 %

SATURAZIONE EMATICA O2

Frail patient 55-year-old male who had existing complications with COPD-related respiratory failure, obesity, and severe cardiovascular disease. He contracted COVID-19 infection together with pneumonitis, cough, fever (38.7 ◦C), and decreased O2
blood saturation down to 84%. After 4 days of HOO treatment, the patient's fatigue and
fever disappeared together with recovery of olfactory and taste capacities.
O2 blood saturation was restored to 98%.

Aumento da 84% a 98%

Izzotti et al., J Pers Med., 2021

RESULTS (HOO+AFA vs AFA only)

VO2 max +49% (P≤0.01)

VO2 max, or maximal oxygen consumption, refers to the maximum amount of oxygen th an individual can utilize during intense or maximal exercise. This measurement is the best indicator of cardiovascular fitness and aerobic endurance

Muscle strength test +31% (P≤0.05)

n=50
T0 vs T1
Females

+

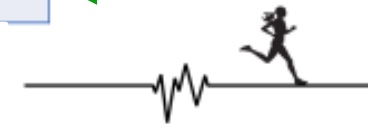
Body fat decrease -3% (NS)

36-Item Short Form Survey – Quality of Life

Adapted Physical Activity (AFA)

	AFA (6 months)	AFA+O3zone 2 months (6 months)
	Paulo et al. (2019)	Gemelli - UNIGE
Physical activity	+25%	+8% (+24%)
Aerobic capacity	+15%	+75% (+225%)
Pain decrease	+33%	+16% (+48%)
Health status	+0%	+24% (+72%)
Viability	+12%	+28% (+84%)
Social activities	+21%	+30% (+90%)
Emotonial wellbeing	+8%	+237% (+711%)
Psycological Health	+10%	+31% (+93%)

FATIGUE



REACTIVE OXYGEN SPECIES (ROS) (O2-,1O2-,OH-)

Nrf2 activation

Antibacterial effect

Anti-inflammatory effect

Blood vessel dilatation (NO)

Nrf2 Activation

ARE
Antioxidant Responsive Elements
Activation

International Journal of *Molecular Sciences*

MDPI

Review

Regulation of Wound Healing by the NRF2 Transcription Factor—More Than Cytoprotection

Tissue-protective genes: ARE, Cyclins

Paul Hiebert * and Sabine Werner *

Institute for Molecular Health Sciences, Department of Biology, Swiss Federal Institute of Technology Zürich, 8093 Zurich, Switzerland

* Correspondence: paul.hiebert@biol.ethz.ch (P.H.); sabine.werner@biol.ethz.ch (S.W.)

Received: 17 July 2019; Accepted: 7 August 2019; Published: 8 August 2019

check for updates

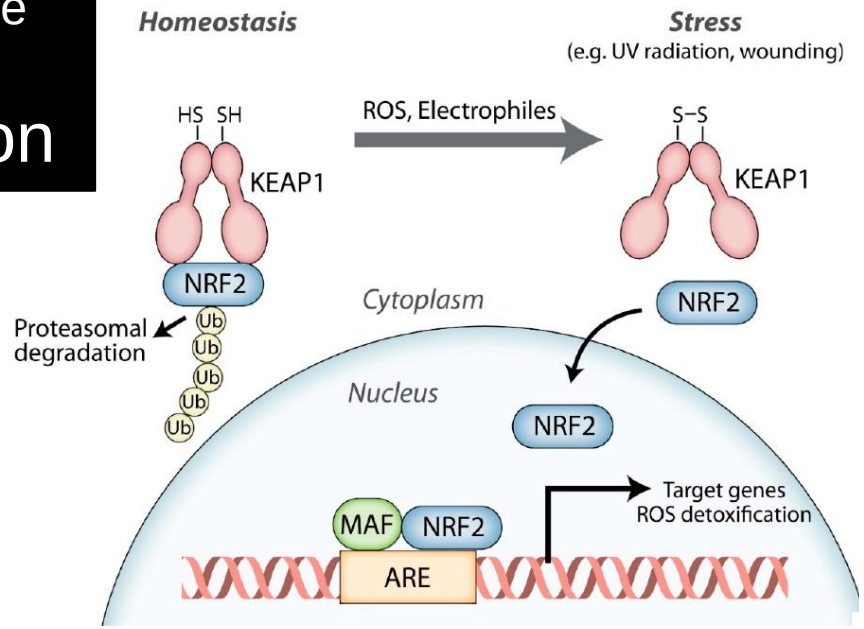


Figure 1. The nuclear factor-erythroid 2-related factor 2 (NRF2) signaling pathway. NRF2 strongly binds to its cytoplasmic inhibitor Kelch-like ECH-associated protein 1 (KEAP1) under homeostatic conditions and only low levels of NRF2 are present in the nucleus. In response to reactive oxygen species (ROS) and/or electrophiles, the NRF2-KEAP1 interaction is weakened and newly formed NRF2 accumulates in the nucleus. Here, NRF2 dimerizes with small musculoaponeurotic fibrosarcoma (MAF) proteins and binds to antioxidant response elements (AREs) in the promoters or enhancers of its target genes, of which many encode ROS detoxifying enzymes and other antioxidant proteins, thereby initiating a cytoprotective response.

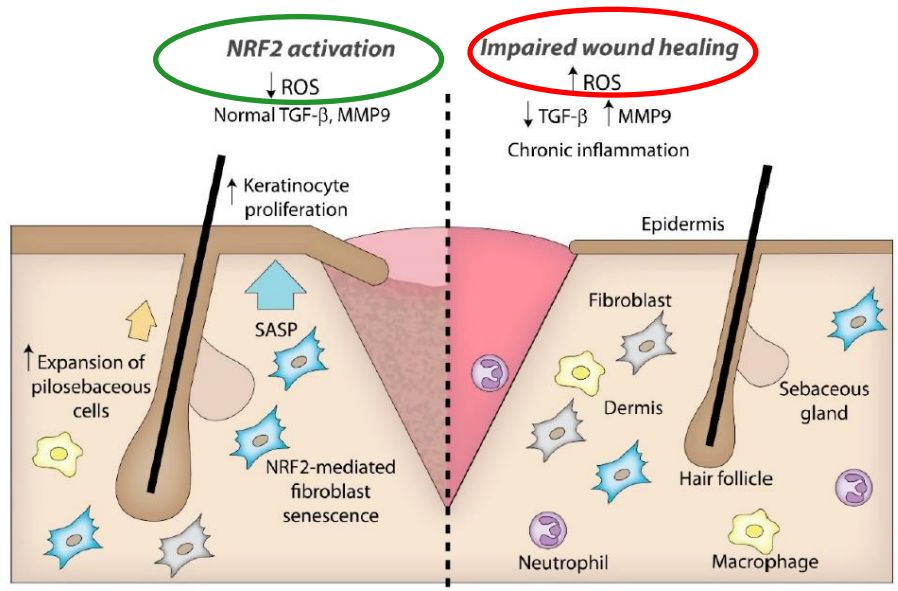
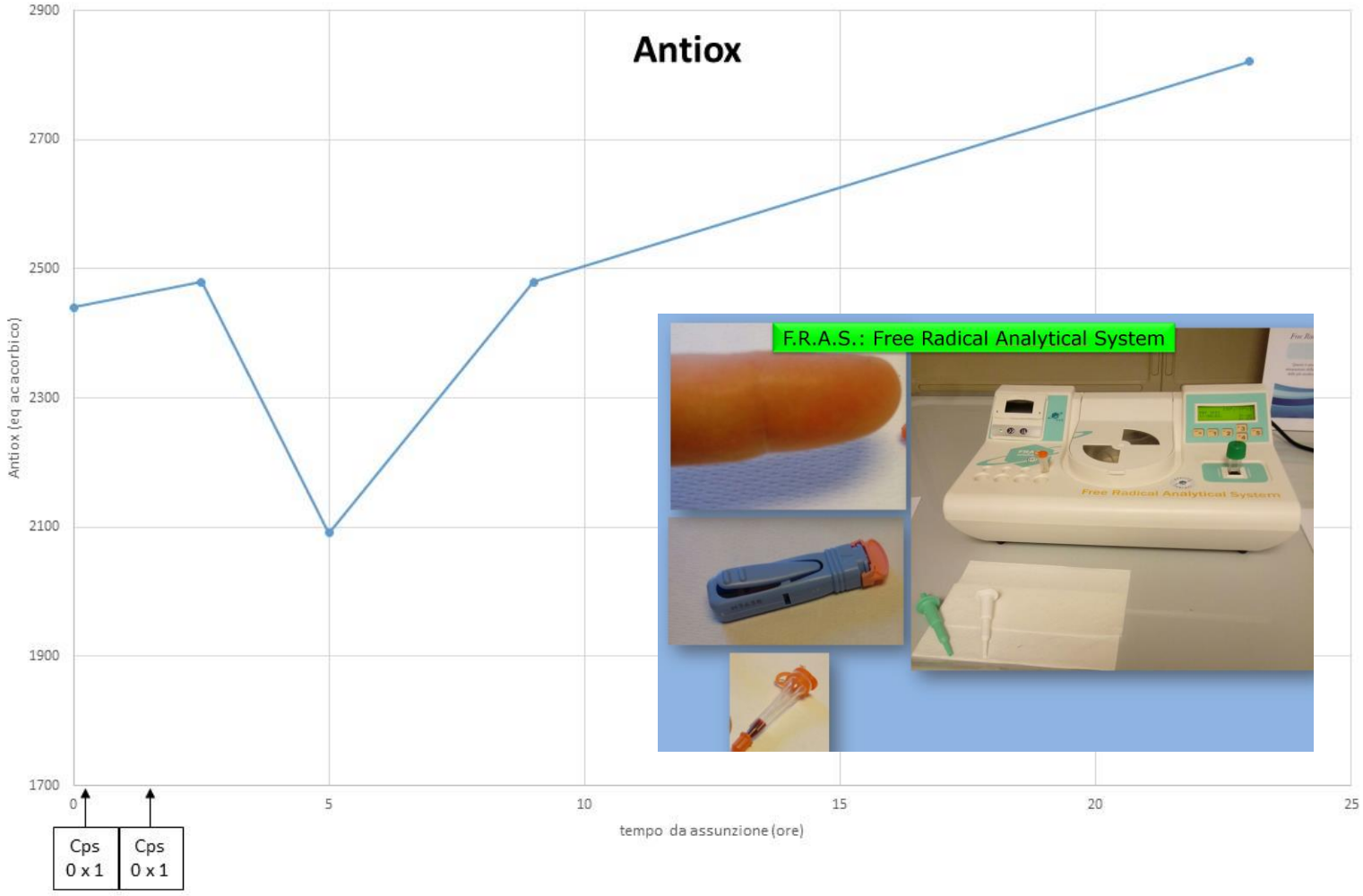


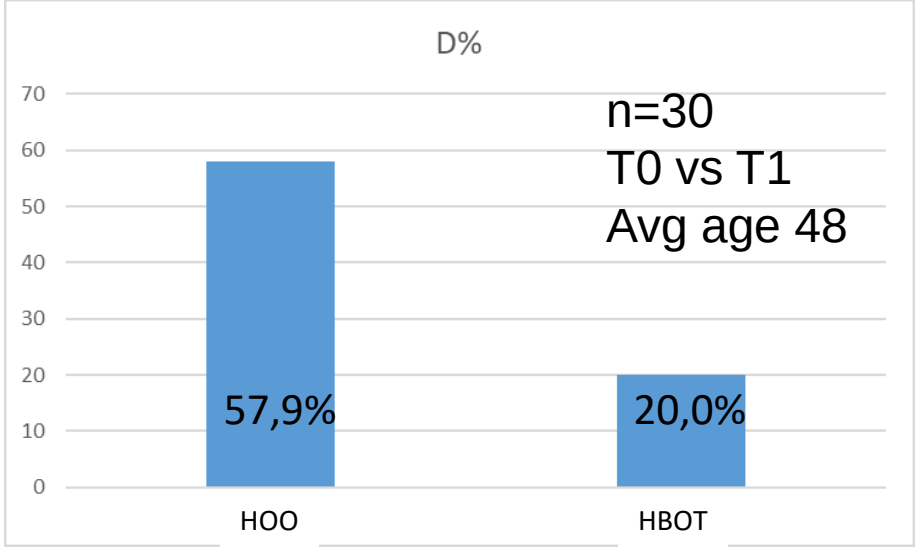
Figure 2. Characteristic features of chronic wounds, which may be improved by treatment with NRF2 activating compounds. NRF2 activation reduces oxidative stress, thereby enhancing production of TGF-β1, which is important for granulation tissue formation and matrix production. Reduction of ROS also suppresses the chronic inflammation and the excessive production of MMP9. Expansion of pilosebaceous cells by activated NRF2 may promote re-epithelialization of the wound. Activation of NRF2 in fibroblasts may promote senescence and associated production of a SASP, which can further promote wound re-epithelialization. Arrows pointing to the top indicate upregulation and arrows pointing to the bottom indicate downregulation.


Antiox
2900
2700
2500
2300
2100
1900
1700
Antiox (eq ac acorbico)
0
5
10
15
20
25
tempo da assunzione (ore)
Cps
0 x 1
Cps
0 x 1
F.R.A.S.: Free Radical Analytical System
Free Radical Analytical System

Oral Active oxygen treatment with O3zone is more effective than hyperbaric chamber in decreasing molecular aging (telomere length)

HOO
Ozonated oil per os
daily for 3 months

Relative Telomere Length (RTL)



Izzotti et al., in preparation

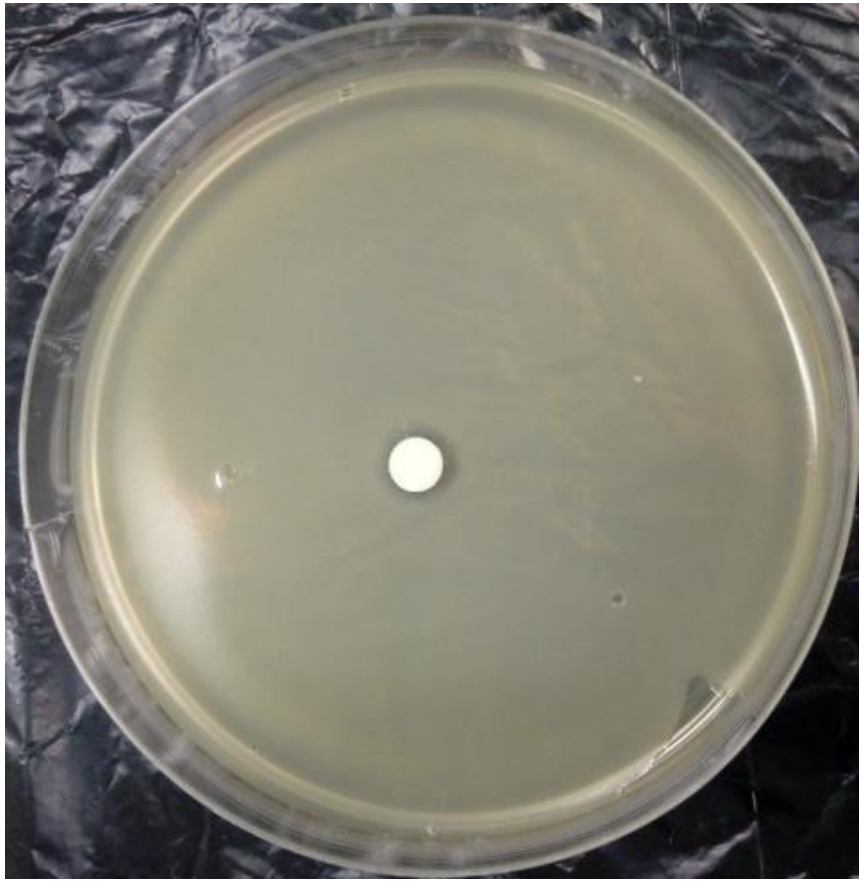
HBOT
hyperbaric oxygen therapy
60 daily sessions for 3 months
(Hachmo et al., *Aging*, 2020)

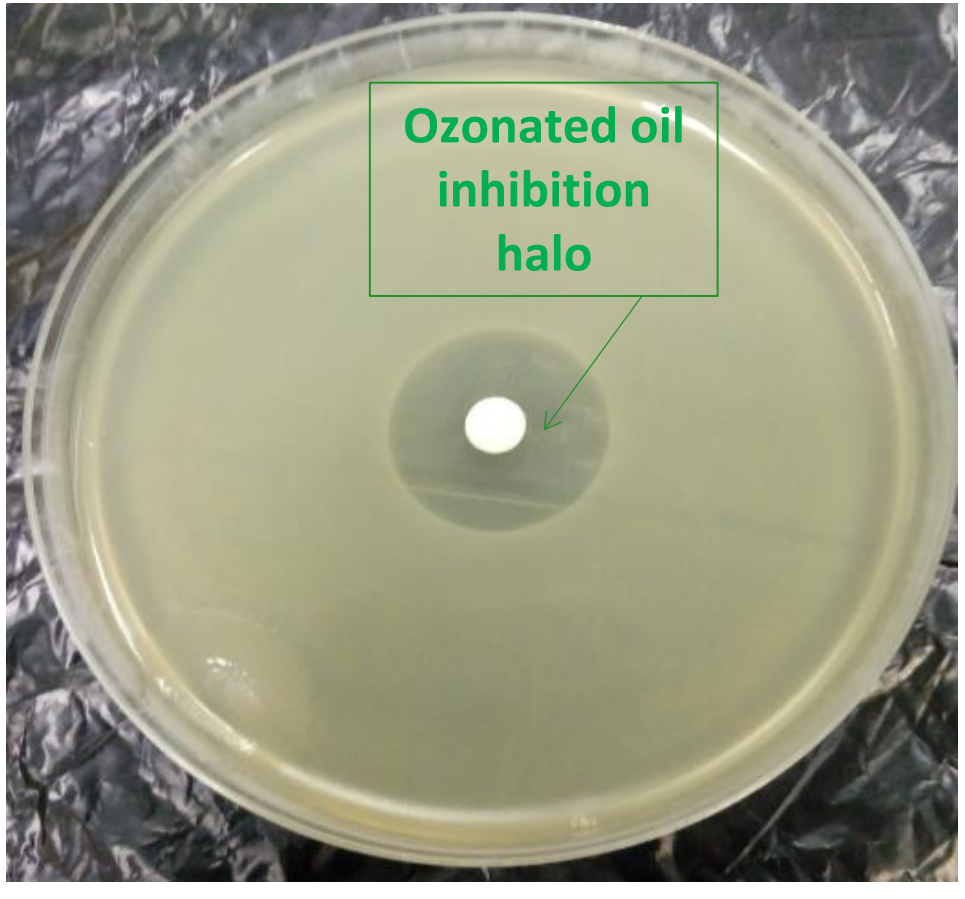
Physiological Antibacterial effect

(avoidance of Antiobitotic resistance)

Bacterial growth test

E. Coli 1 x 10^9 / ml





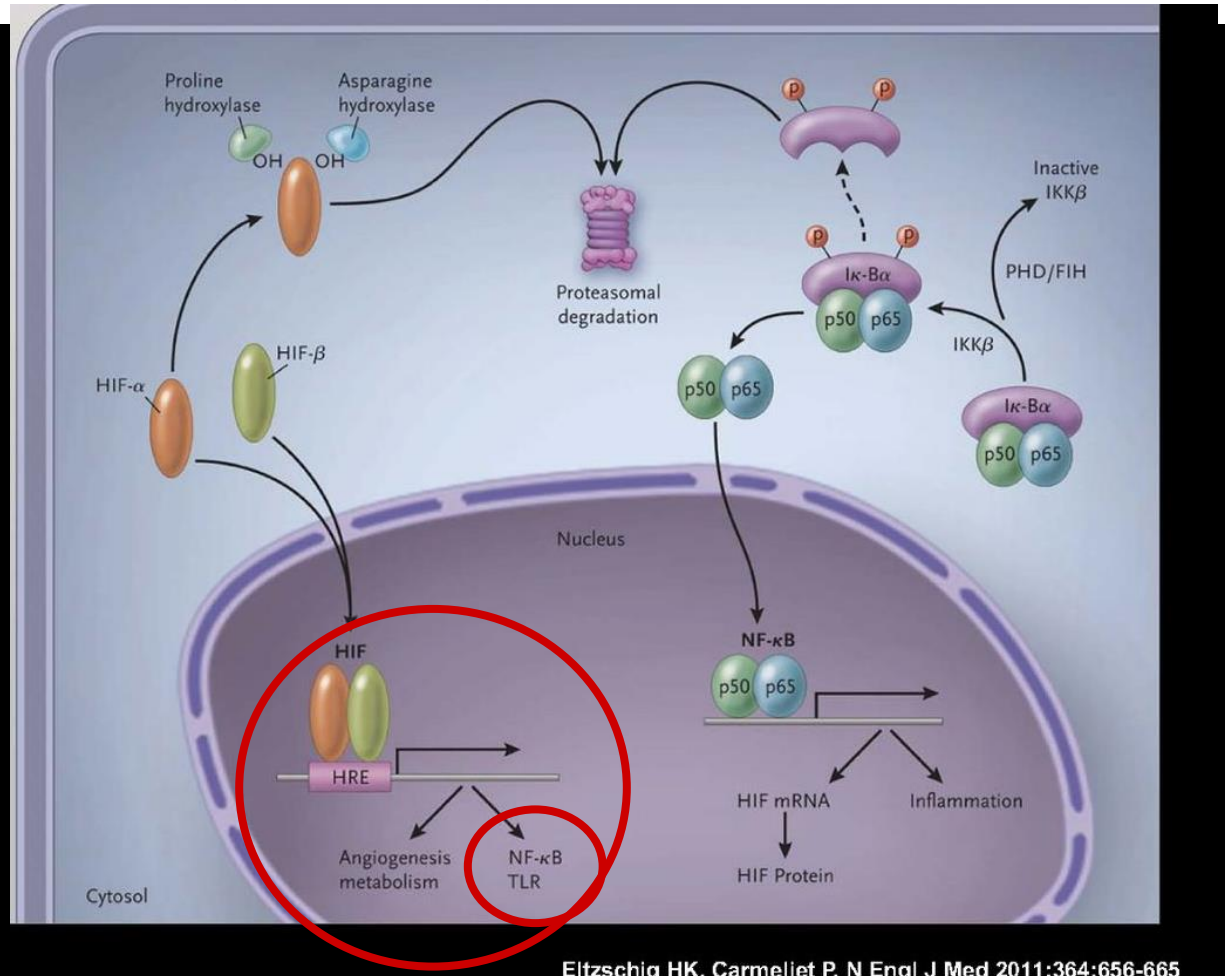
Inflammation and Hypoxia

COMMENTARY | BIOCHEMISTRY |

Hypoxia and inflammation are two sides of the same coin

Karsten Bartels, Almut Grenz, and Holger K. Eltzschig Authors Info & Affiliations

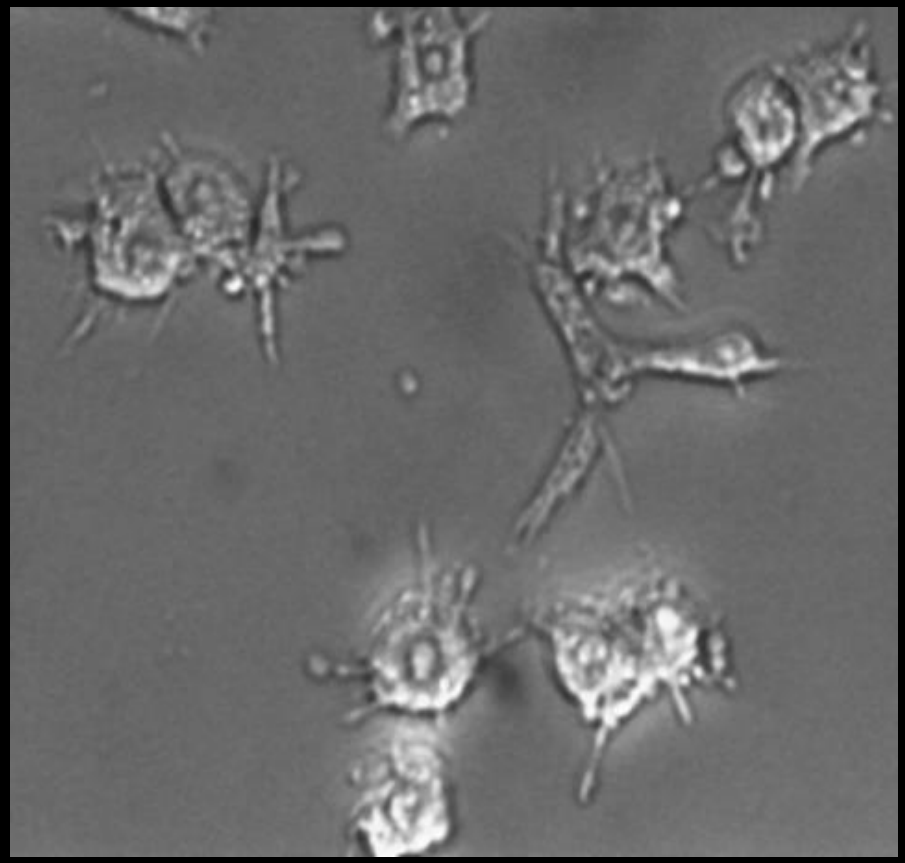
November 1, 2013 | 110 (46) 18351-18352 | https://doi.org/10.1073/pnas.1318345110



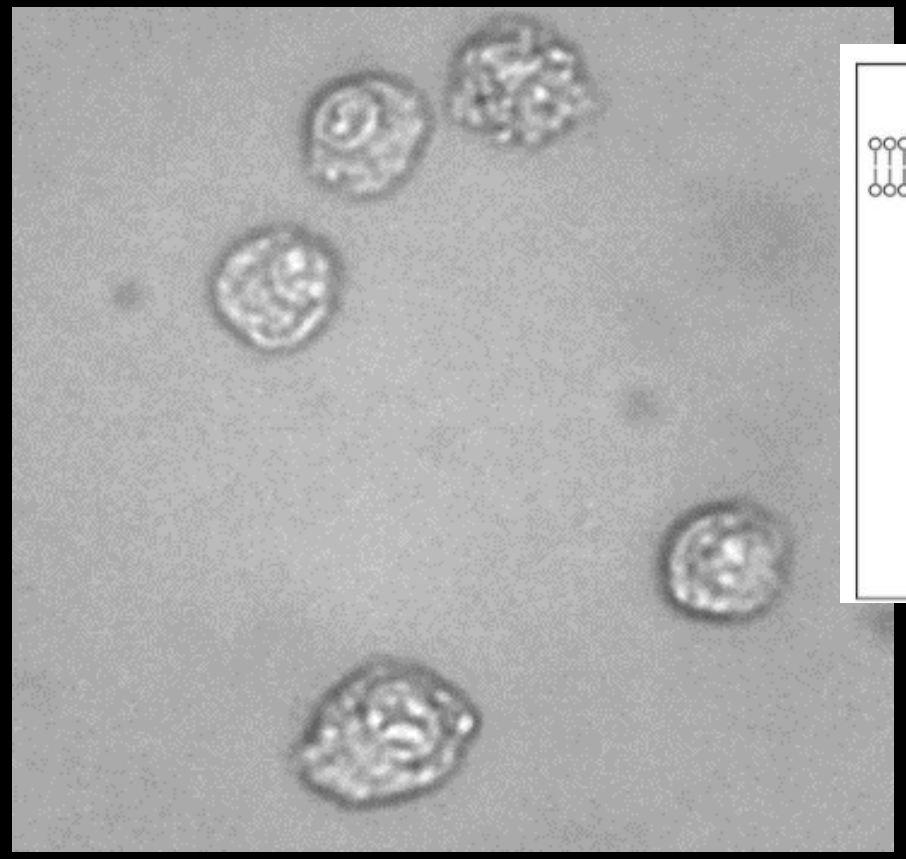
Eltzschig HK, Carmeliet P. N Engl J Med 2011;364:656-665

Inhibition of macrophage-related inflammation by oxonized o

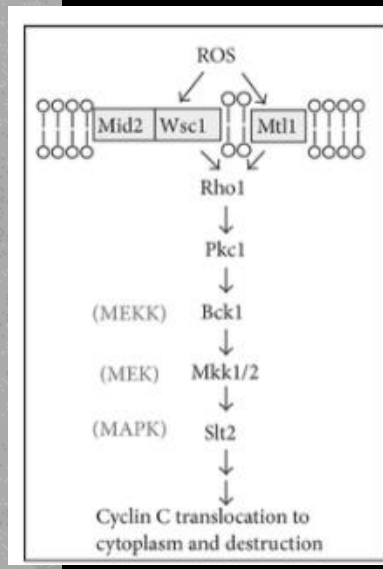
Lps = Main wall antigen of Gram- bacteria



Macrophages + Lps



Ozonized lipid +
Macrophages + Lps



CWI

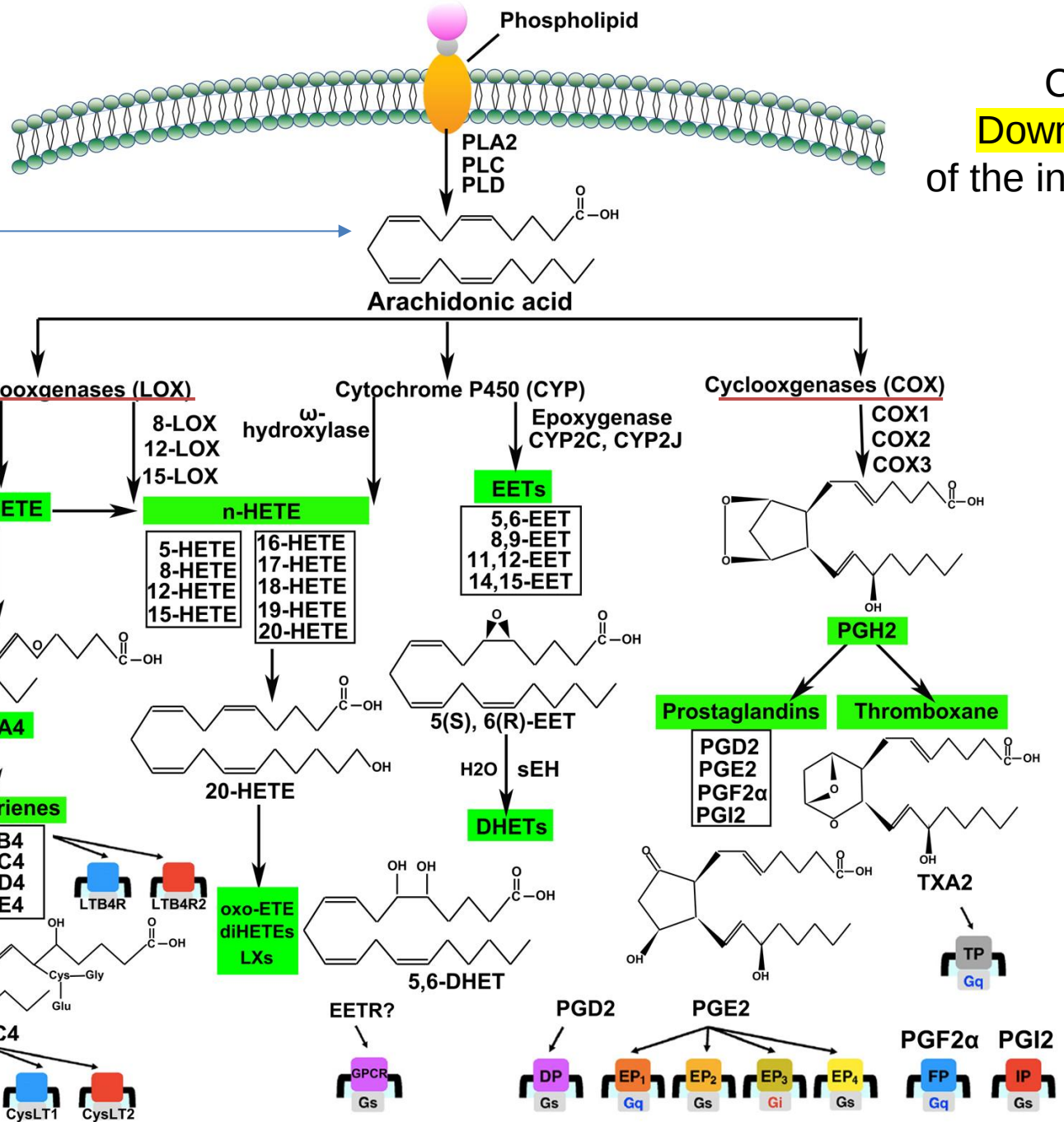
Intracellular ozonized oil inhibits Macrophage activation induced by Lps

Ozone
Upstream inhibitor
of the inflmmation cascade

O3

COX inhibitors
Downstream inhibitors
of the inflammation cascade

THE INTRACELLUALR INFLAMMATION CASCADE



Wang et al., 2021

REPORT

Ozone Selectively Inhibits Growth of Human Cancer Cells

FREDERICK SWEET, MING-SHIAN KAO, SONG-CHIAU LEE, WILL L. HAGAR, AND WILEEN E. SWEET Authors Info & Affiliations

SCIENCE • 22 Aug 1980 • Vol 209, Issue 4459 • pp. 931-933 • DOI: 10.1126/science.7403859

Abstract

The growth of human cancer cells from lung, breast, and uterine tumors was selectively inhibited in a dose-dependent manner by ozone at 0.3 to 0.8 part per million of ozone in ambient air during 8 days of culture. Human lung diploid fibroblasts served as noncancerous control cells. The presence of ozone at 0.3 to 0.5 part per million inhibited cancer cell growth 40 and 60 percent, respectively. The noncancerous lung cells were unaffected at these levels. Exposure to ozone at 0.8 part per million inhibited cancer cell growth more than 90 percent and control cell growth less than 50 percent. Evidently, the mechanisms for defense against ozone damage are impaired in human cancer cells.

CURRENT ISSUE

Group 2 innate lymphoid cells promote inhibitory synapse development and social behavior

BY JERIKA J. BARRON, NICHOLAS M. MROZ, *ET AL.*

A cytoplasmic osmosensing mechanism mediated by molecular crowding–sensitive DCP5

BY ZHENYU WANG, QIUHUA YANG, *ET AL.*

cancers

MDPI

Article

Efficacy of High-Ozonide Oil in Prevention of Cancer Relapses Mechanisms and Clinical Evidence

Alberto Izzotti [1,2,*], Enzo Fracchia [3], Camillo Rosano [2], Antonio Comite [4], Liliana Belgioia [2,5], Salvatore Sciacca [6], Zumama Khalid [5], Matteo Congiu [5], Cristina Colarossi [6], Giusi Blanco [6], Antonio Santoro [7,8], Massimo Chiara [7,8] and Alessandra Pulliero [5]

Cancers **2022**, *14*, 1174. https://doi.org/10.3390/cancers14051174

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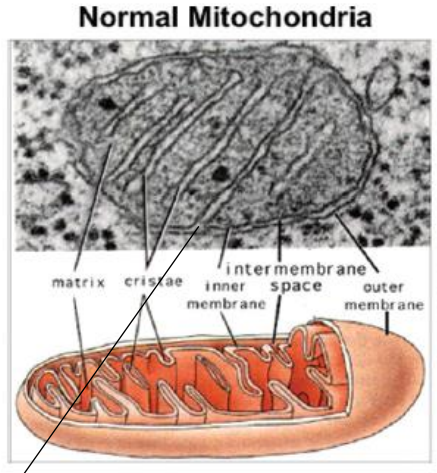
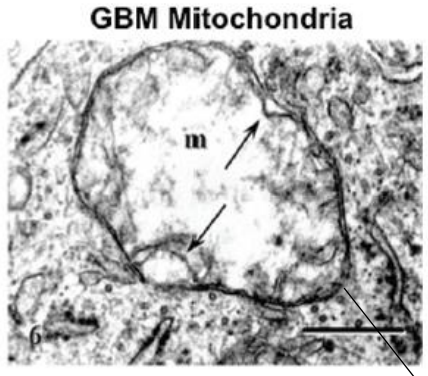
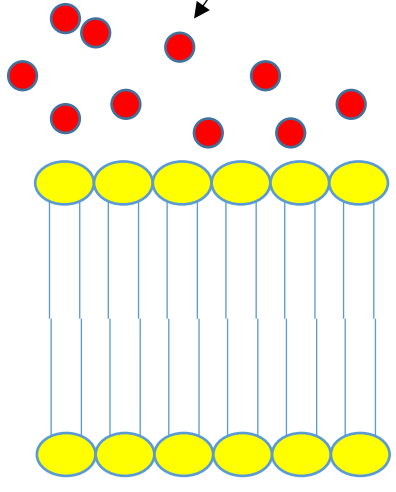
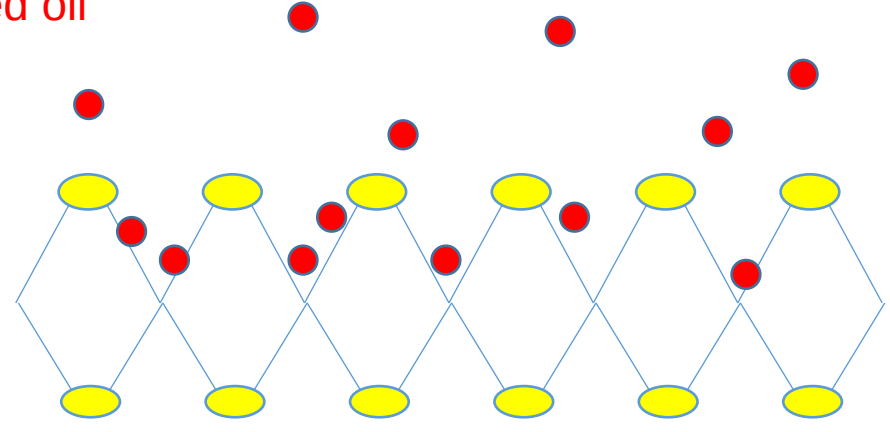
8 Department of Surgery, La Sapienza University, 00185 Rome, Italy
* Correspondence: izzotti@unige.it; Tel.: +39-010-3538522





Ozonated oil

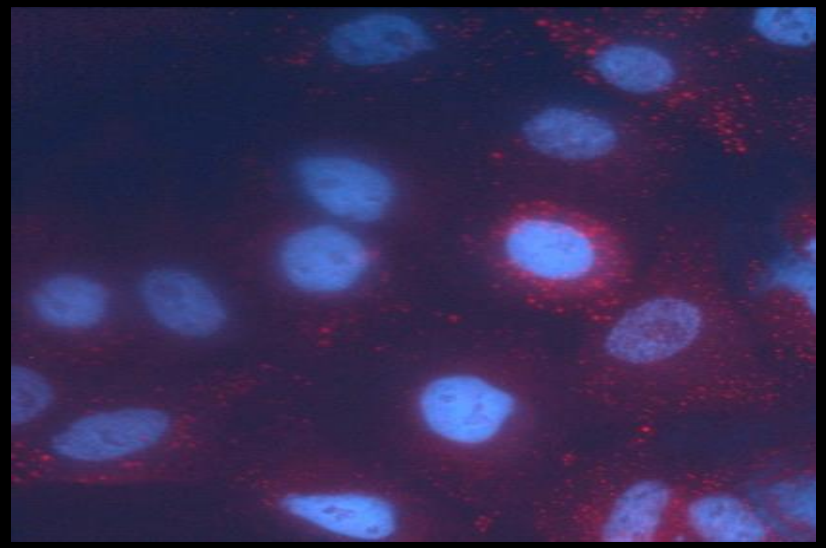




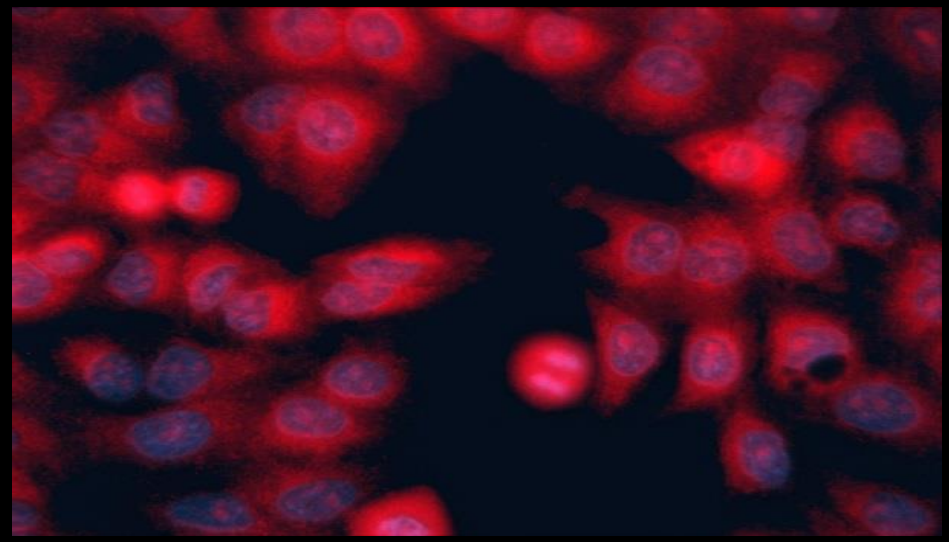
membrane thining (TEM)

Intracellular delivery of ozonized lipid carrier in A549 lung cancer cell.
1. Dose dependent Calcium (Rhod2) release from mitochondria

Control

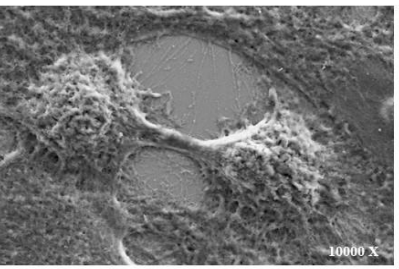


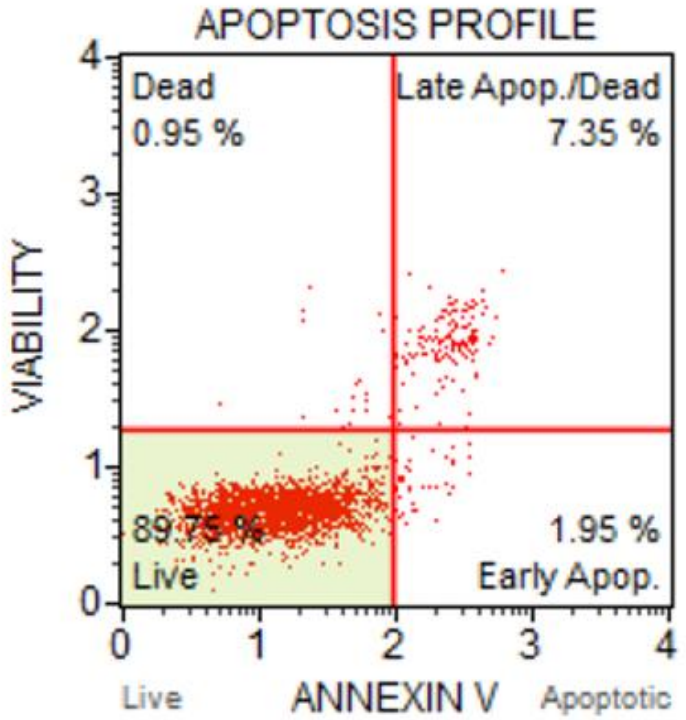
10% O3 lipid carrier



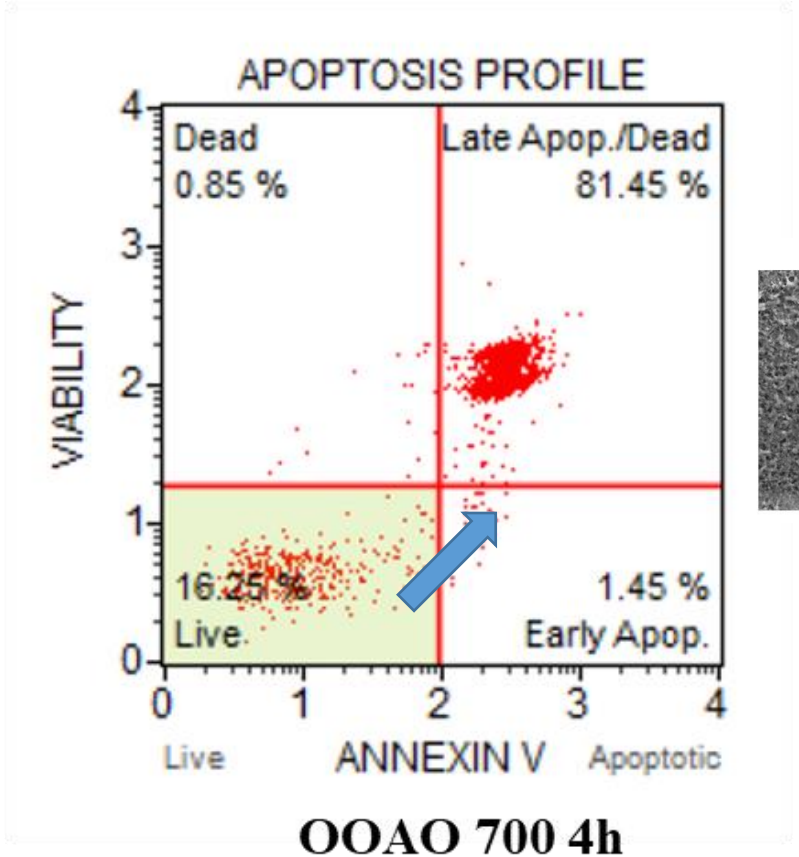
FACS ANALYSIS DEMONSTRATES THAT CANCER CELLS KILLING BY OZONIZED OIL IS DUE TO APOPTOSIS ACTIVATION

A549 controllo



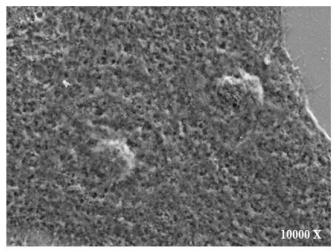


K 4h



OOAO 700 4h

A549 O3 100% 700 ozonuri



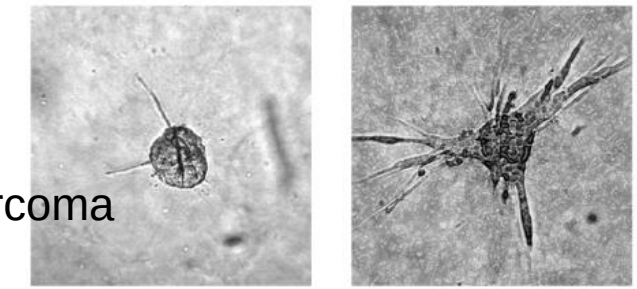
Effects of increased O2 availability inside solid tumors

met inhibition

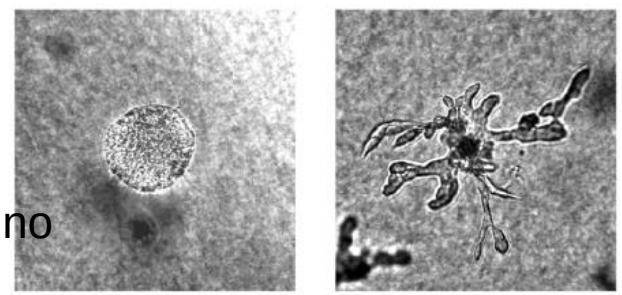
Hypoxia promotes invasive growth by transcriptional activation of the *met* protooncogene

Selma Pennacchietti,[1,2] Paolo Michieli,[1,2]* Maria Galluzzo,[1] Massimiliano Mazzone,[1] Silvia Giordano,[1] and Paolo M. Comoglio[1]

[1]Division of Molecular Oncology, Institute for Cancer Research and Treatment, University of Torino Medical School, I-10060 Candiolo (Torino), Italy



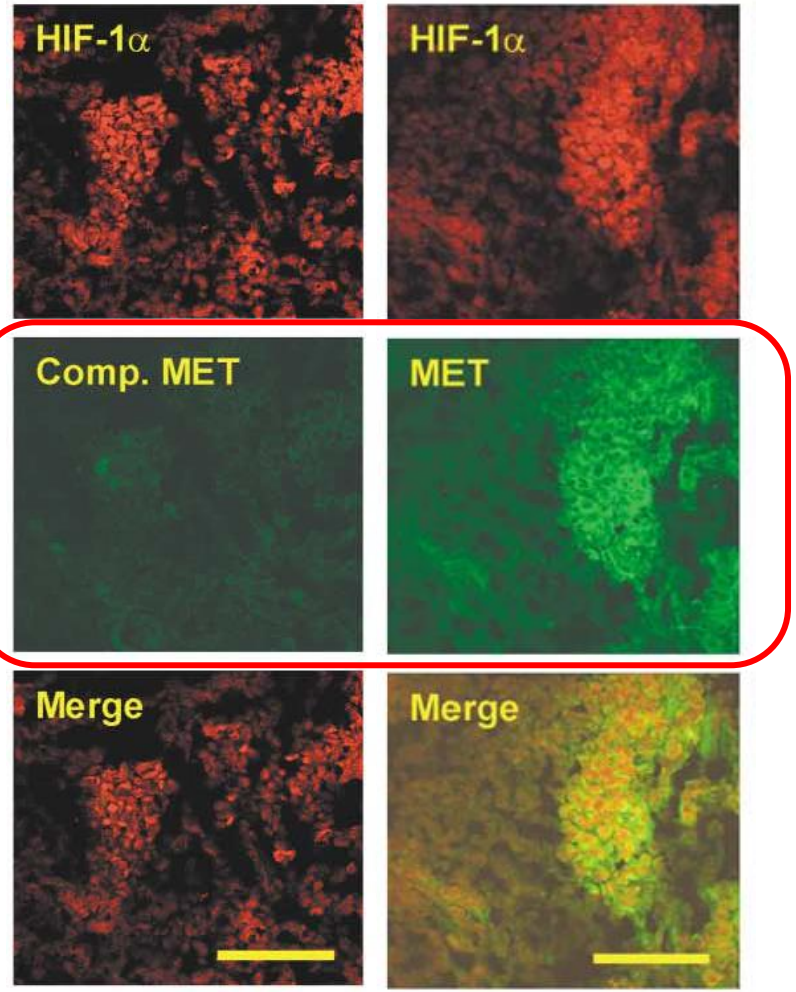
U2-OS
Osteosarcoma



MLP-29
hepatocarcinoma

N
O2
21%

H
O2
3%



O2
21%

O2
3%

Seduta 3

Seduta 4

Seduta 5

Seduta 6

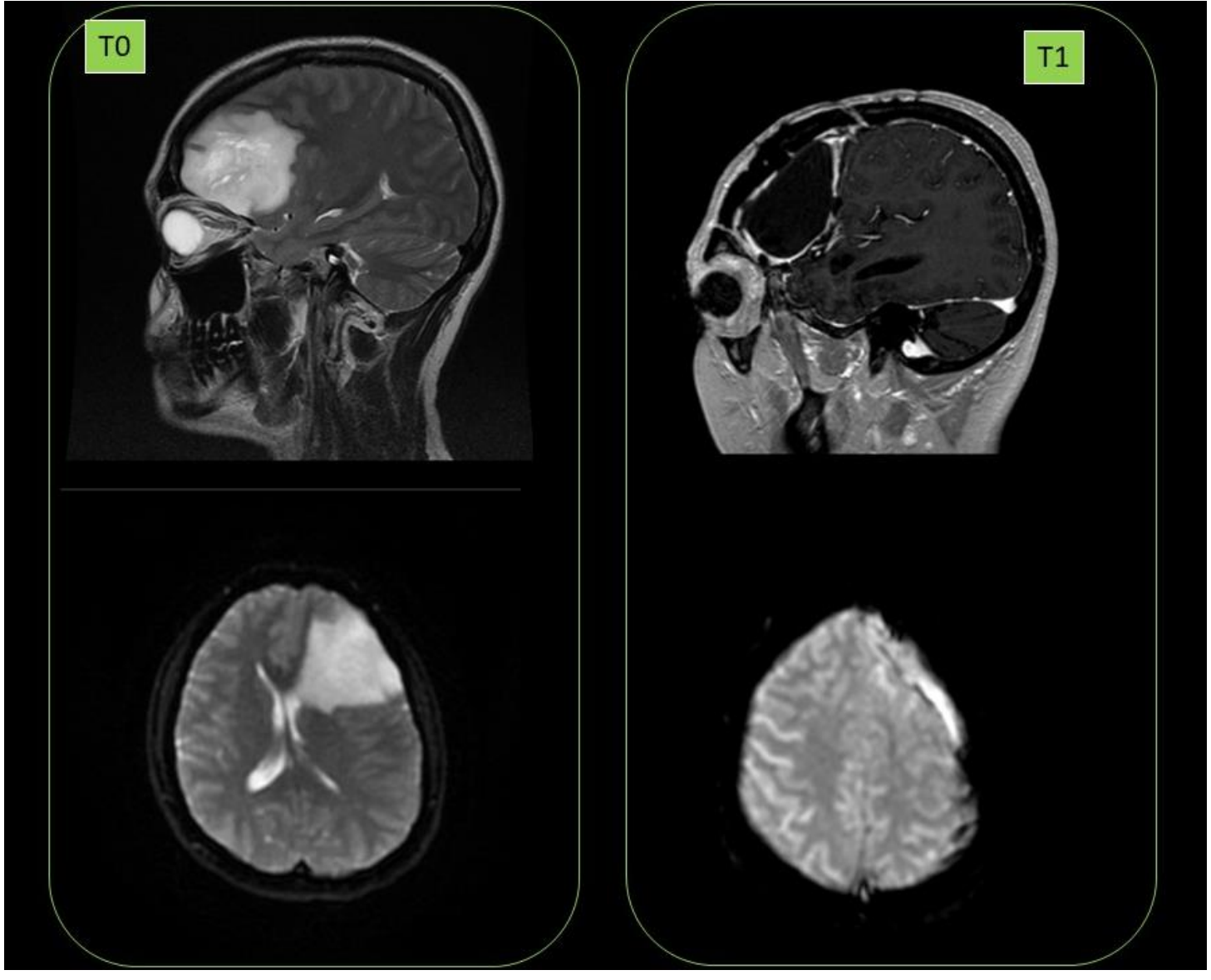
Seduta 8

Follow up 20 giorni

Follow up 35 giorni

Follow up 42 giorni

Treatment time-span: 42 days



Female subject, 38 years old affected by **brain glioblastoma** in left emisphere (diagnosis **July 2014**. 1st NMR, **(T0**). High malignancy (grade III). 1st surgery , chemoradiotherapy, relapse , 2nd surgery. Chemo/radiotherapy (60 Gy) paralleled by oral ozonized oil therapy. **Full recovery with no relapses** (**February 2025**) (4th NMR, **T1)**.

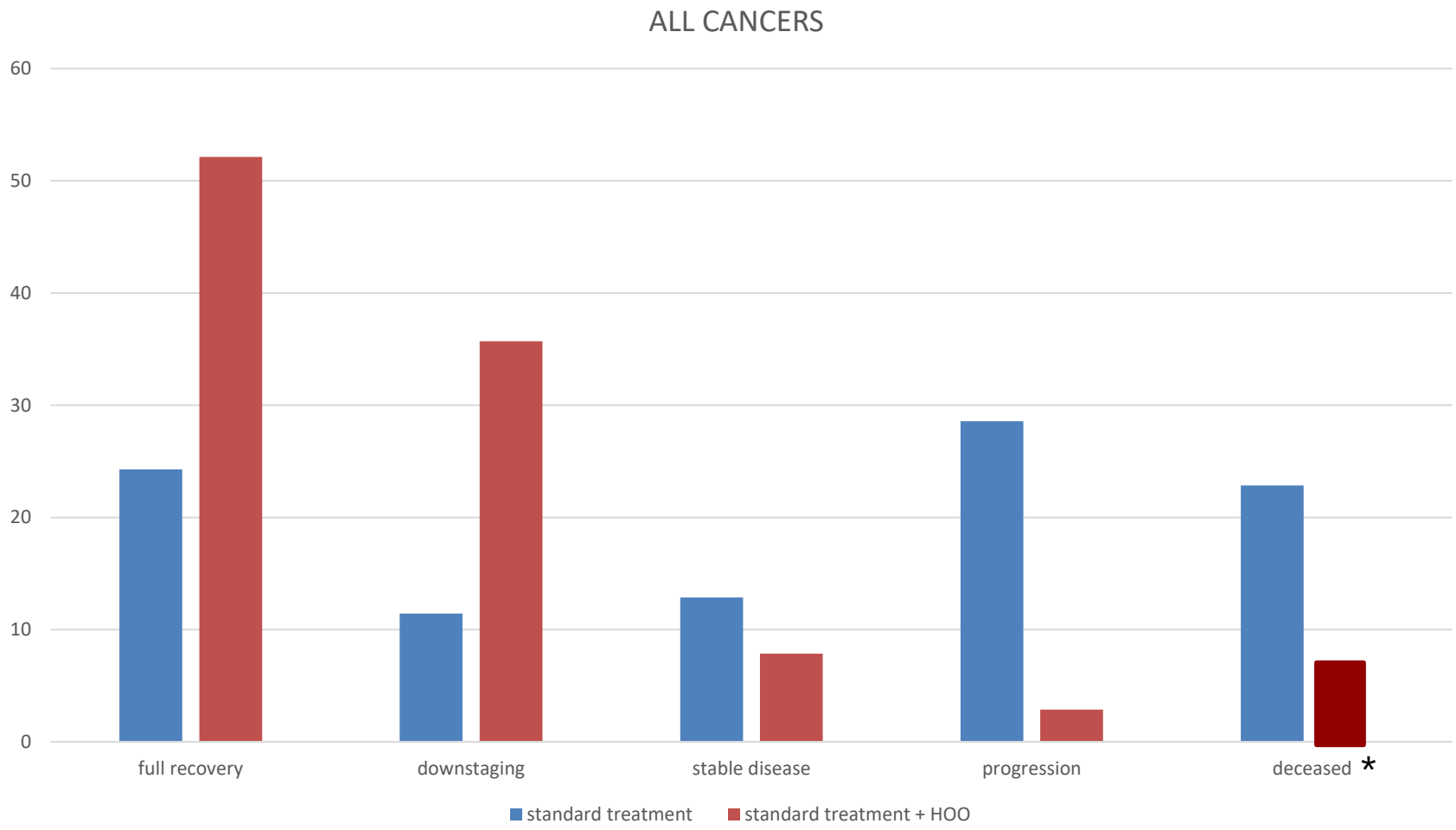
HOO treated chemo-radio resistant patients = 115*
(July 2024 update =610)

Brain=96
Pancreas=95
Skin = 68
Lung= 66
Colon=81
Breast = 138
Prostate= 45
Ovary and womb = 16
Kidney = 13
Liver = 15
LNH = 22

* Izzotti et al., Cancers, 2022

Follow up 5 years

Comparison of clinical outcomes in cancer patiens treated with standard therapeutic protocols in absence (blue) or presence (red) of ozonized oil complimentary teratment



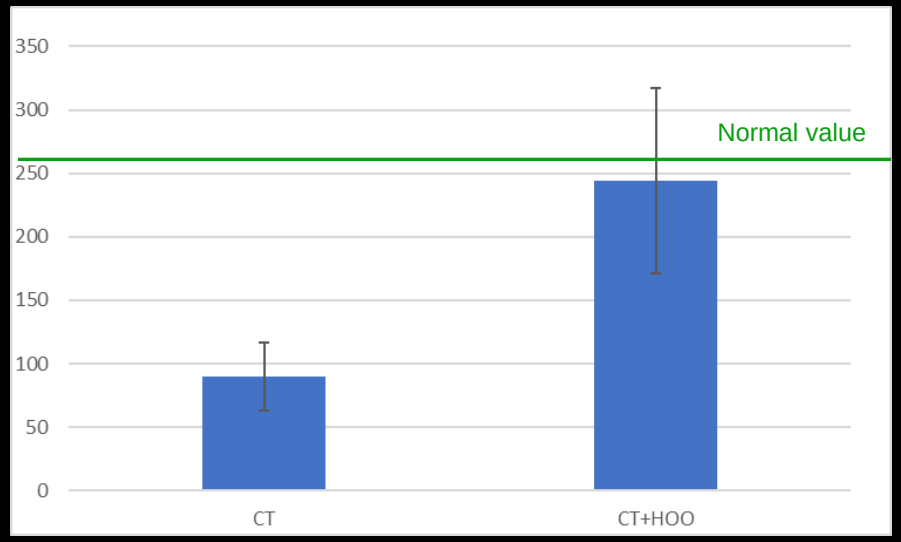
** Excluding 3 patients recruited at T4-M1-N3*

Alopecia

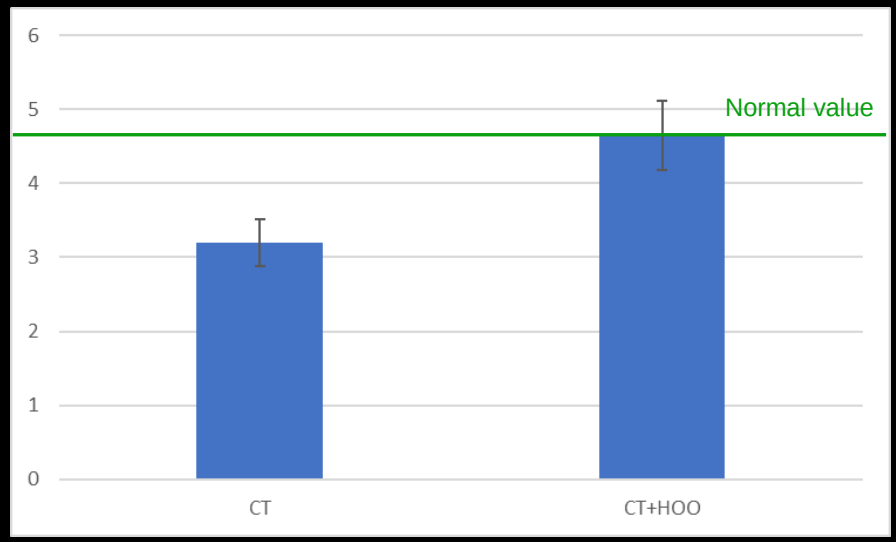
Chemotherapy

Chemotherapy + oral ozonated oil

OZONATED OIL ATTENUATION OF CT-INDUCED BONE MARROW SUPPRESSION

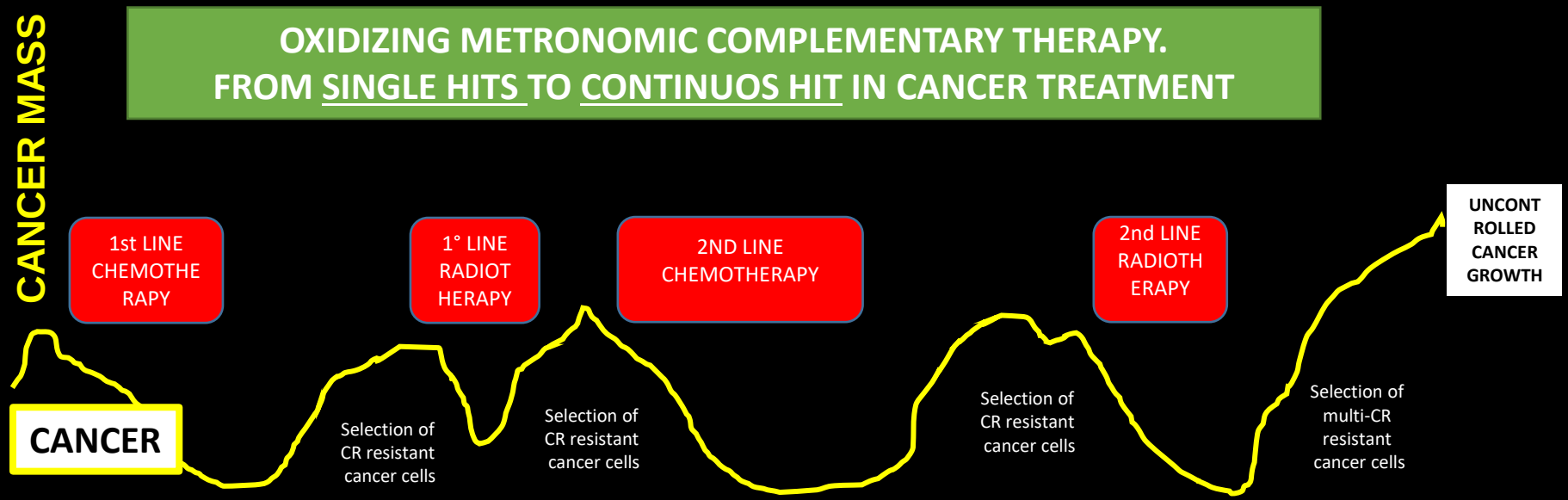


Platelet
(nx10e3/mm3)
(Temozolamide)



RBC
(nx10e6/mm3)

OXIDIZING METRONOMIC COMPLEMENTARY THERAPY.
FROM SINGLE HITS TO CONTINUOS HIT IN CANCER TREATMENT



HIGH-OZONIDE OIL COMPLEMENTARY THERAPY

HYPOXIA IS DRIVING FORCE OF CANCER
GROWTH

HYPEROXIA INDUCED BY OZONATED OIL
IS DRIVING FORCE OF CANCER
DEATH

OZONATED OIL AT HIGH OZONIDES IN ORAL GASTRO-RESISTANT PILLS. DOSES AND INDICATIONS

LOW (1x2, 2 per day – 2x2 4 per day)

Primary prevention of chronic degenerative diseases (atherosclerosis, macular degeneration)
Fragile patients (elderly, e.g., ≥75 yo)
Poorly trained sportsmen
Healthy subjects for mood and aerobic thresold improvement (physical activity mimicking agent)

INTERMEDIATE (3x2, 6 per day)

Inflammatory diseases (arthritis, arthrosis, fibromyalgia, dermatatis)
Anti-bacterial therapy (first line treatment)
Prevention of bacterial and viral infection
Well trained athlets to increase aerobic threshold and to prevent overtraining
Cancer survivors to decrease risk of relapses

HIGH (4x2, 8 per day – 6x3, 18 per day)

Cancer patients

ACTIVE Oxygen in capsules