Entropia, mitocòndria i inflamació: formulant l'elixir de l'eterna juventut.

Victor Puntes ICREA, ICN2, VHIR

1. THE ANTIOXIDANT PARADOX

THE BIOLOGY OF AGEING

BIOLOGICAL BASIS OF AGING

FARHAD ZARGARI, MD, PHD

THE RISE AND FALL OF ANTIOXIDANT THERAPIES 1st ROUND

(1960s)

CANCER PAPER PUBLISHED

Dr. Ewan Cameron and Dr. Linus Pauling

The American Association for Cancer Research in its journal *Cancer Research* has published a paper "Ascorbic Acid and Cancer - A Review" in its March 1979 issue. The journal *Cancer Research* is recognized as being one of the world's most prestigious medical journals, and the acceptance of this article by the editors indicates the growing interest of the medical profession in vitamin C in relation to cancer - a significant step forward.

In this thorough review the authors, Ewan Cameron, Linus Pauling, and Brian Leibovitz, trace the history of vitamin C, describe its chemical and physiological properties, and discuss the dynamic relationship between host resistance to cancer and the availability of ascorbate. The work refers to over 350 original publications.

In the introduction to "Ascorbic Acid and Cancer - A Review," the authors state that "Few would dispute that the behavior of every human cancer is determined to a significant extent by the natural resistance of the patient to his or her disease. As a result there is now widespread recognition that very substantial benefits in cancer management would be achieved if practical methods could be devised to enhance resistance. There is a growing body of theoretical and practical evidence suggesting that the availability of ascorbate is the determinant factor in controlling and potentiating many aspects of host resistance to cancer. We have prepared this review as an aid to investigators in this field and as a source of information to others."

A continuation of the review article, with authors Ewan Cameron and Linus Pauling, is being published at about the same time in *Journal of the International Academy of Preventive Medicine*. This paper, with title "Ascorbic Acid as a Therapeutic Agent in Cancer," deals with the studies that have been conducted with cancer patients.

Copies of both papers will be available soon from the Institute. □

THE RISE AND FALL OF ANTIOXIDANT THERAPIES 2nd ROUND

American Journal of Epidemiology
Vol. 139, No. 12
Printed in U.S.A.

Antioxidant Vitamin Intake and Coronary Mortality in a Longitudinal Population Study

Paul Knekt,[1] Antti Reunanen,[1] Ritva Järvinen,[2] Ritva Seppänen,[1] Markku Heliövaara,[1] and Arpo Aromaa[1]

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30–69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966–1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of vitamin C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection. *Am J Epidemiol* 1994;139:1180–9.

antioxidants; ascorbic acid; carotenoids; coronary disease; mortality; risk factors; vitamin E

THE ANTIOXIDANDTS PARADOX

*"Indeed, despite patophysiologic, epidemiologic, and mechanistic evidence, these **clinical trials** have been, to date, mostly **negative.***

WHY HAVE ANTIOXIDAND FAILED IN CLINCIAL TRIALS?

Review > Am J Cardiol. 2008 May 22;101(10A):14D-19D. doi: 10.1016/j.amjcard.2008.02.003.

Why Have Antioxidants Failed in Clinical Trials?

Steven R Steinhubl [1]

Affiliations + expand

PMID: 18474268 DOI: 10.1016/j.amjcard.2008.02.003

Abstract

Antioxidant therapies have been evaluated in placebo-controlled trials involving tens of thousands of patients. Despite pathophysiologic, epidemiologic, and mechanistic data suggesting otherwise, these clinical trial results have been, to date, mostly negative in the setting of chronic preventative therapy. On the other hand, a much smaller number of trials involving handfuls of patients have been much more encouraging in terms of the acute benefit of antioxidants reflected by the data on N-acetylcysteine. However, the seemingly overwhelmingly data not supporting a role for antioxidants in the chronic suppression of atherosclerosis must be kept in perspective. Most antioxidant therapies that have been tested were not chosen because they were proved to be the best antioxidants, but rather because of their easy availability. An excellent example is vitamin E. Although easily available, it

WHY HAVE ANTIOXIDAND FAILED IN CLINCIAL TRIALS?

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Why Have Antioxidants Failed in Clinical Trials?

Steven R Steinhubl [1]

Affiliations + exp

PMID: 18474268

*This has been attributed **to the non-drug-likeness** of available antioxidant compounds. These compounds have both high unspecific reactivity and poor solubility and consequent limited absorption profiles, hence low bioavailability and low concentrations at the target site."*

Abstract

Antioxidant therap thousands of patients. Despite p erwise, these clinical trial results tive therapy. On the other hanc been much more encouraging N-acetylcysteine. Ho ntioxidants in the chronic suppression of atherosclerosis must be kept in perspective. Most antioxidant therapies that have been tested were not chosen because they were proved to be the best antioxidants, but rather because of their easy availability. An excellent example is vitamin E. Although easily available, it

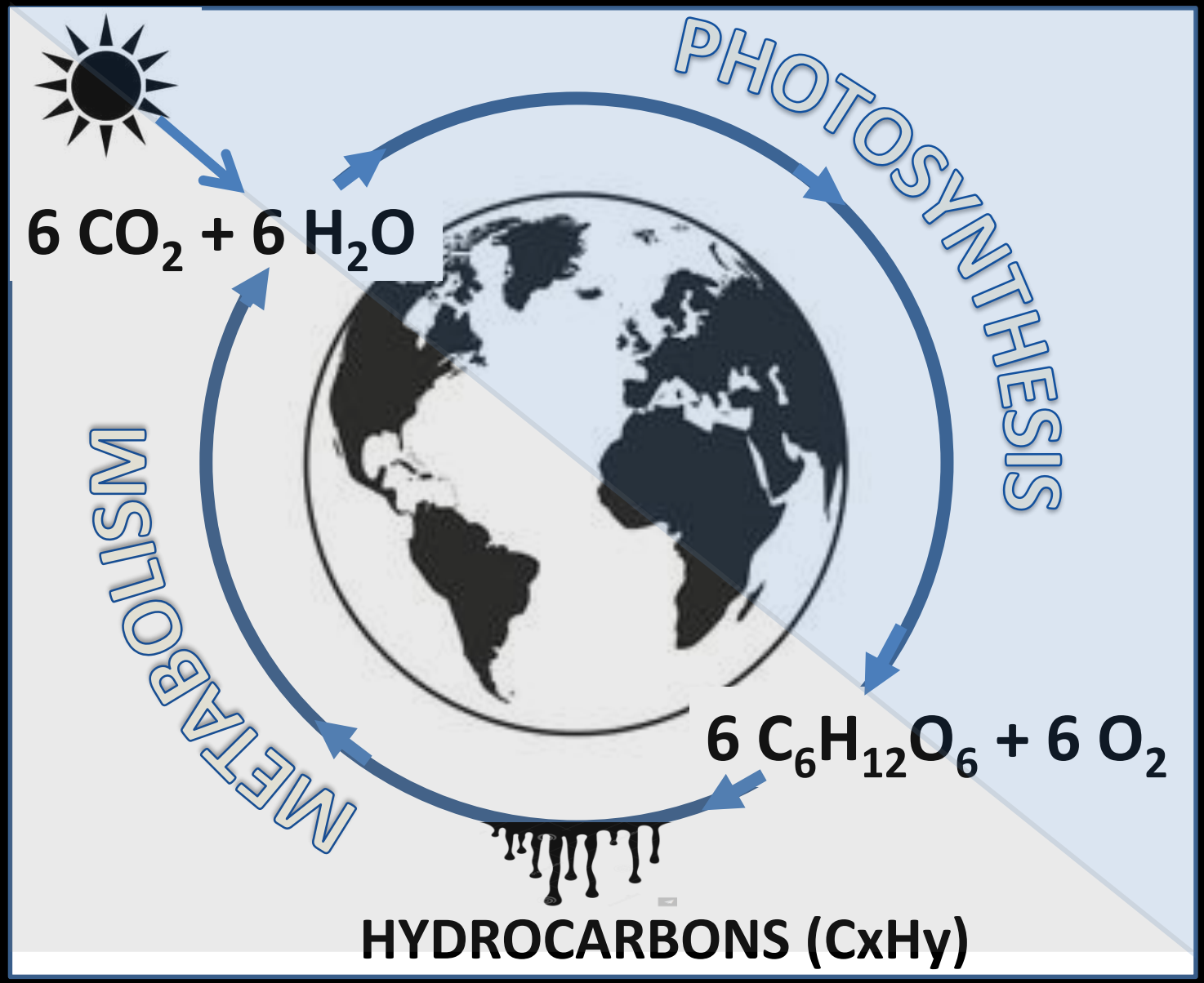
METABOLISM AND THE CHEMISTRY OF LIFE

In this context, radically new antioxidant safe substances like nanoceria, may overcome previous limitations and finally enable antioxidant therapies to improve human health.

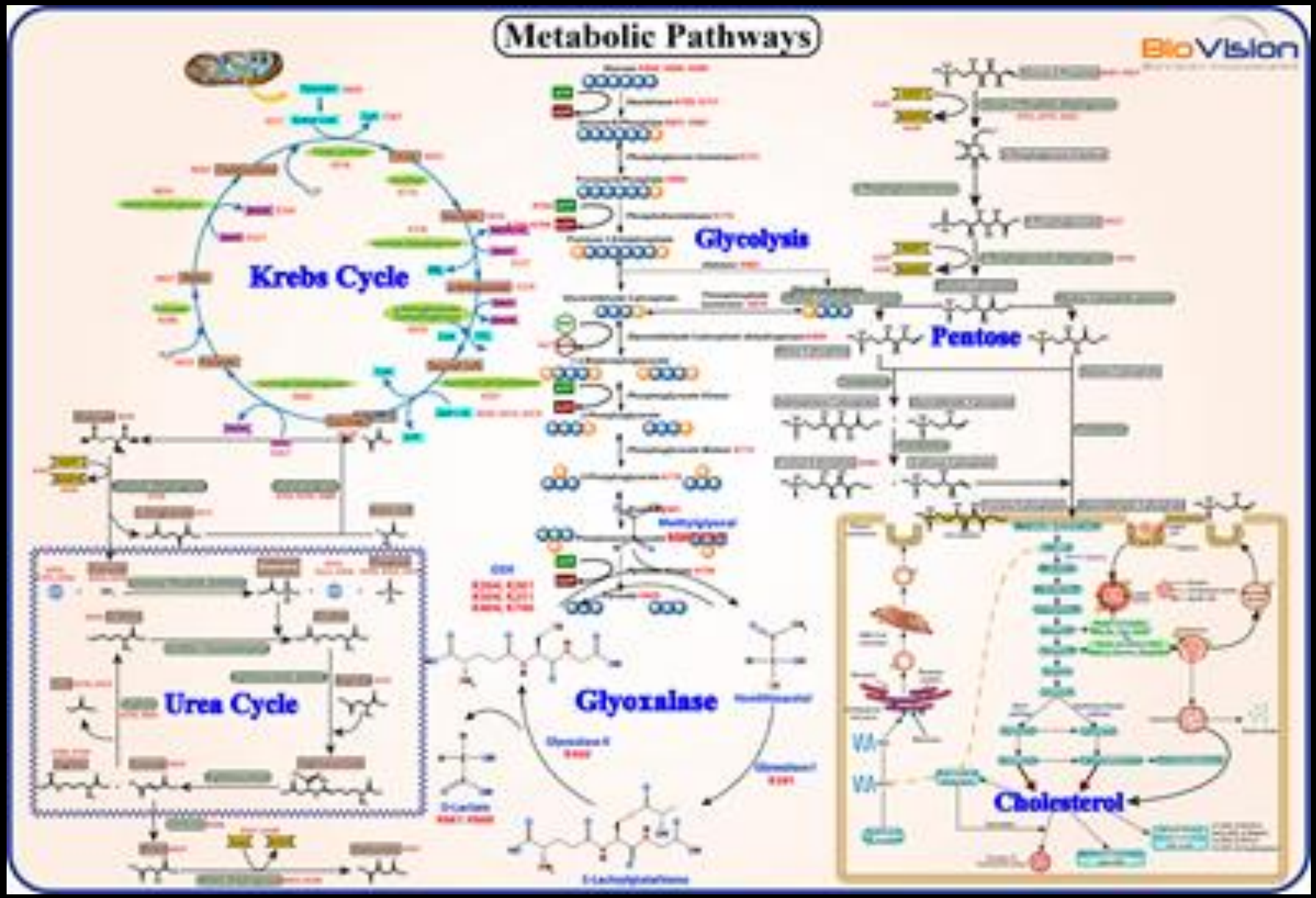
In order to understand how does nanoceria works, it is useful to start by focusing on the chemical substrate that supports any biological system and state, understanding the fundamental bases of metabolism and the chemistry of life.

2. **THE CHEMISTRY OF LIFE**

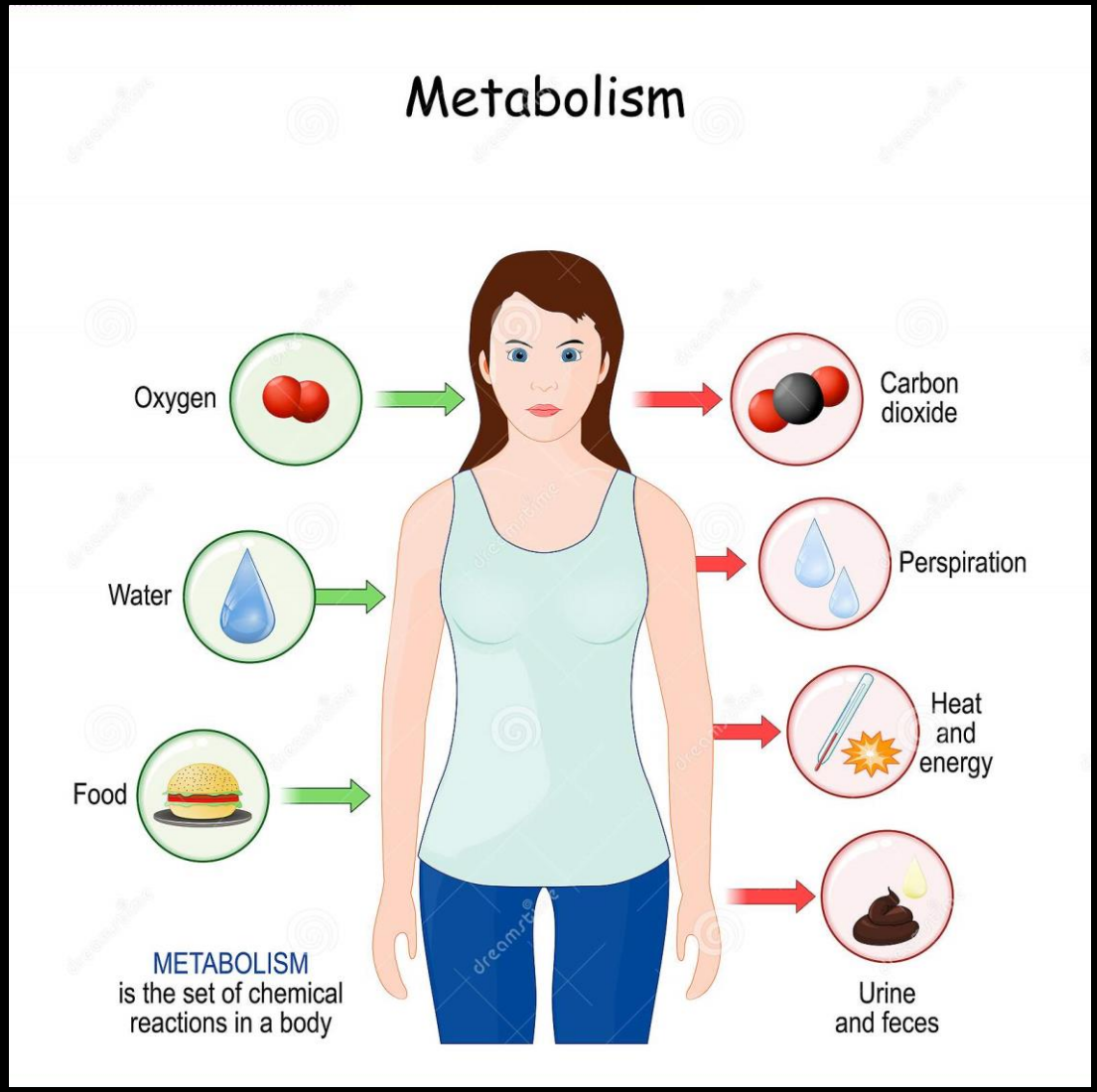
LIFE IS THE COMBUSTION ASSISTED CARBON REDUCTION,



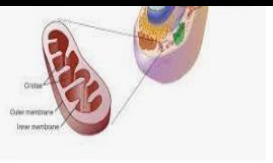
METABOLISM AND THE CHEMISTRY OF LIFE



METABOLISM, CATABOLISM AND ANABOLISM



METABOLISM: ENERGY IS PRODUCED AT THE MITOCHONDRIA



Mitochondria
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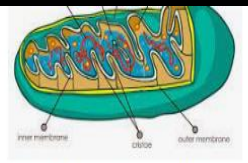

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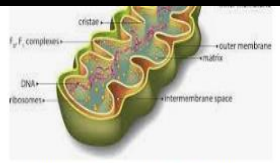

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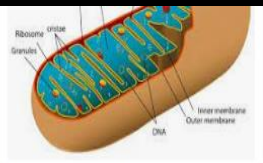

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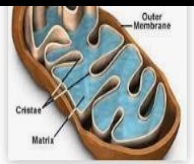

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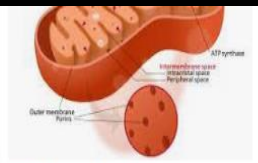

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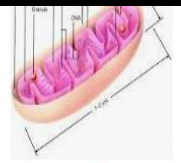

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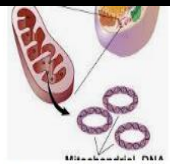

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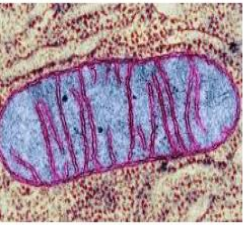

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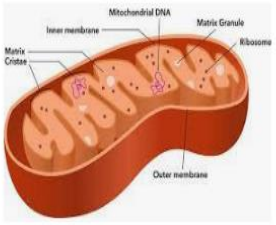

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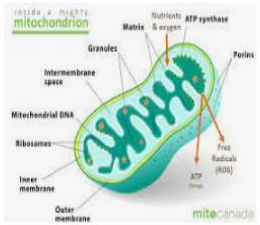

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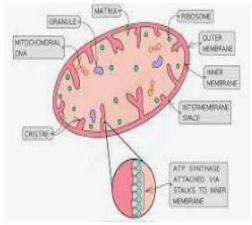

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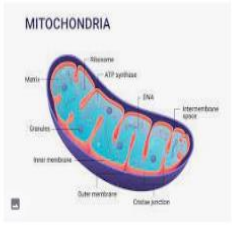

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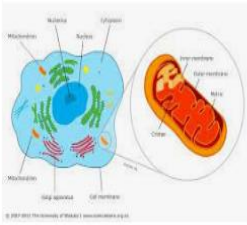

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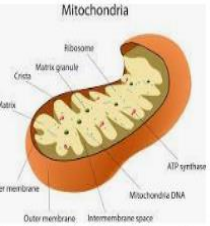

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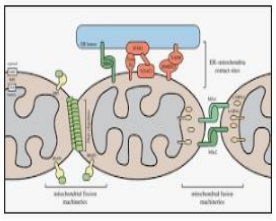

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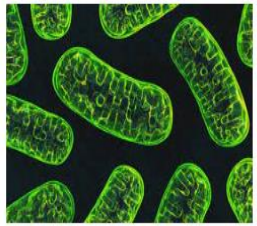

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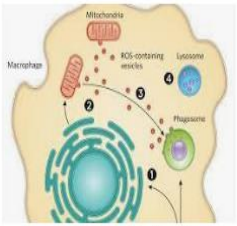

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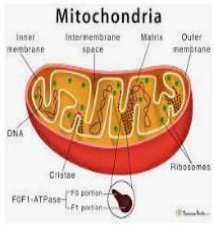

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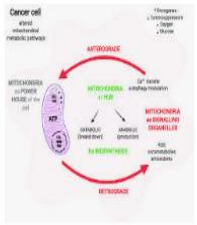

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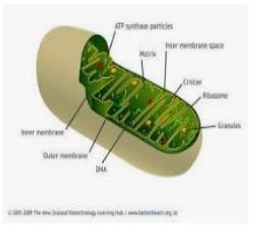

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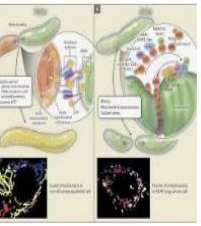

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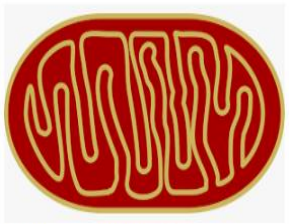

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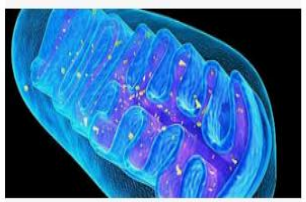

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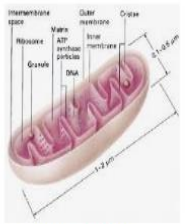

2: Structure of mitochondria [2 ...
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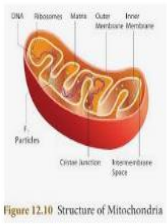

Figure 12.10 Structure of Mitochondria

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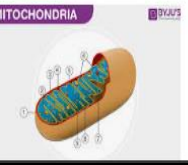
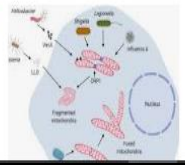
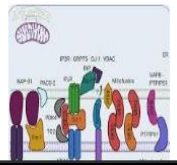
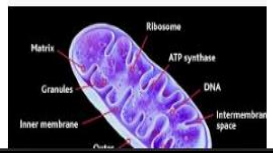
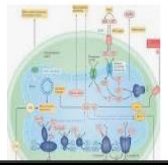
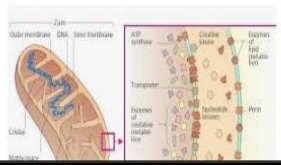




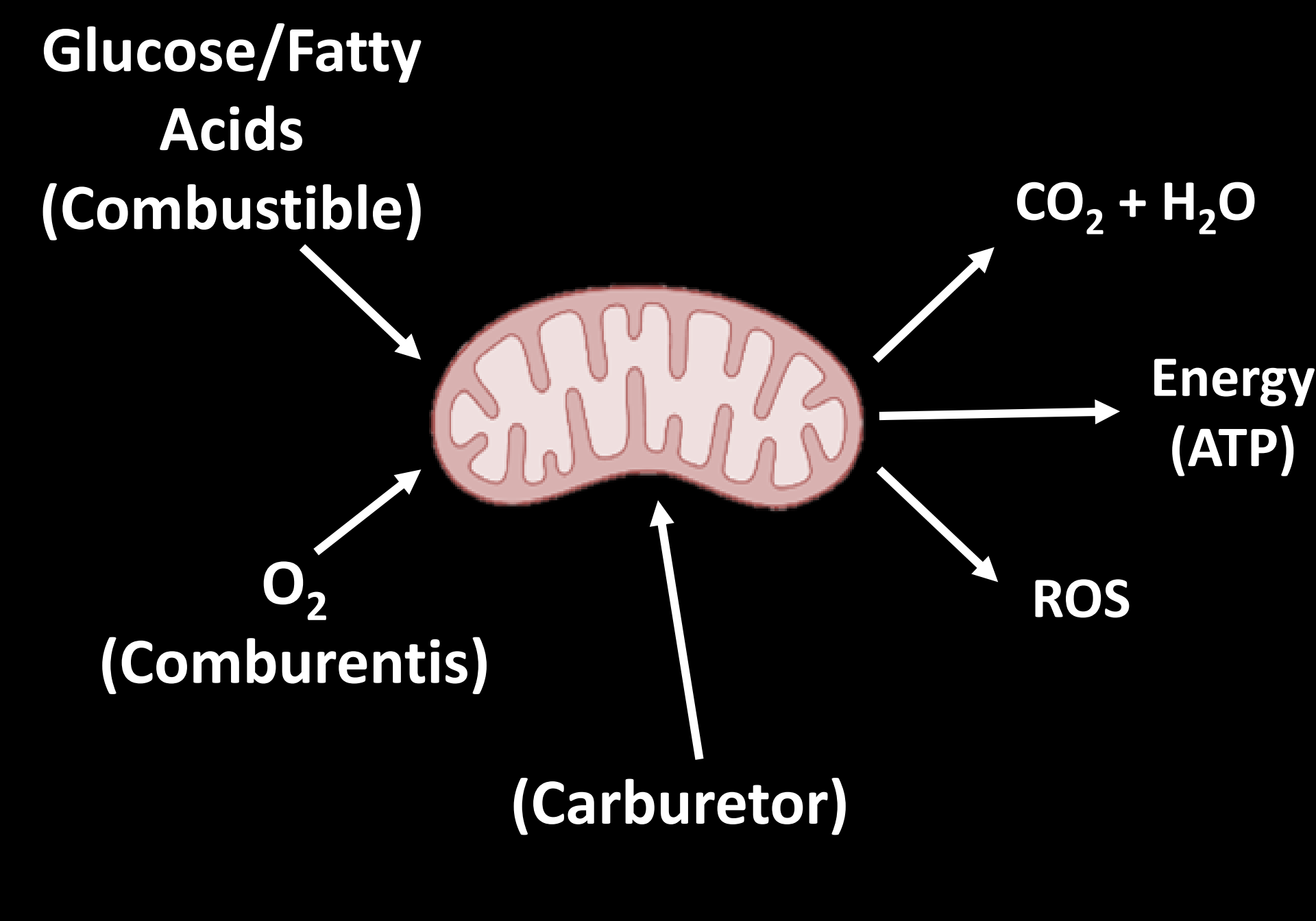




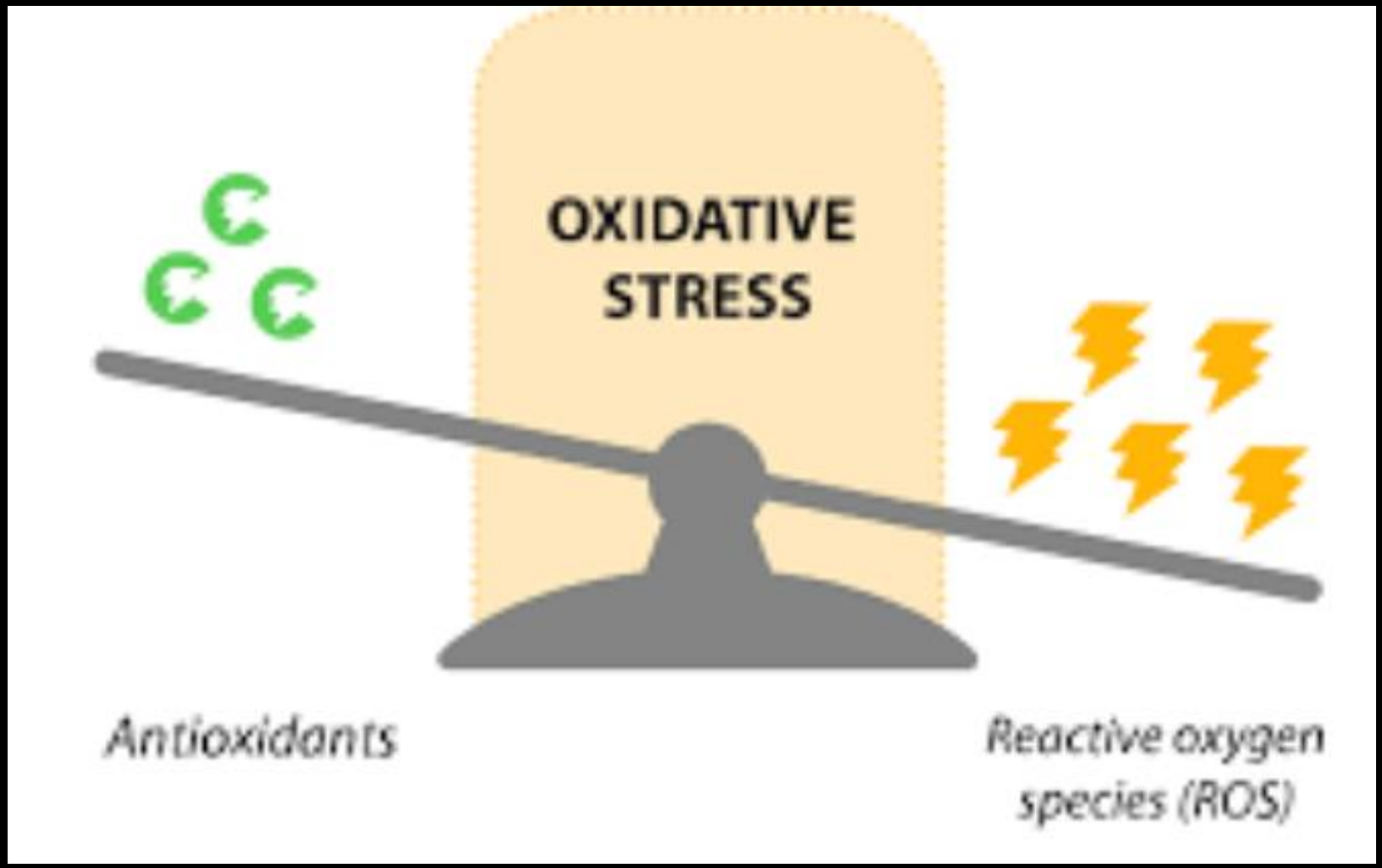




MITOCHONDRIA AS AN INTERNAL COMBUSTION ENGINE



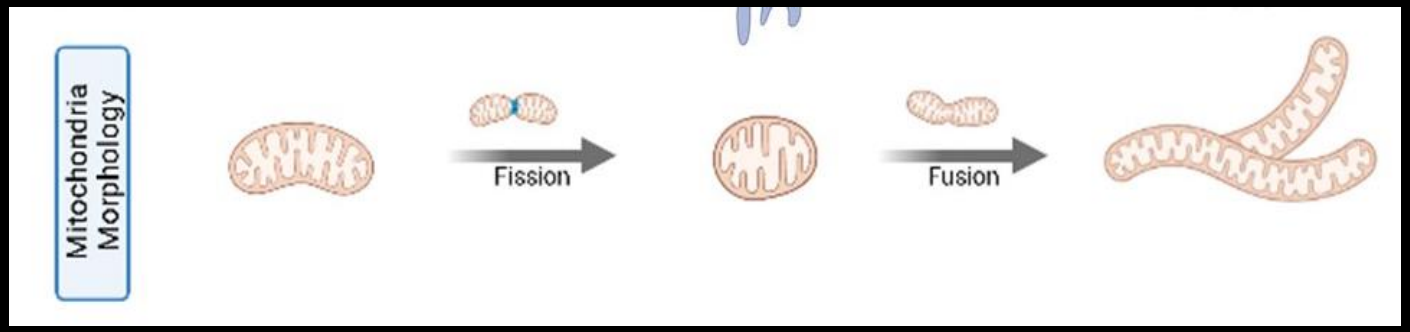
ROS AND OXIDATIVE STRESS

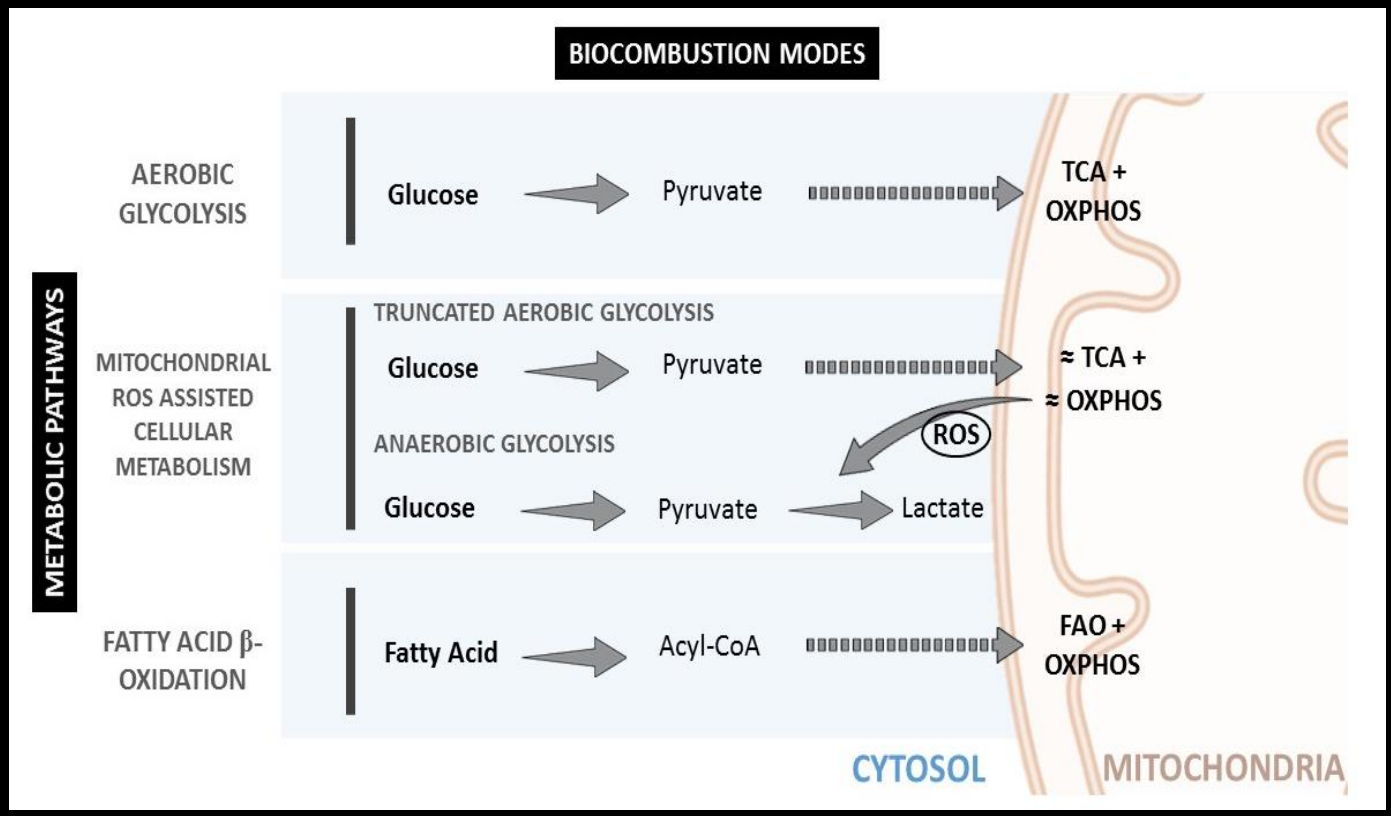


METABOLISM AND THE CHEMISTRY OF LIFE

CATABOLIC PATHWAY	FUEL	OXIDIZER	OXYDATION MODE	Mitochondria SHAPE	ATP production	POWER provision	ROS Production
Aerobic Glycolysis	Glucose	Oxygen	Aerobic	Elongate Tubular	2	Low	Basal
Cellular Metabolism. **Anaerobic glycolysis**	Glucose	Oxygen &ROS	Anaerobic/ OXPHOS dysfunction	Spherical	2	High	High
Fatty Acid β-oxidation	Fatty Acid	Oxygen	Aerobic	Hyperfused	106	Medium	Medium

MITOCHONDRIA MODES OF WORK





3. THE BIOLOGY OF DISEASE

THE BIOLOGY OF DISEASE

$$\Delta G = \Delta H - T\Delta S$$

G for Gibbs or Free energy
H for Entalhpy
T for Temperature
S for Entropy

DISEASE: ENTALPHY AT EXPENSES OF ENTROPY

1.- Biological matter is intrinsically out-of-equilibrium, where intermolecular interactions operate at the edge of chaos.

2.- This is better satisfied with high entropy gains.

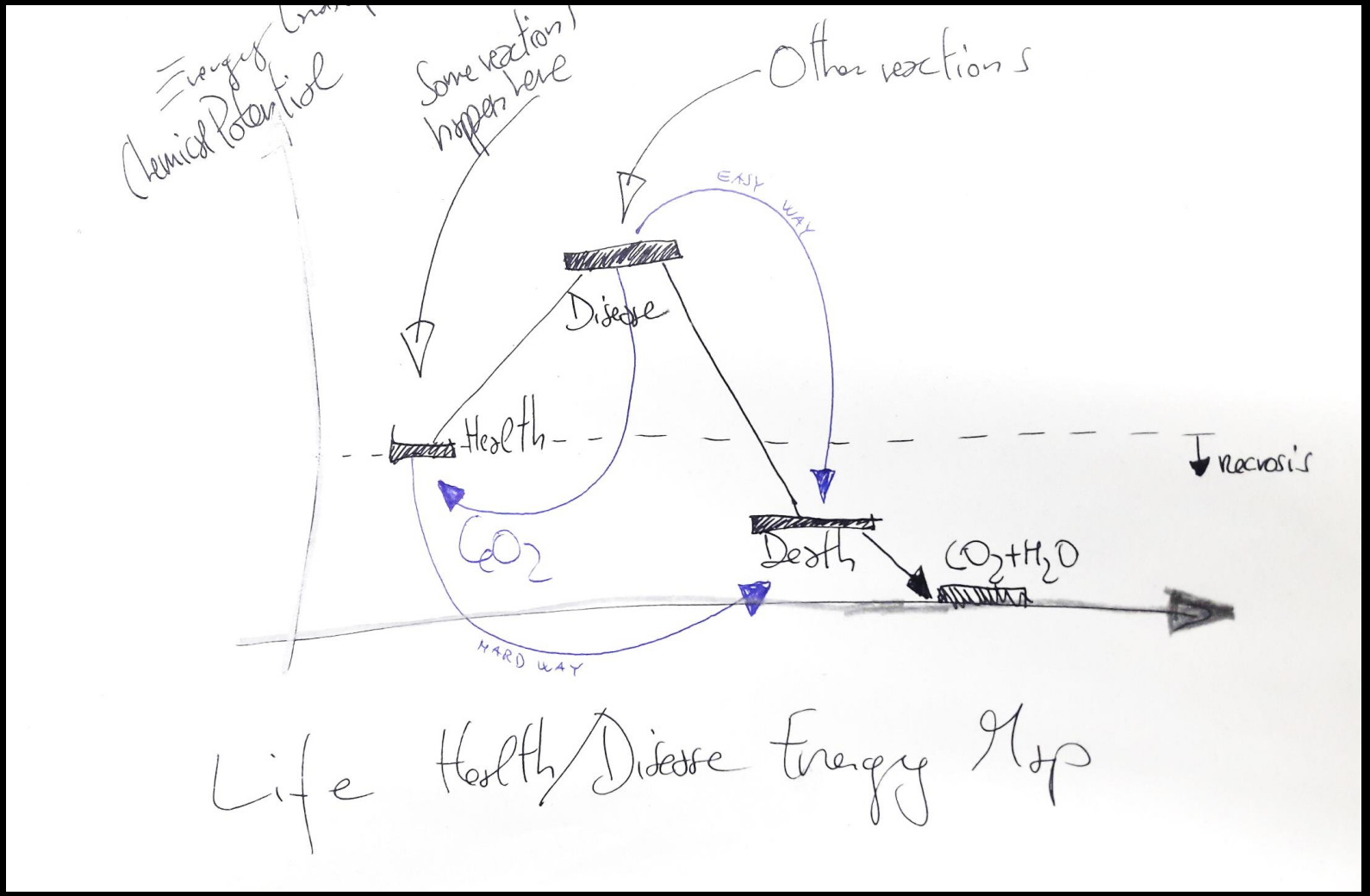
3.- Disease and damage to tissue results in a loose of entropy and increase of enthalpy.

4.- Inflammation, which literally means *setting in flammes* is the biologial expression of this solution to the Gibbs equation.

5.- Immune cells have adapted to this metabolic mode to defend our body from commensal organisms and have the ability to set on and off inflammation.

6.- Impossibility of ending inflammation and restoring homeostasis results in pathological inflammation and tissue damage

THE BIOLOGY OF DISEASE

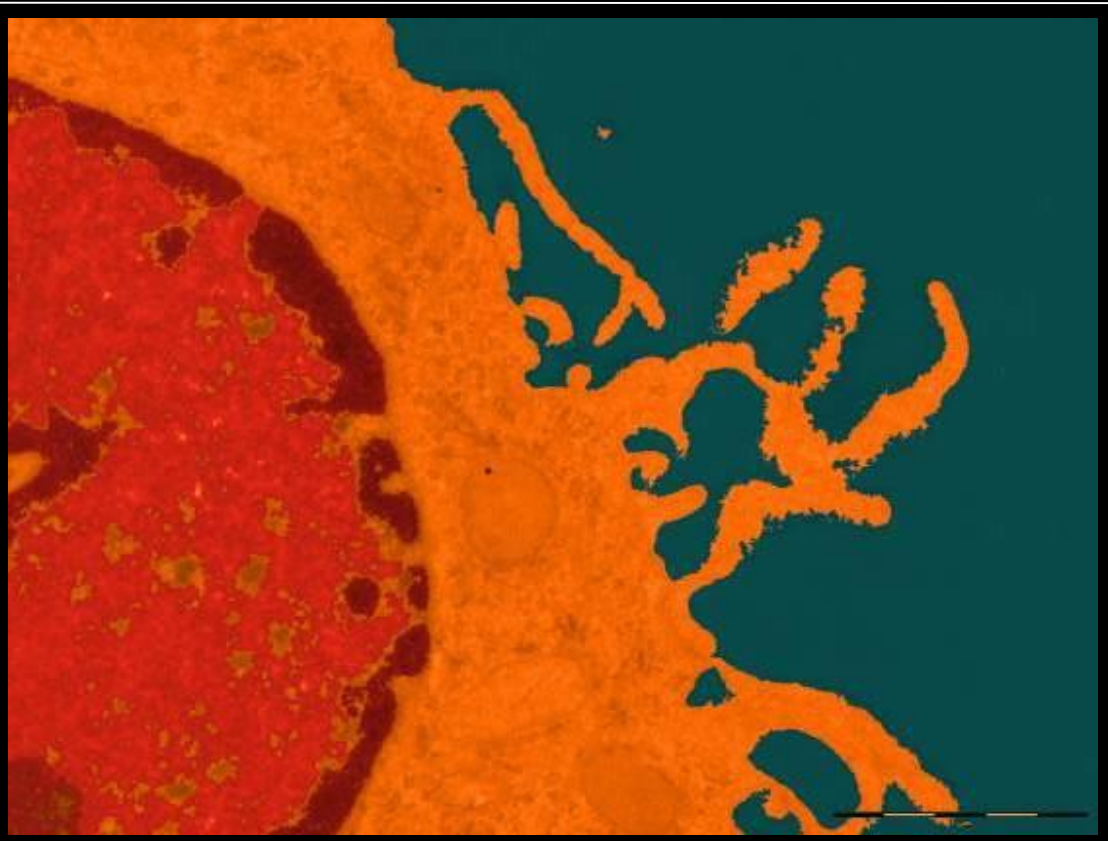


THE BIOLOGY OF DISEASE

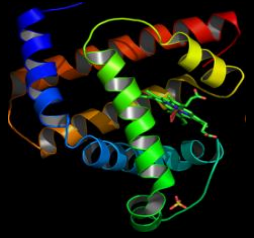

(*cortisone is not so good*)

THE INNATE IMMUNE SYSTEM

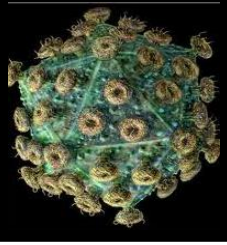
THE JANITOR (M0)
THE SOLDIER (M1)
THE PLUMBER (M2)



PROTEINS

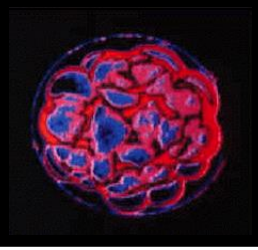


VIRUS

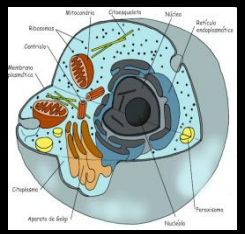


BACTERIES

DEATH CELL



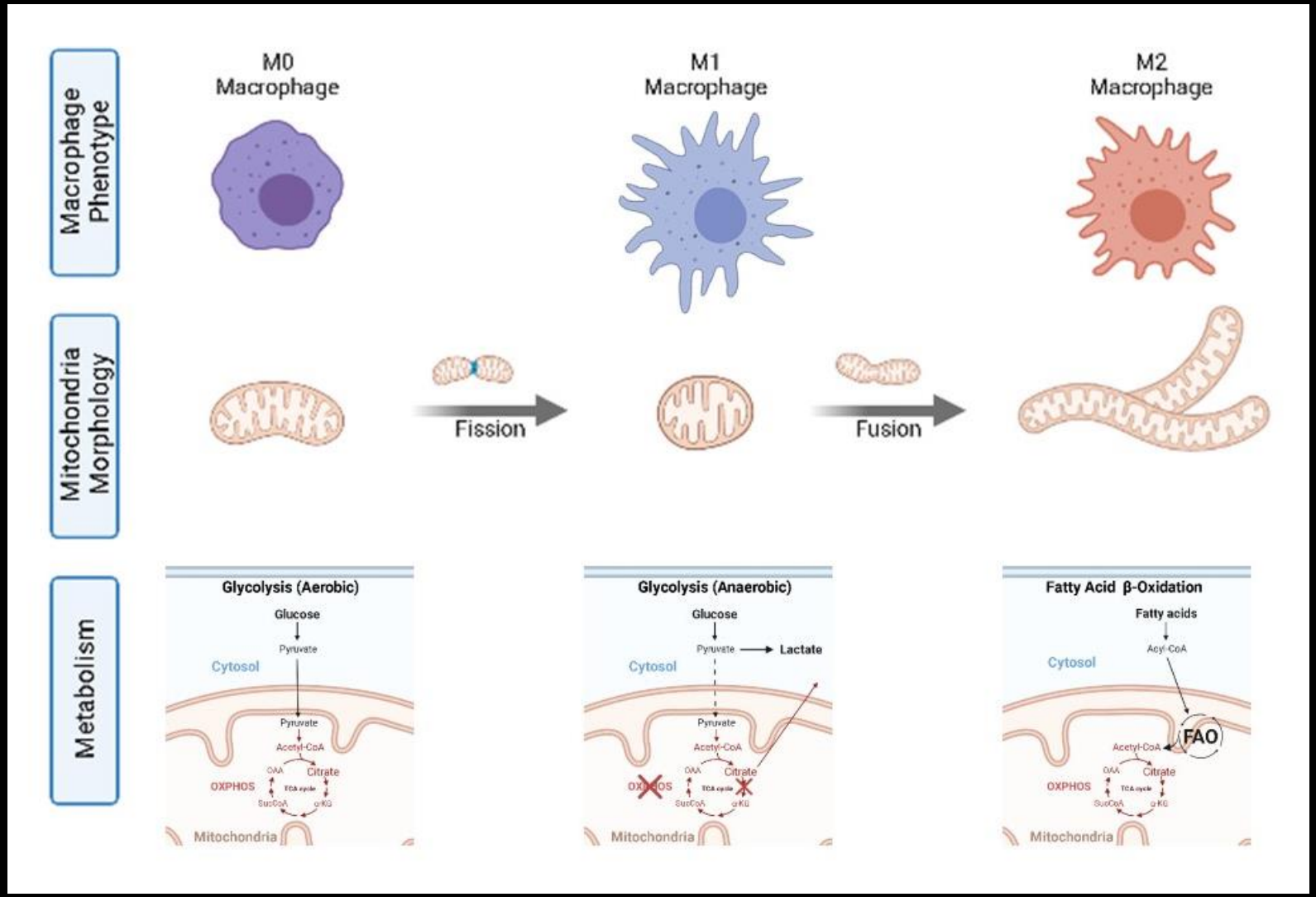
CELL



10 - 30 nm

5.000 nm

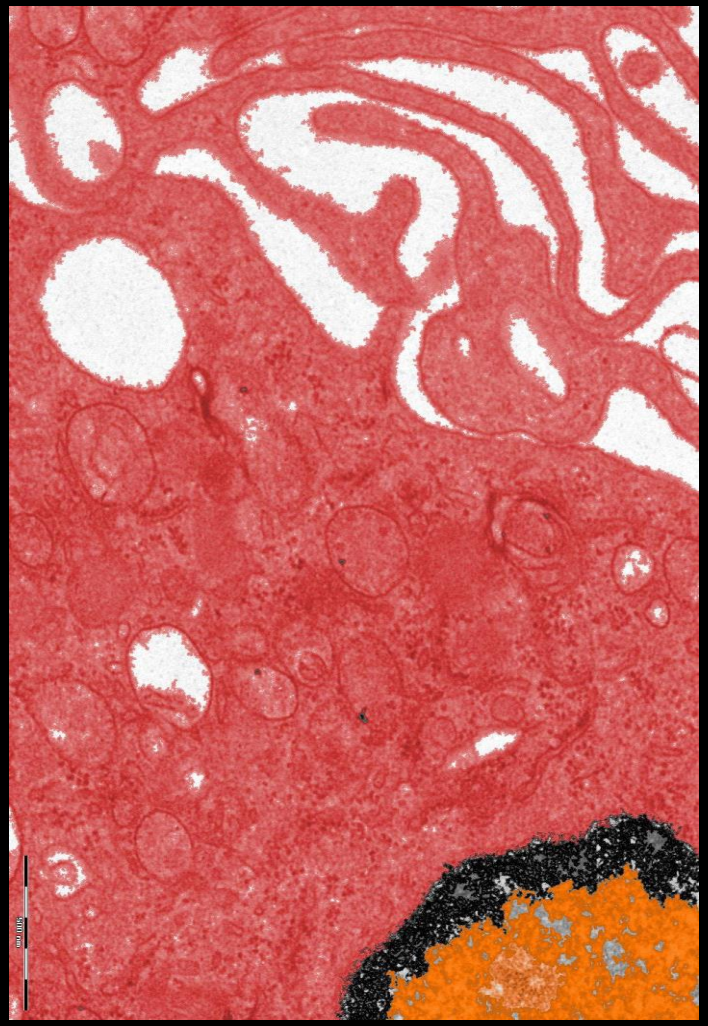
THE IMMUNE SYSTEM PHENOTYPES (POLARIZATION)

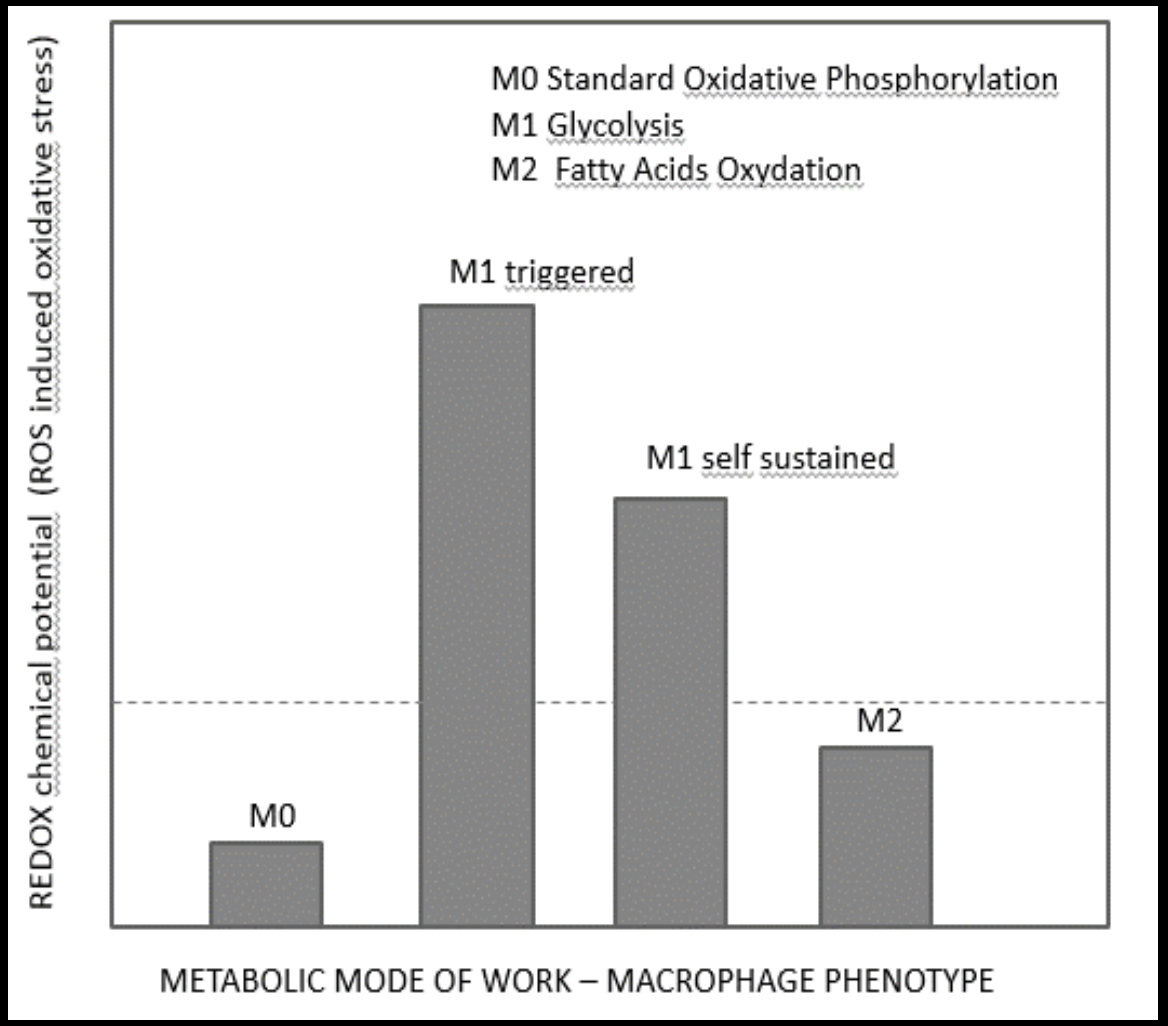


HOW WE DEAL WITH EXCESS T

BODY TEMPERATURE CONTROL ED BY HYPOTHALAMUS AND FOOLED BY PYROGENS

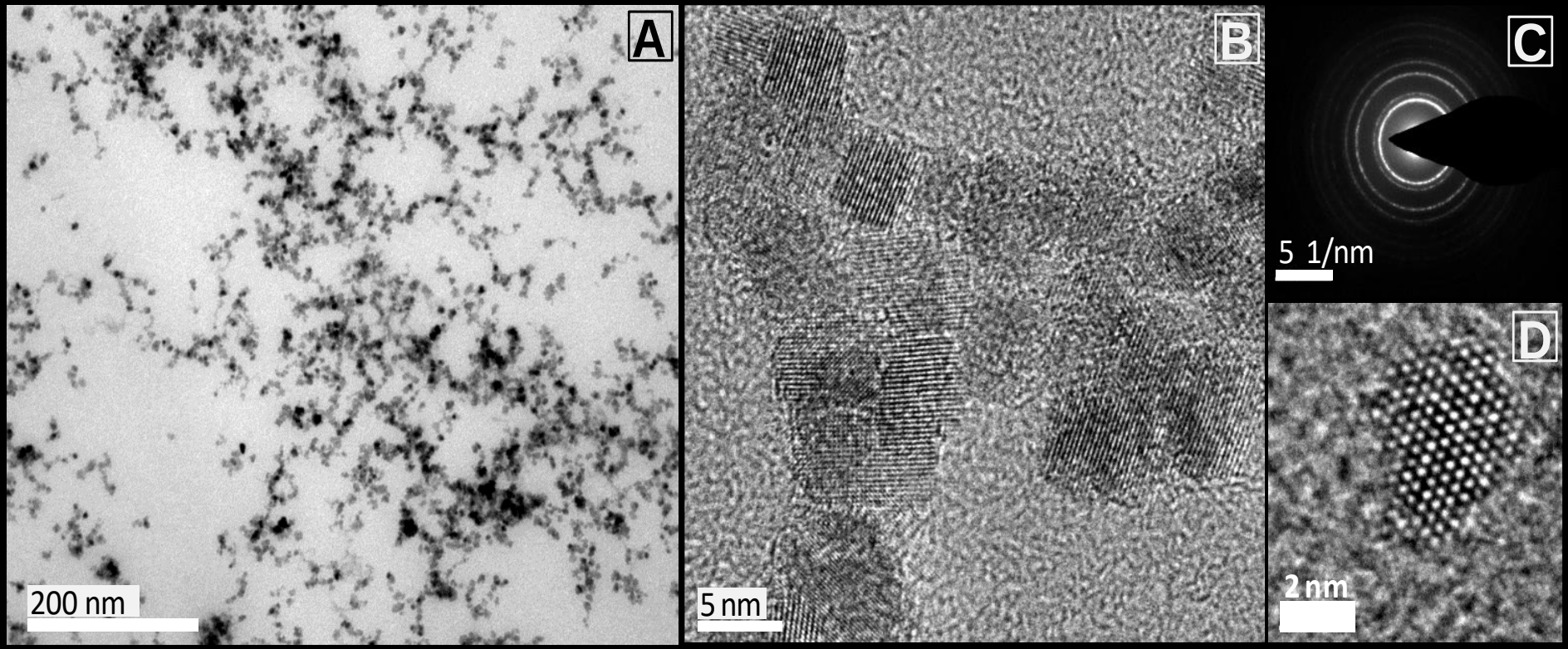
HOW WE DEAL WITH EXCESS ROS



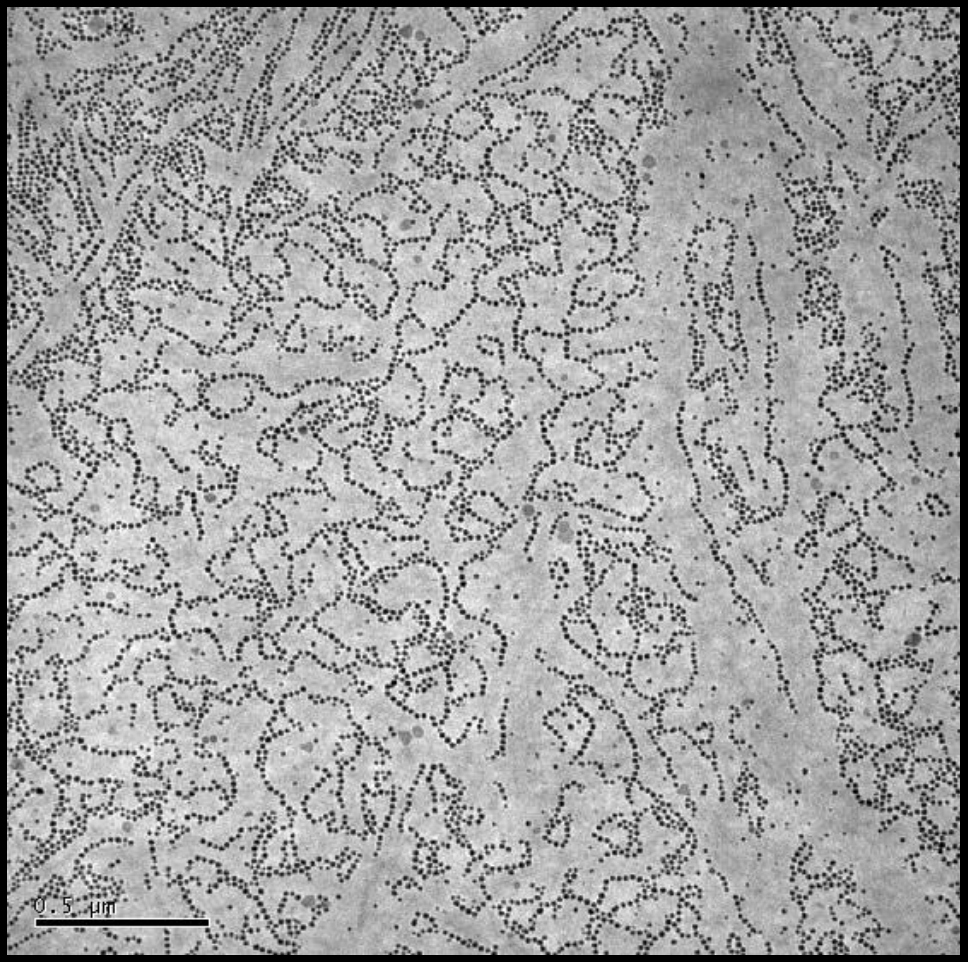


3. THE NANOCERIA PARADIGM

CeO_2 - CERIUM OXIDE NANOPARTICLES: NANOCERIA

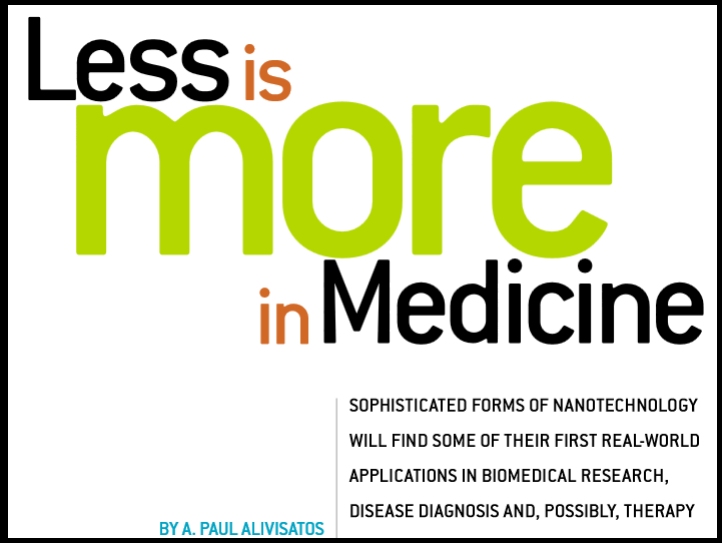


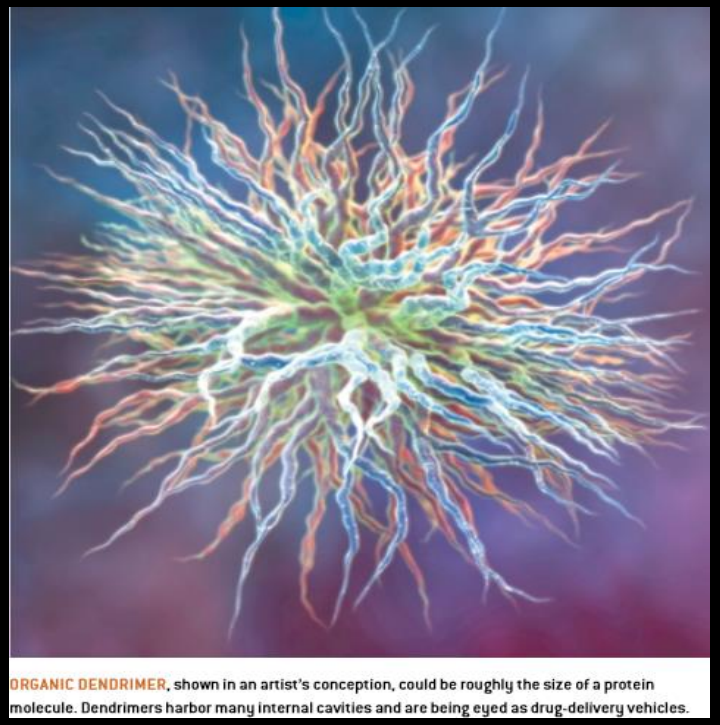
NANOPARTICLES AND CERES



THE ADVENT OF NANOMEDICINA

"An examination of the annual statistical data compiled by the American Cancer Society quickly reveals that the rate of mortality from cancer has changed very little over the past 50 years. Yet despite progress in understanding cancer, its diagnosis and treatment have remained essentially unchanged for decades, and death rates from the disease are about what they were in 1950" P.A Kiberstis et al **Celebration a Glass Half-Full**, *Science* 312, 1157 (2006)




ORGANIC DENDRIMER, shown in an artist's conception, could be roughly the size of a protein molecule. Dendrimers harbor many internal cavities and are being eyed as drug-delivery vehicles.

-El cáncer se queda sin tratamiento. La quimioterapia y la radioterapia causan una depresión en el sistema inmunológico, por lo que sin antibióticos el tratamiento se volvería tan peligroso como la propia enfermedad.

El fin de los medicamentos: cómo será el mundo sin antibióticos

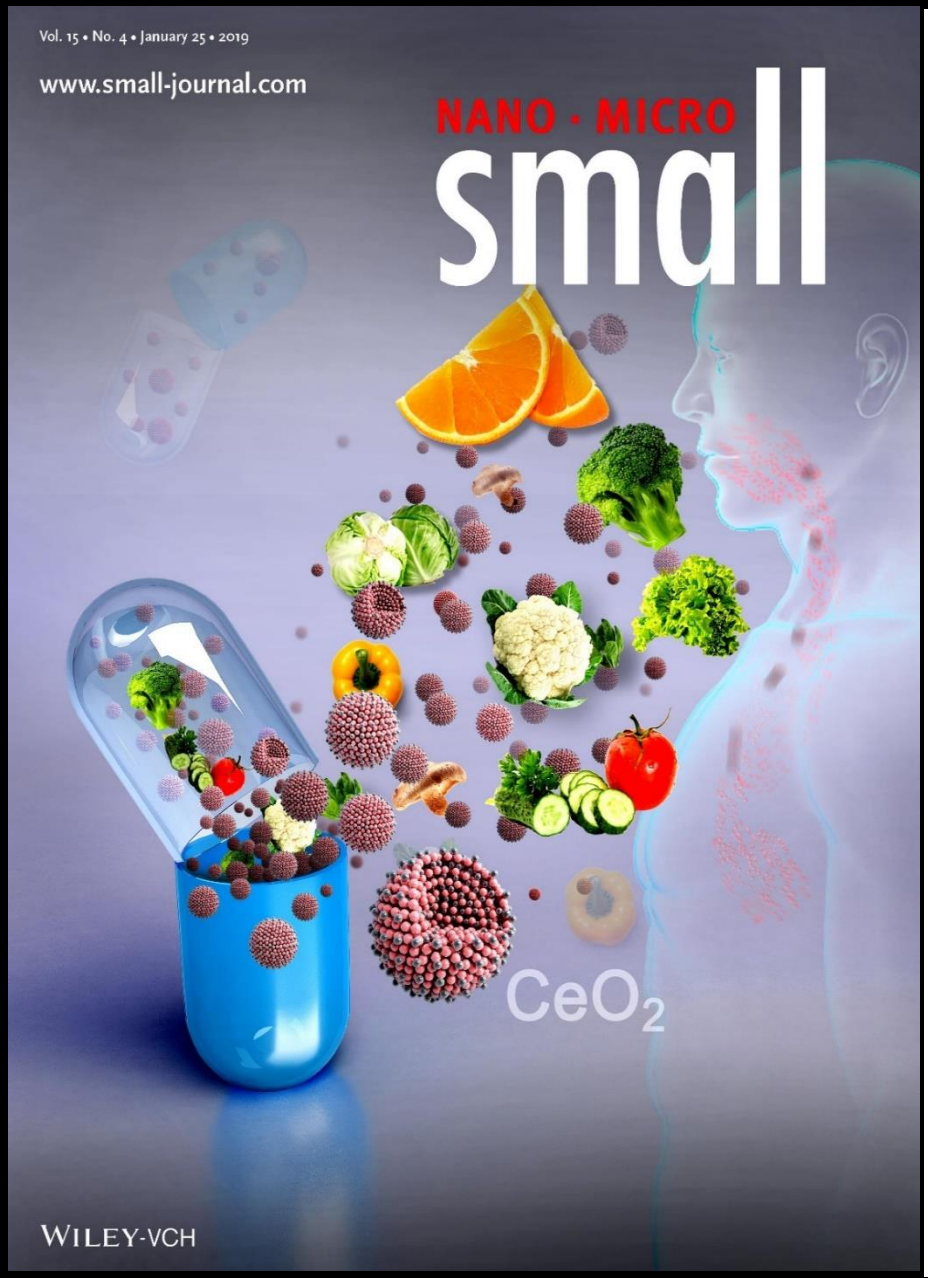
Sally Davies NIHR

THE ADVENT OF NANOMEDICINA

THE ADVENT OF NANOCERIA

Prof. Dr. Beverly A. Rzigalinski,
Professor of Pharmacology at VCOM and the director of NanoNeuro Laboratory and is known, by nickname, as Dr Z. She (or Bev)...
https://lifeboat.com/ex/bios.beverly.a.rzigalinski

THE NANOCERIA LONG STORY



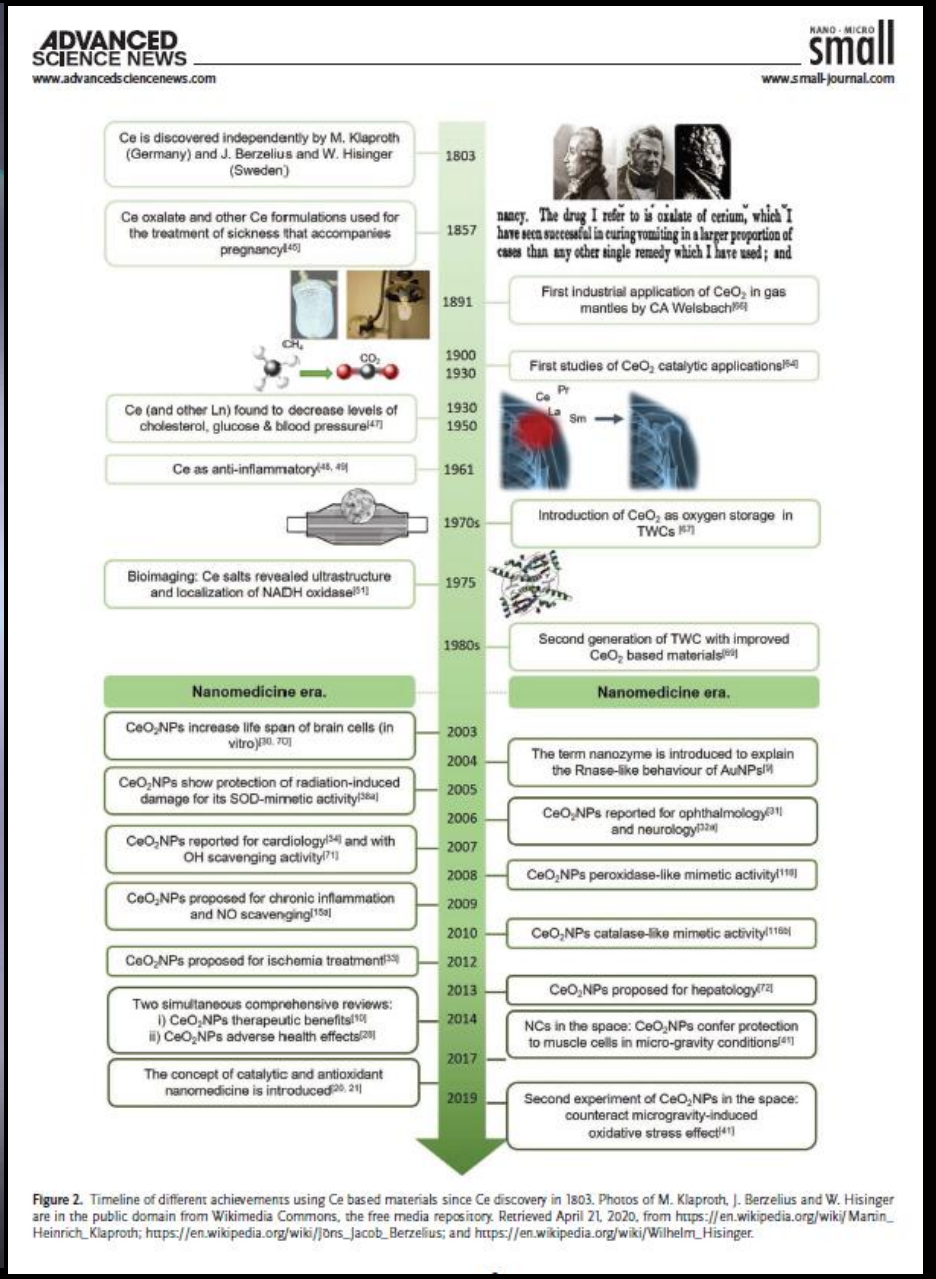
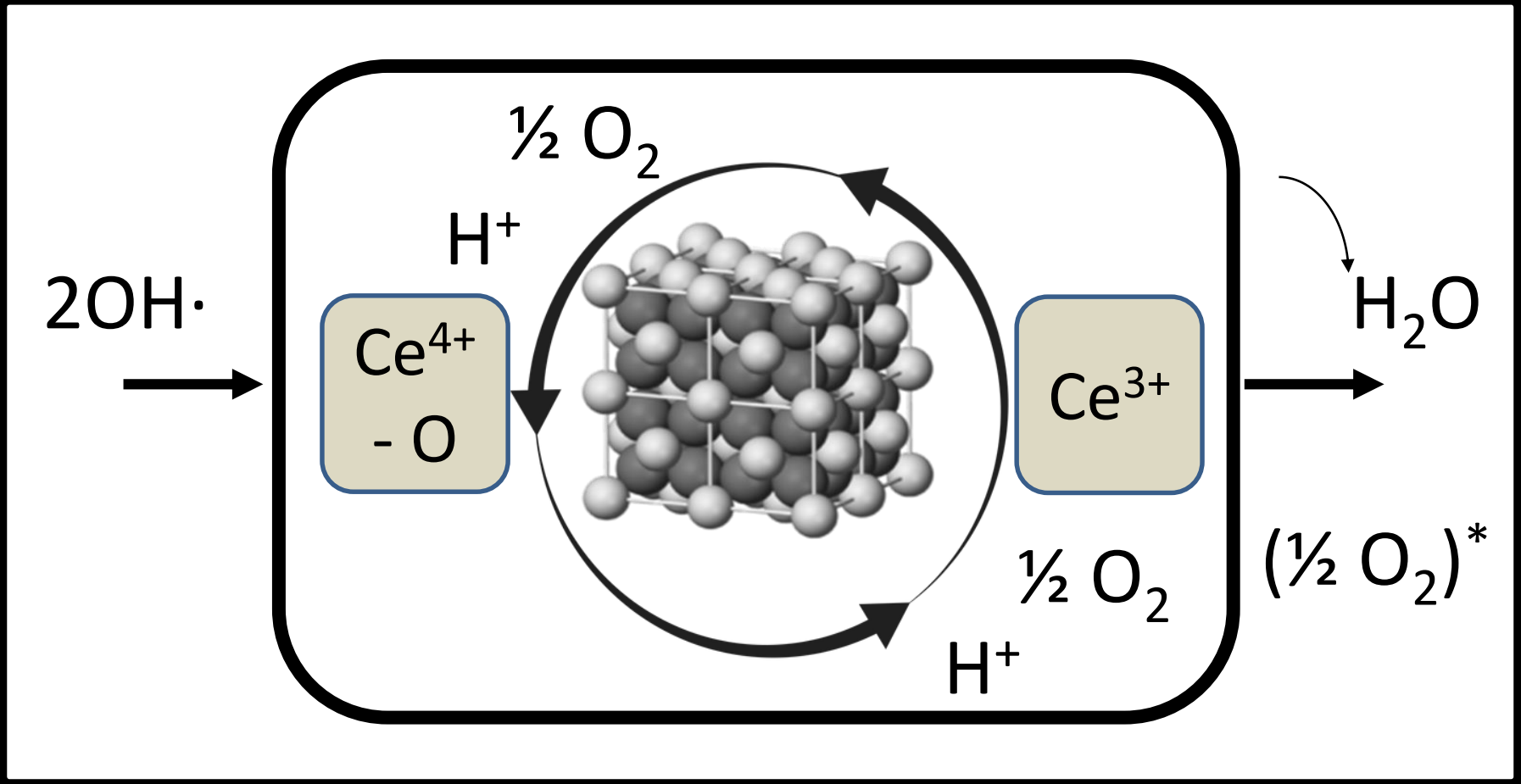


Figure 2. Timeline of different achievements using Ce based materials since Ce discovery in 1803. Photos of M. Klaproth, J. Berzelius and W. Hisinger are in the public domain from Wikimedia Commons, the free media repository. Retrieved April 21, 2020, from https://en.wikipedia.org/wiki/Martin_Heinrich_Klaproth; https://en.wikipedia.org/wiki/Jöns_Jacob_Berzelius; and https://en.wikipedia.org/wiki/Wilhelm_Hisinger.

NANOCERIA: HOW IT WORKS



NANOCERIA: HOW IT WORKS

$$Ce^{4+}_{(s)} + OH\cdot_{(l)} \rightarrow Ce^{3+}_{(s)} + 1/2O_{2(g)} + H^{+}_{(l)} \quad (1)$$

$$Ce^{3+}_{(s)} + OH\cdot_{(l)} \rightarrow Ce^{4+}_{(s)} + OH^{-}_{(l)} \quad (2)$$

If we add the two equations:

$$2OH\cdot_{(l)} \rightarrow H_2O_{(l)} + 1/2O_{2(g)} \quad (3)$$

NANOCERIA: HOW IT WORKS

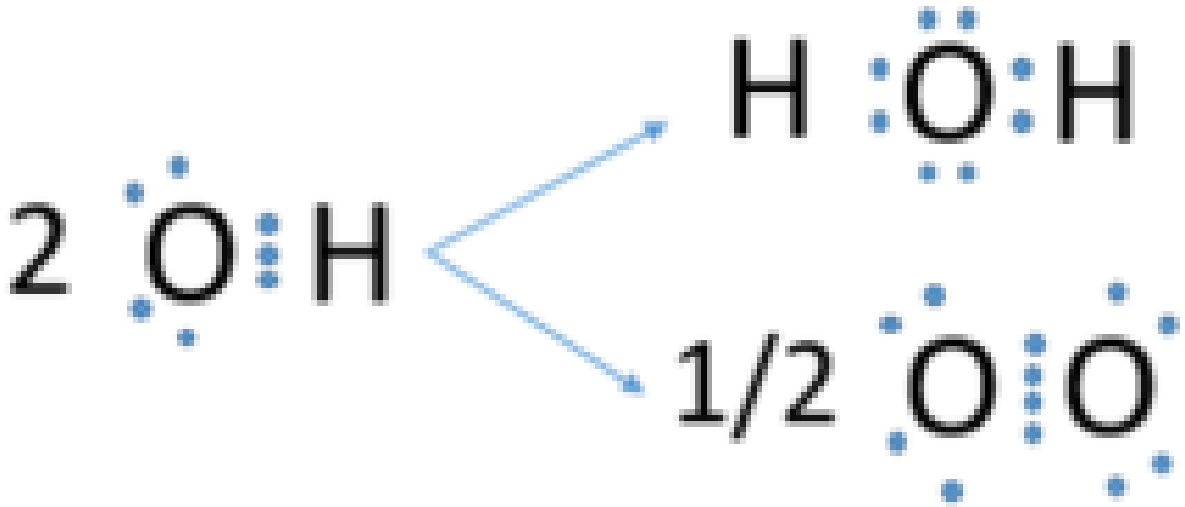
However, we have also to take two other equations into account. At low OH· concentration, reaction (2) can be outcompeted by:

$$Ce^{3+}_{(s)} + 1/2O_{2(g)} + H^{+}_{(l)} \rightarrow Ce^{4+}_{(s)} + OH\cdot_{(l)} \quad (4)$$

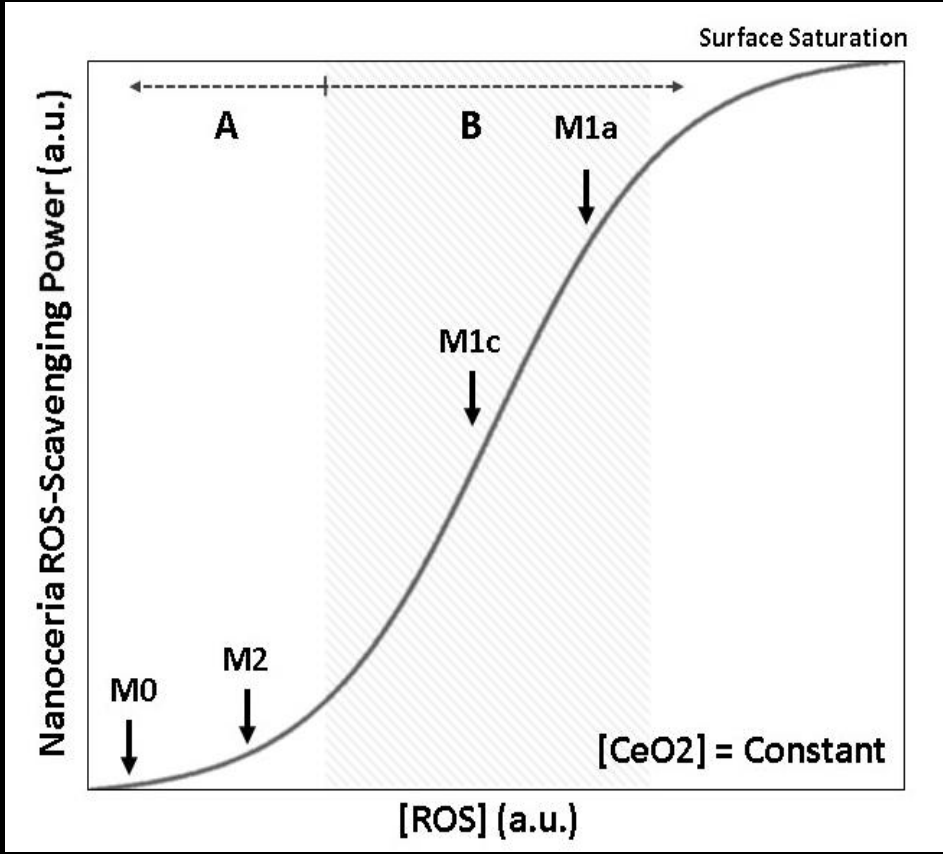
and the ROS scavenging stopped. Additionally, at low ROS and O_2 concentrations, the Ce^{3+} ion, which is soluble at pH below 8, may dissolve

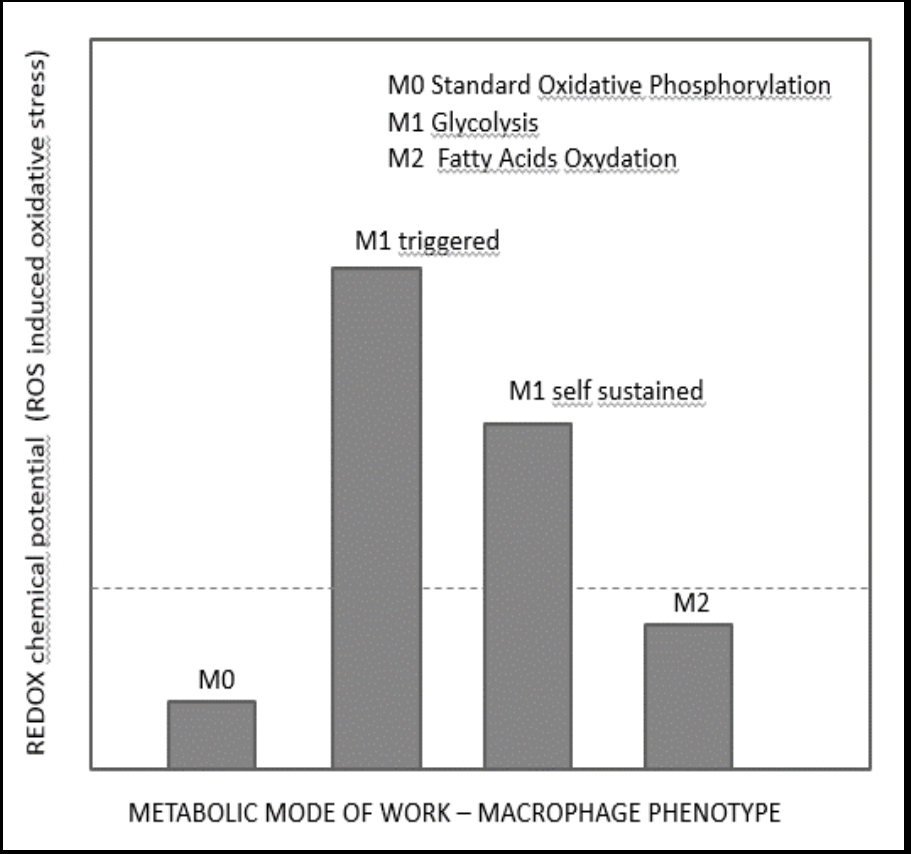
$$Ce^{3+}_{(s)} \rightarrow Ce^{3+}_{(l)} \quad (5)$$

NANOCERIA: HOW IT WORKS



NANOCERIA: THE FACTO REDOX BUFFER





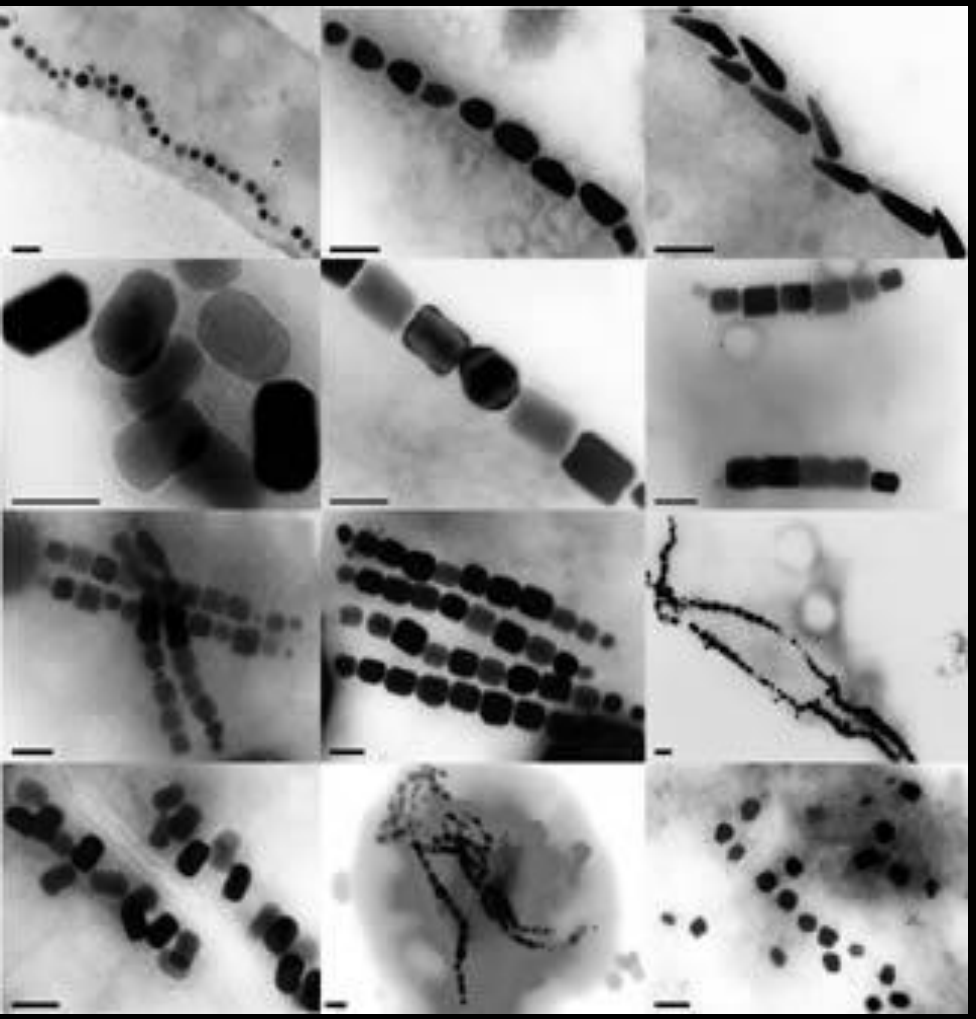
3. FORMULATING NANOCERIA

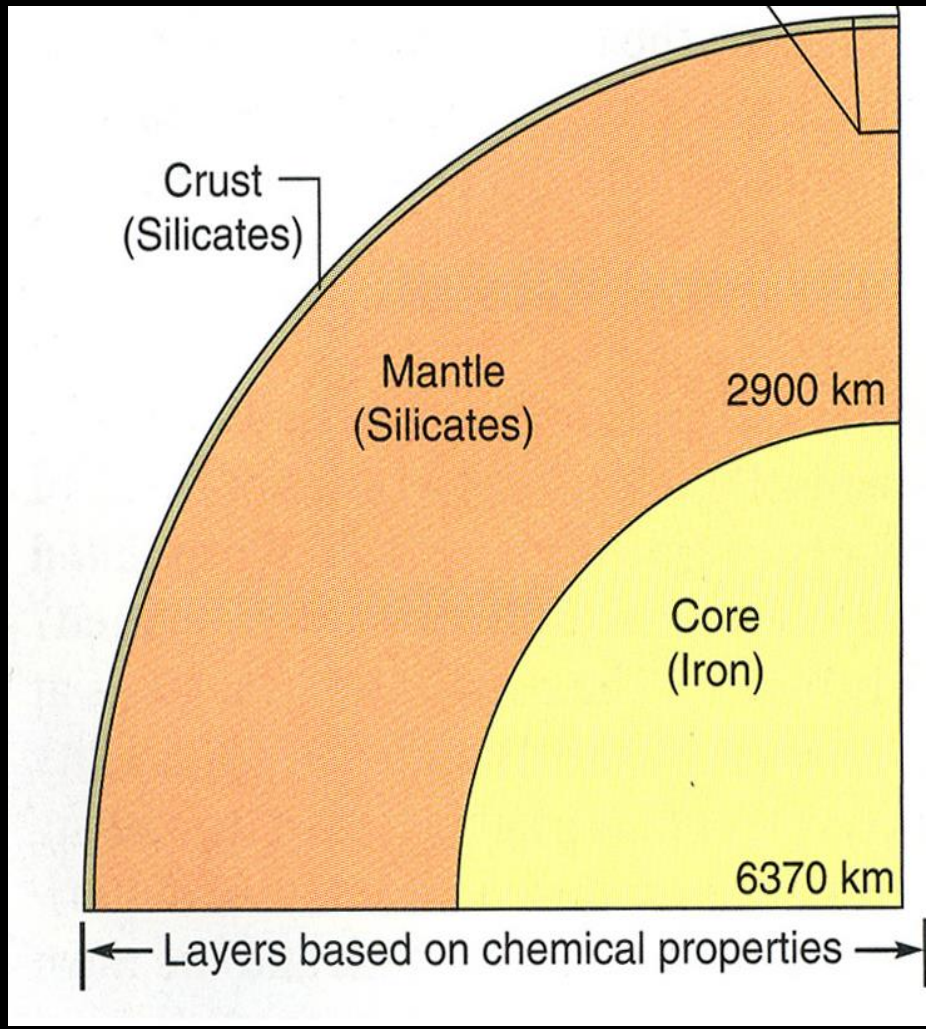
NANOTOXICOLOGY

SOLE DOSIS FACIT VENUM

Philippus Aureolus **Theophrastus Bombastus von Hohenheim**

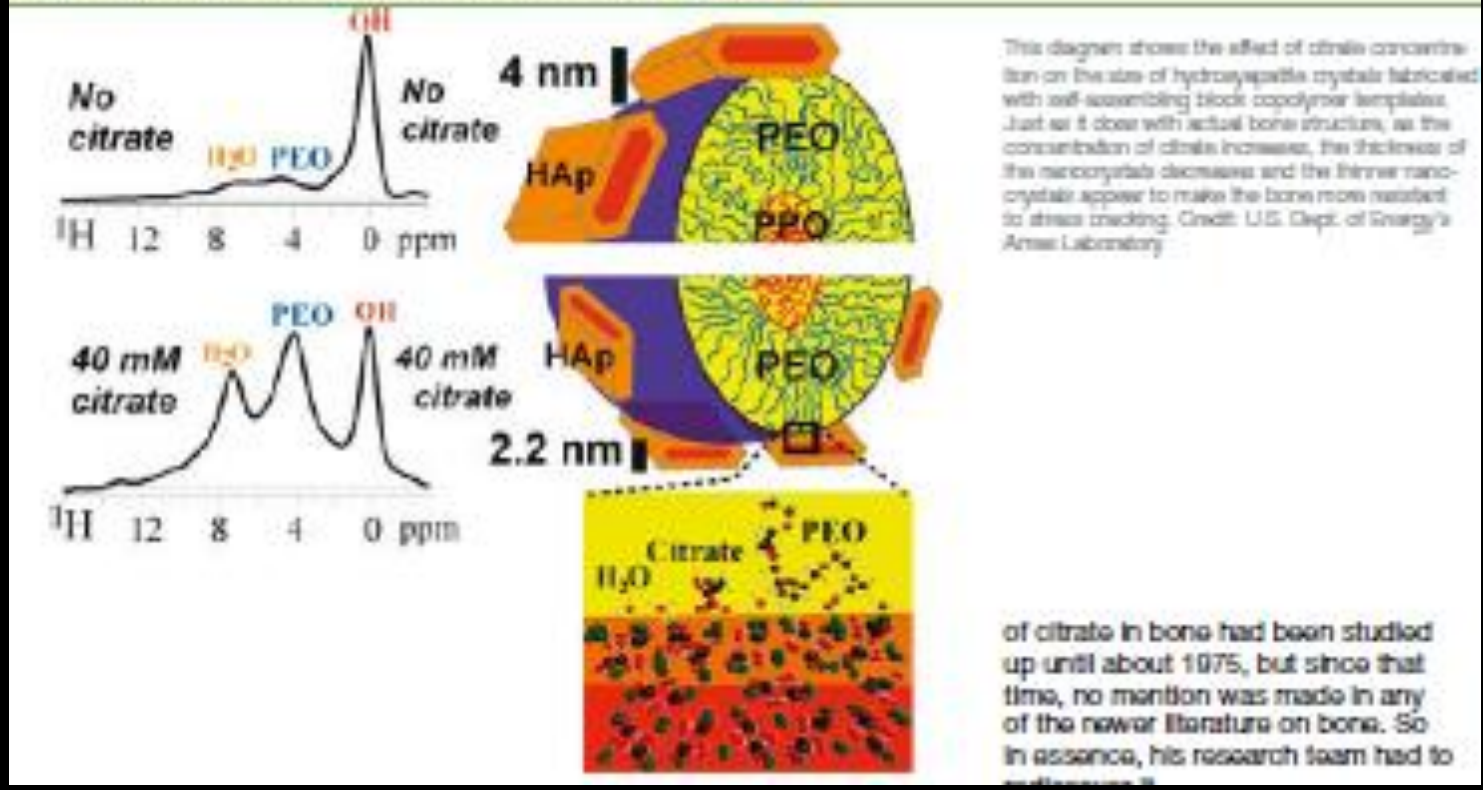
NANOPARTICLES BEFORE NANOTECHNOLOGY





NANOPARTICLES BEFORE NANOTECHNOLOGY

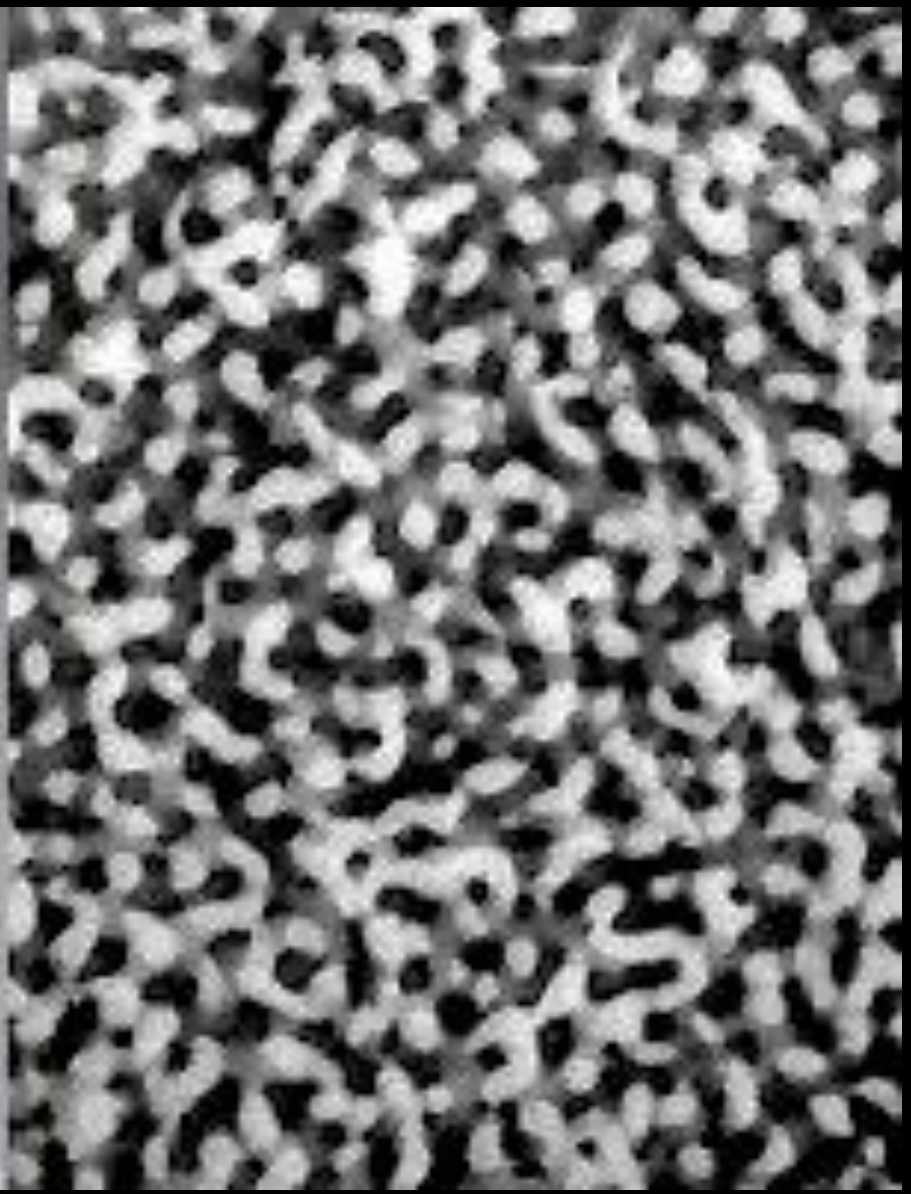
Bone's Nanostructure



This diagram shows the effect of citrate concentration on the size of hydroxyapatite crystals fabricated with self-assembling block copolymer templates. Just as it does with actual bone structure, as the concentration of citrate increases, the thickness of the nanocrystals decreases and the thinner nanocrystals appear to make the bone more resistant to stress cracking. Credit: U.S. Dept. of Energy's Ames Laboratory

of citrate in bone had been studied up until about 1975, but since that time, no mention was made in any of the newer literature on bone. So in essence, his research team had to

NANOPARTICLES BEFORE NANOTECHNOLOGY



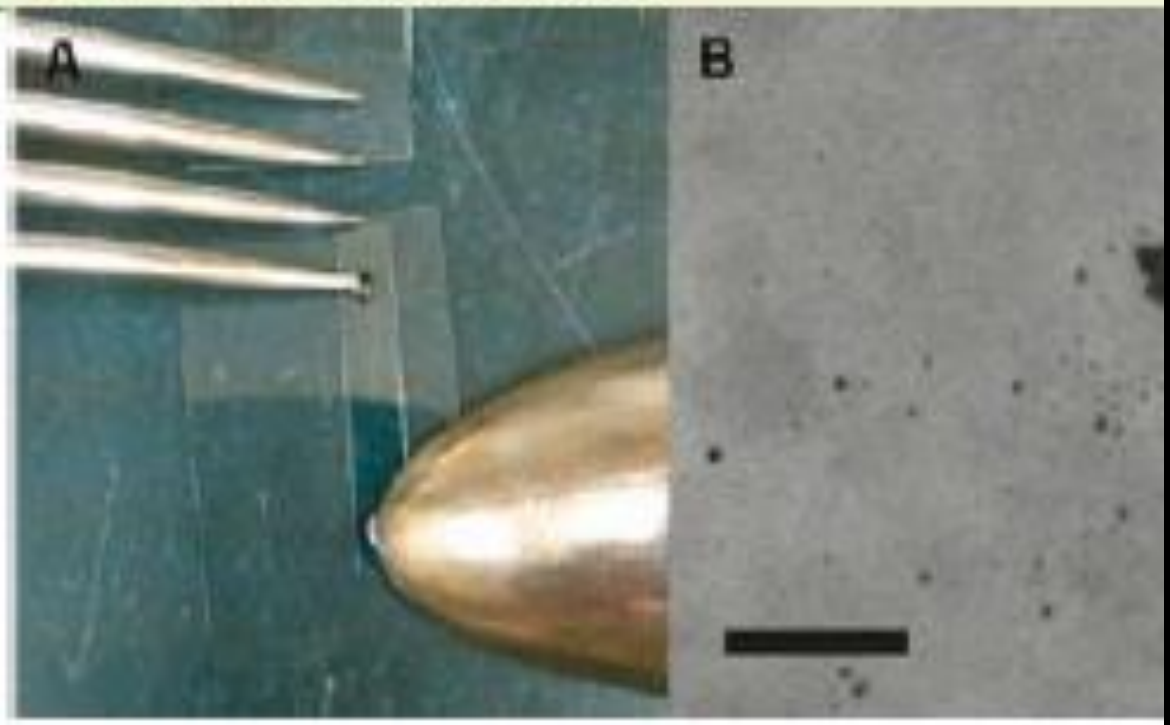
NANOPARTICLES BEFORE NANOTECHNOLOGY

Challenging conventional thinking on the reactivity of nanoparticles

[illegible] October 25, 2011
Tags: nano before nanotech + nanotoxicology + concerns + regulation + nanoparticles + nanosilver

f you've ever eaten from silverware
or worn copper jewelry, you've been
n a perfect storm in which nanopar-
ticles were dropped into the environ-
ment, say scientists at the University
of Oregon. Since the emergence of
nanotechnology, researchers, regula-
tors and the public have been con-
cerned that the potential toxicity of
nano-sized products might threaten
human health by way of environmental
exposure.

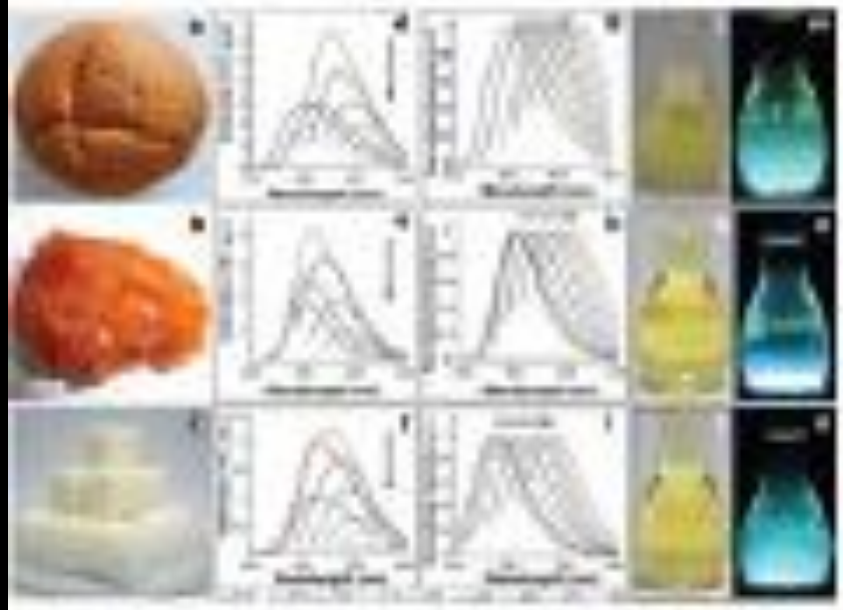
Now, with the help of high-powered
transmission electron microscopes,
chemists captured never-before-seen
views of minuscule metal nanoparticles

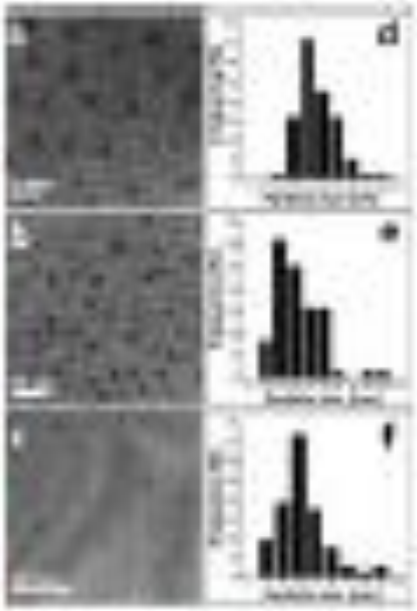


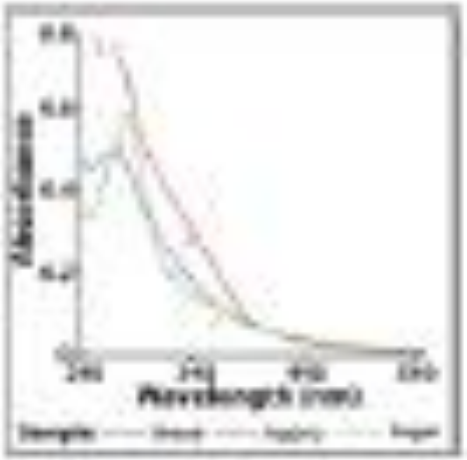
Common flatware releases nanoparticles under certain conditions

NANOPARTICLES BEFORE NANOTECHNOLOGY

Nanoparticles in caramels, sugar, bread...







NANOPARTICLES BEFORE NANOTECHNOLOGY

Candle flames contain millions of tiny diamonds

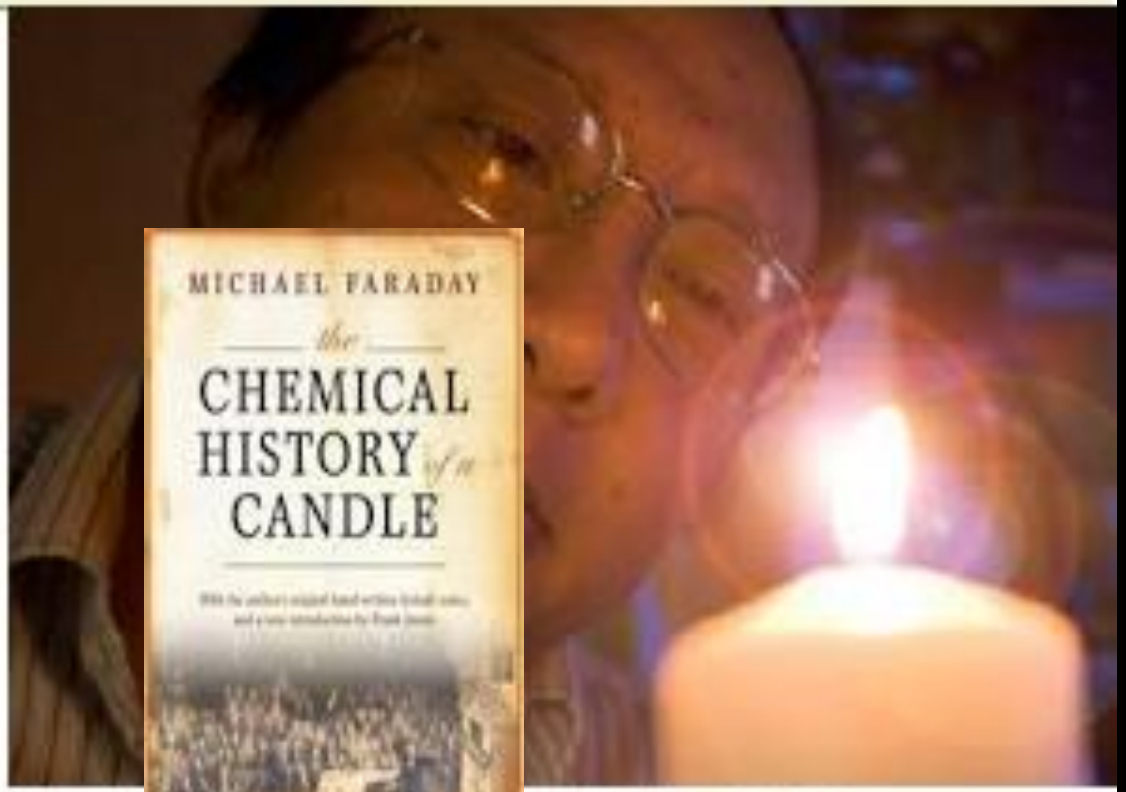
josap saldaña, August 19, 2011
tags: nano before nanotech + nanoparticles

The flickering flame of a candle has generated comparisons with the twinkling sparkle of diamonds for centuries, but new research has discovered the likeness owes more to science than the dreams of poets.

Professor Wuzong Zhou, Professor of Chemistry at the University of St Andrews has discovered tiny diamond particles exist in candle flames.

His research has made a scientific leap towards solving a mystery which has befuddled people for thousands of years.

Since the first candle was invented in ancient China more than 2,000 years ago, many have longed to know what hidden secrets its flames contained.

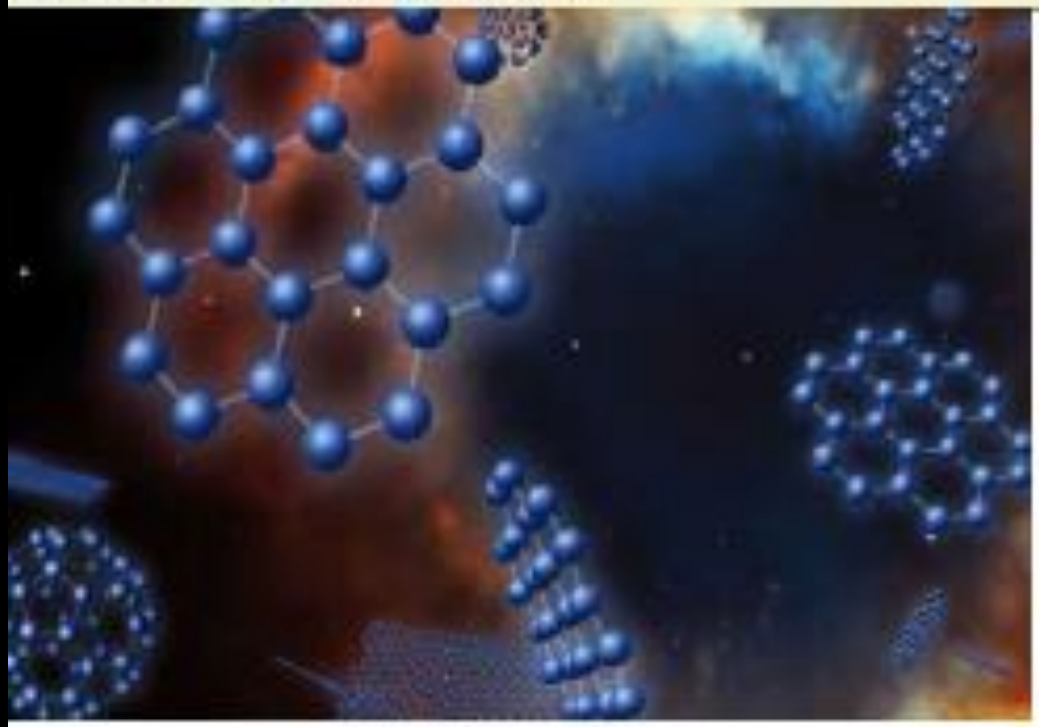


Courtesy of University of St Andrews

NANOPARTICLES BEFORE NANOTECHNOLOGY

Has graphene been detected in space?

Josip Katsikis, August 23, 2011
tags: graphene + nano before nanotech + astronomy



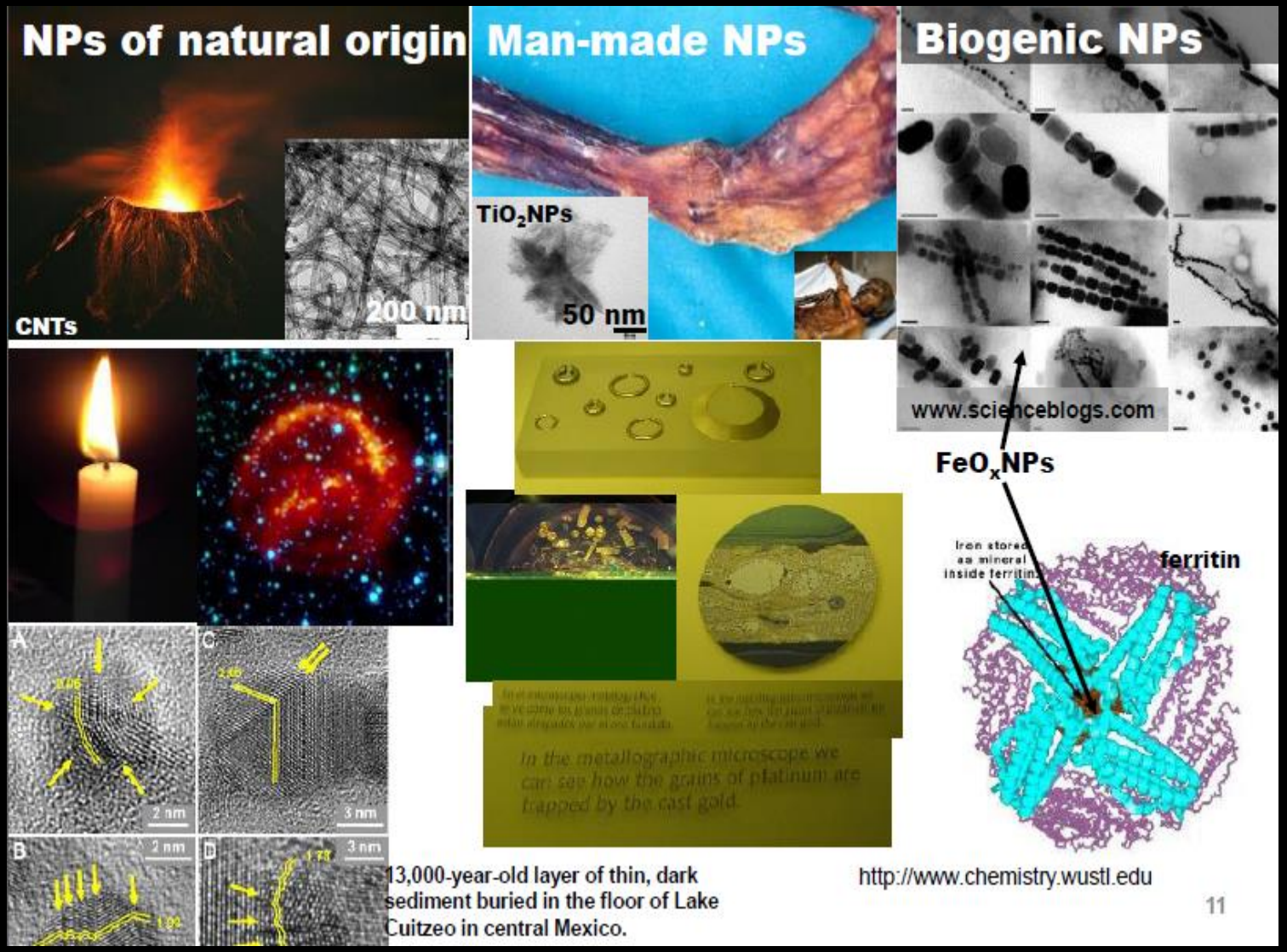
Artist's impression of the graphenes (C24) and fullerenes found in a Planetary Nebula. The detection of graphenes and fullerenes around old stars as common as our Sun suggests that these molecules and other allotropic forms of carbon may be widespread in space. Credits: IAC, original image of the Helix Nebula (NASA, NOAO, ESA, the Hubble Helix Nebula Team, M. Meixner, STScI, & T.A. Rector, NRAO)

the 2010 Nobel Prize in physics. "If confirmed with laboratory spectroscopy – something that is almost impossible with the present techniques – this would be the first detection of graphene in space" said team member García-Hernández.

The team has proposed that fullerenes and graphene are formed from the shock-induced (i.e., grain-grain collisions) destruction of hydrogenated amorphous carbon grains (HACs). Such collisions are expected in the stellar winds emanating from planetary nebulae, and this team sees evidence for strong stellar winds in the ultraviolet spectra of these stars. "What is particularly surprising is that the existence of these molecules does not depend on the stellar temperature, but

NANOPARTICLES BEFORE NANOTECHNOLOGY

NANOPARTICLES BEFORE NANOTECHNOLOGY



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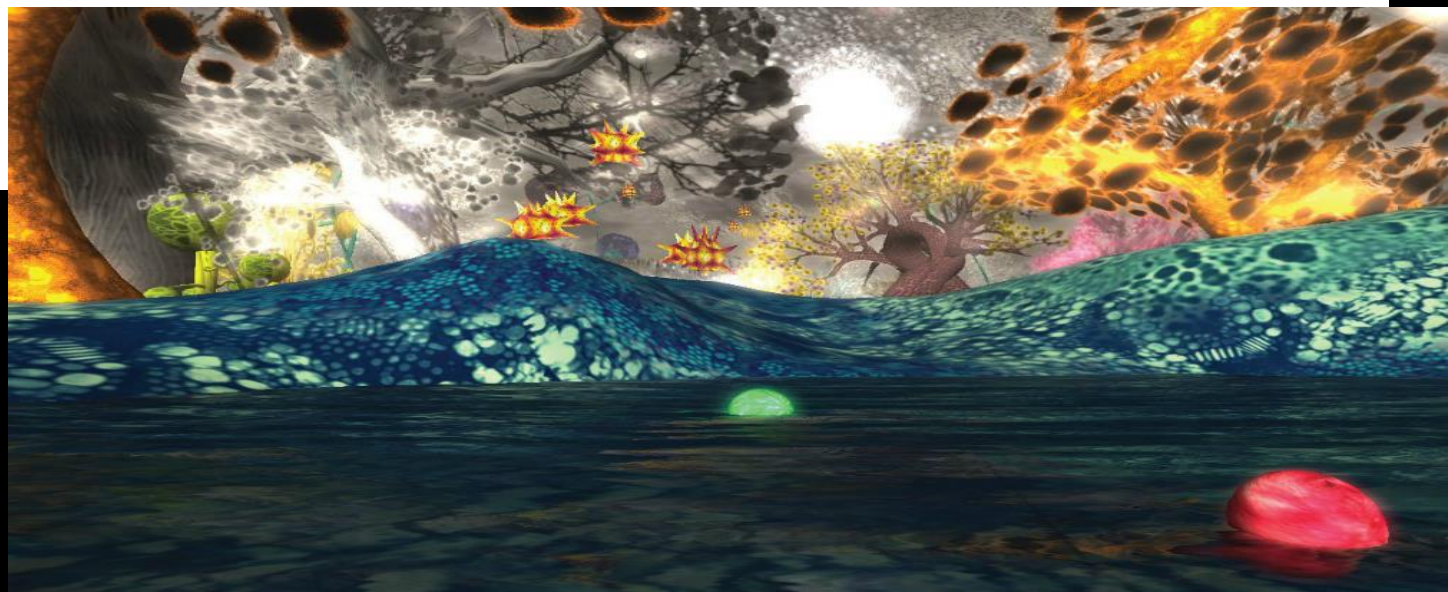
Nanoparticles Before Nanotechnology

editor, 16 February 2013 (created 16 January 2013)

We are glad to present another NanoWiki compilation, following **'Balancing the promises'** and **'Engines On'**.



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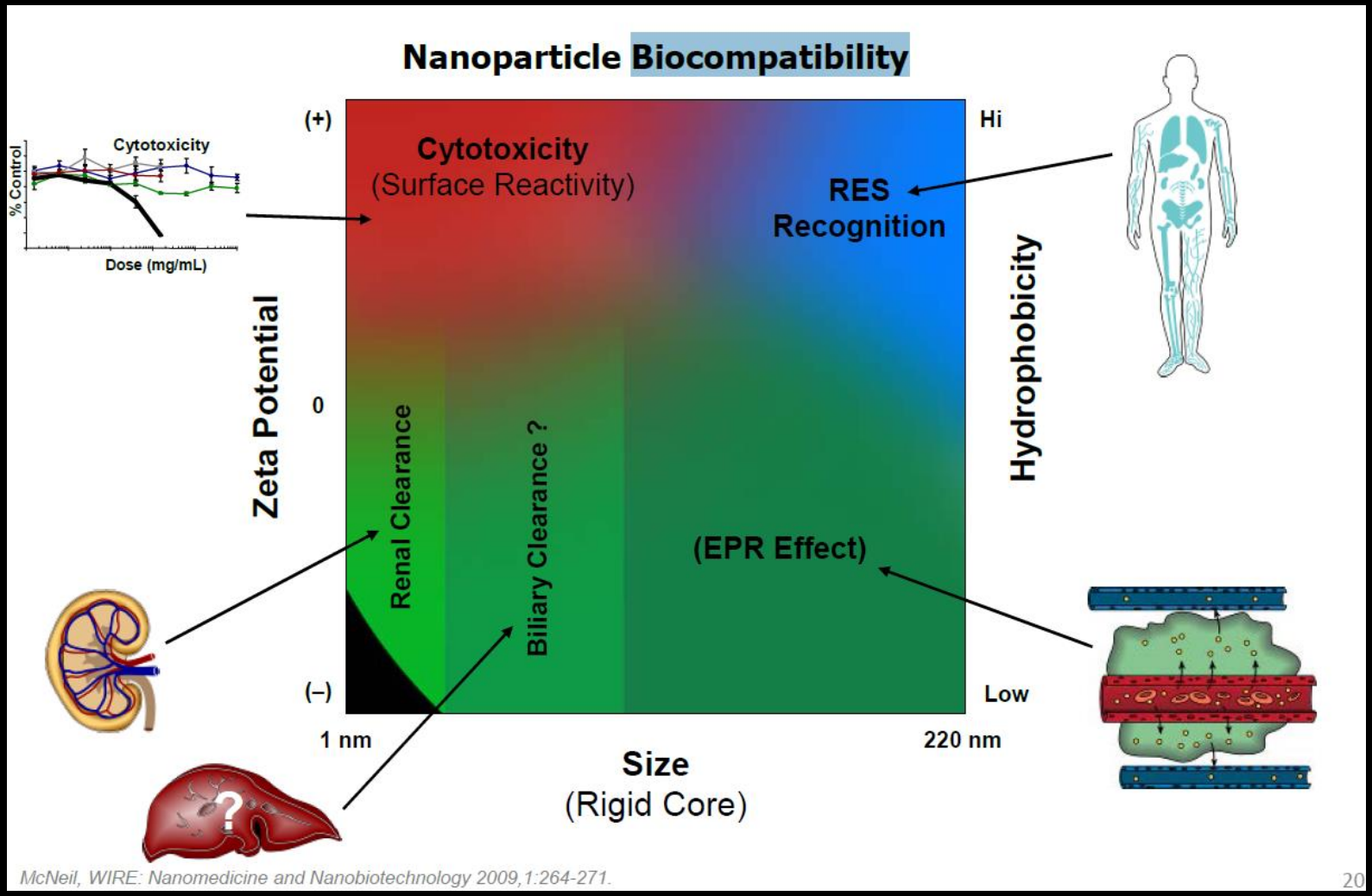
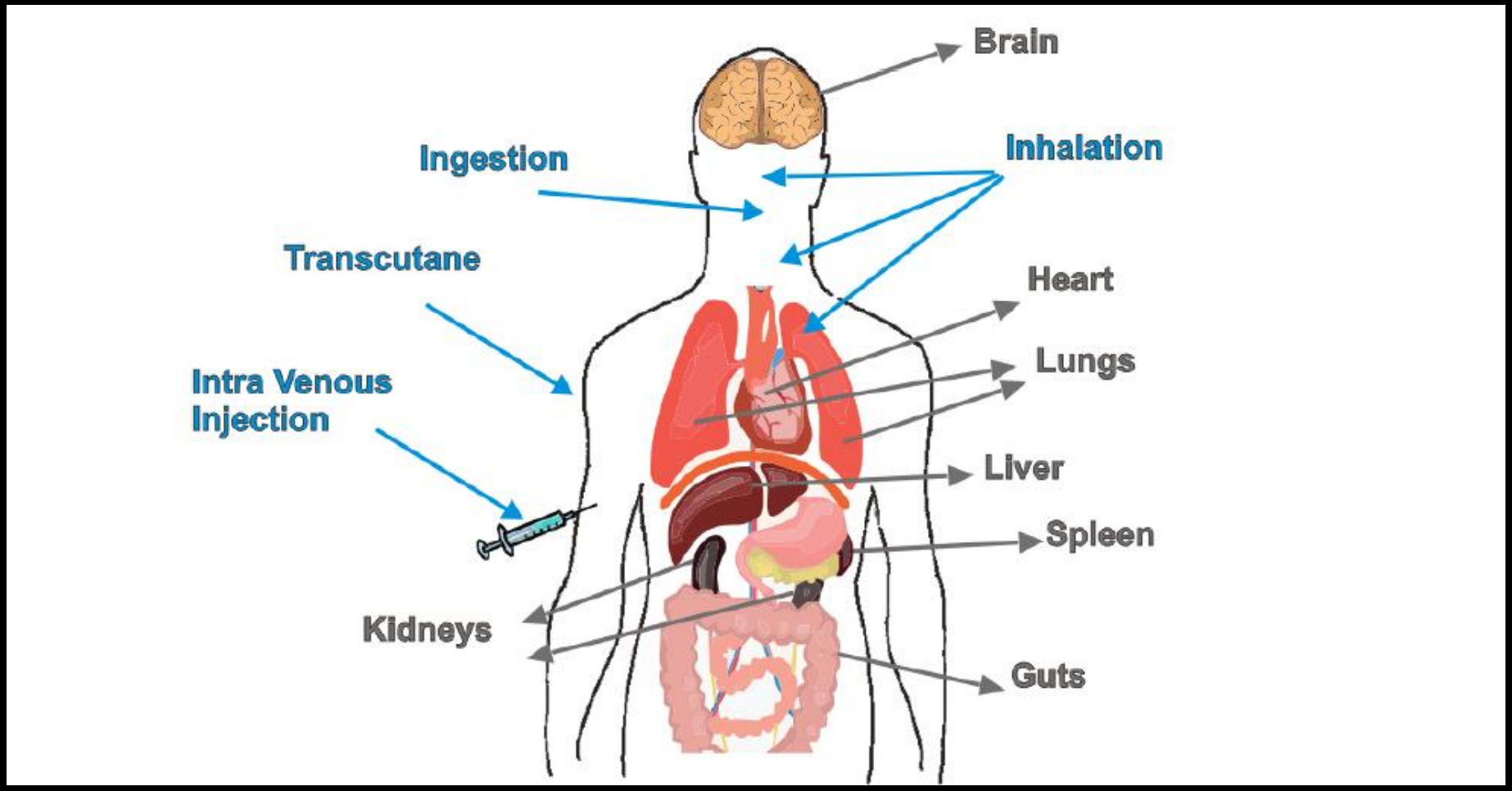
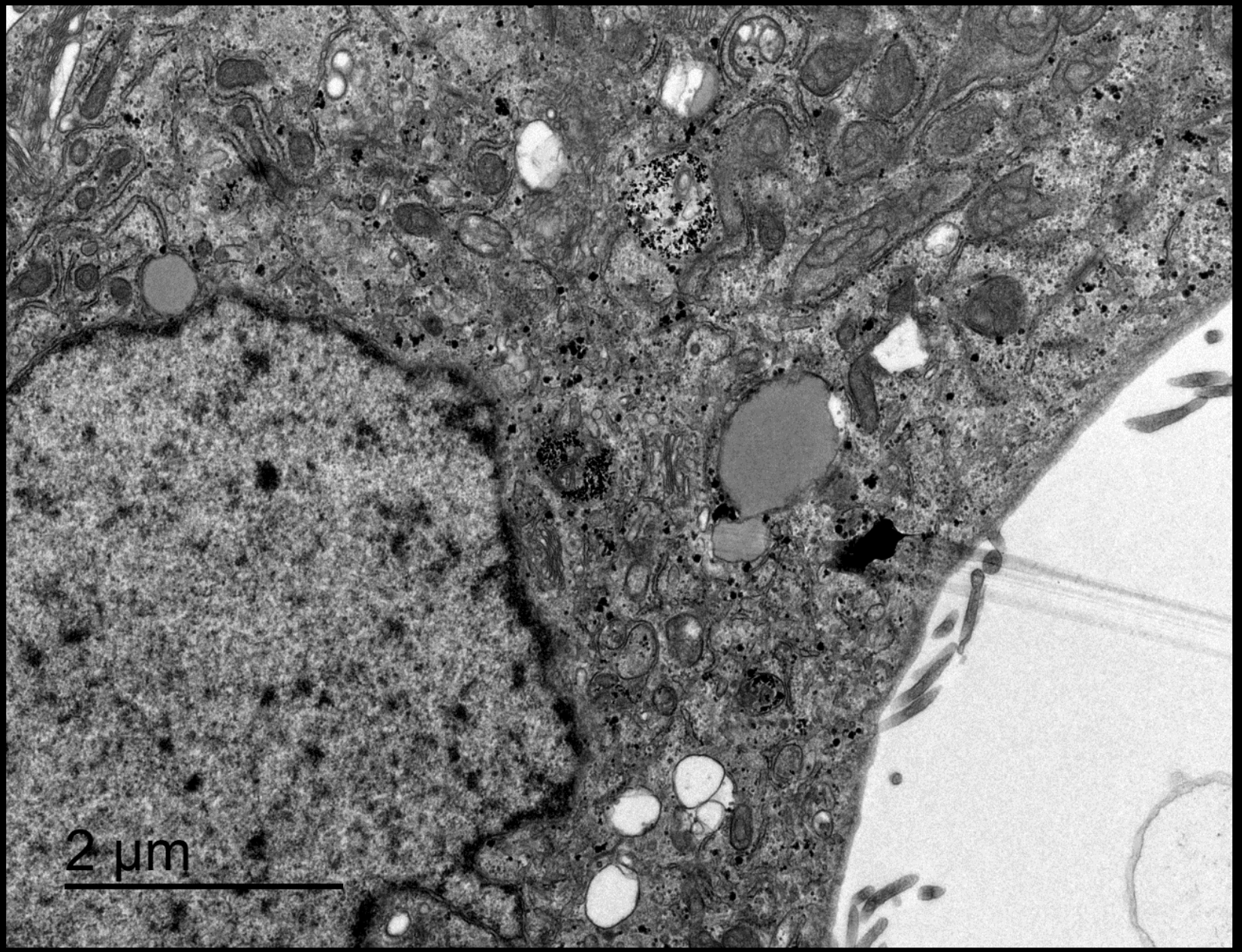


McNeil, WIRE: Nanomedicine and Nanobiotechnology 2009,1:264-271.

NANOPARTICLES BIODISTRIBUTION



THE CERIASOME



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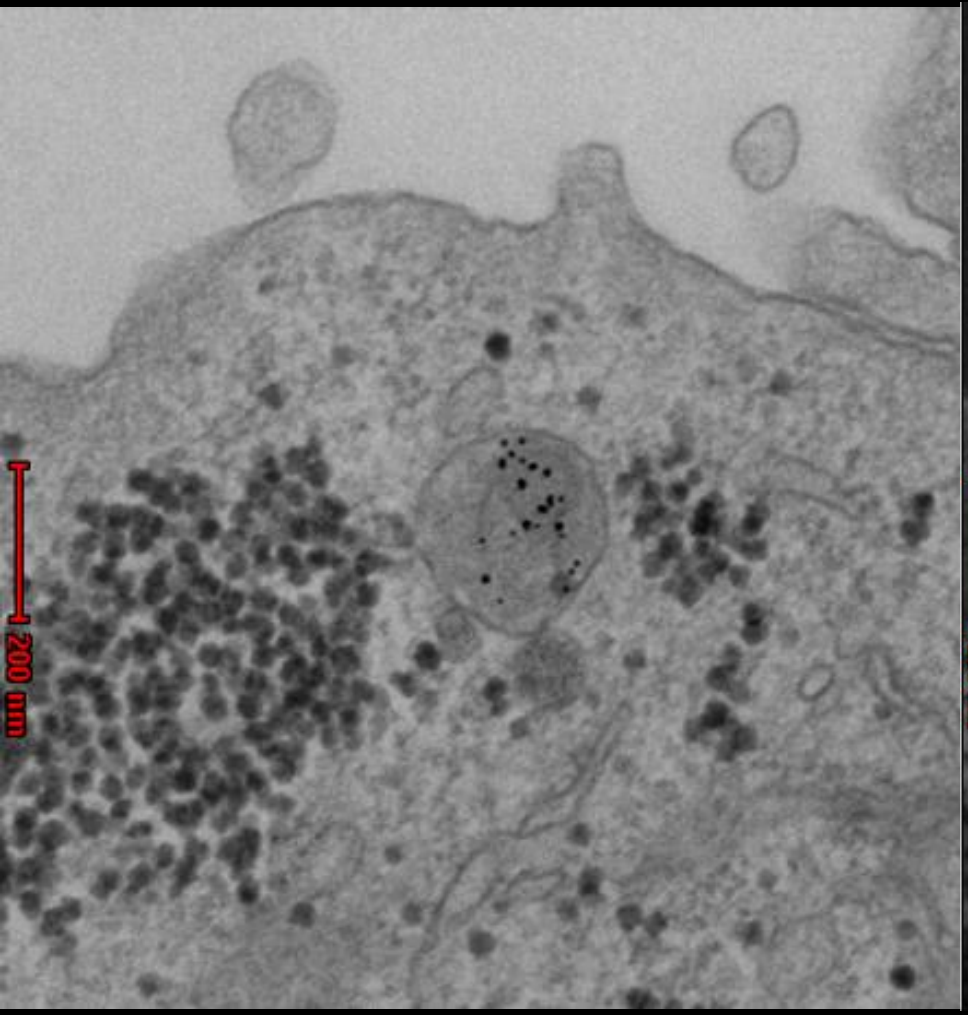
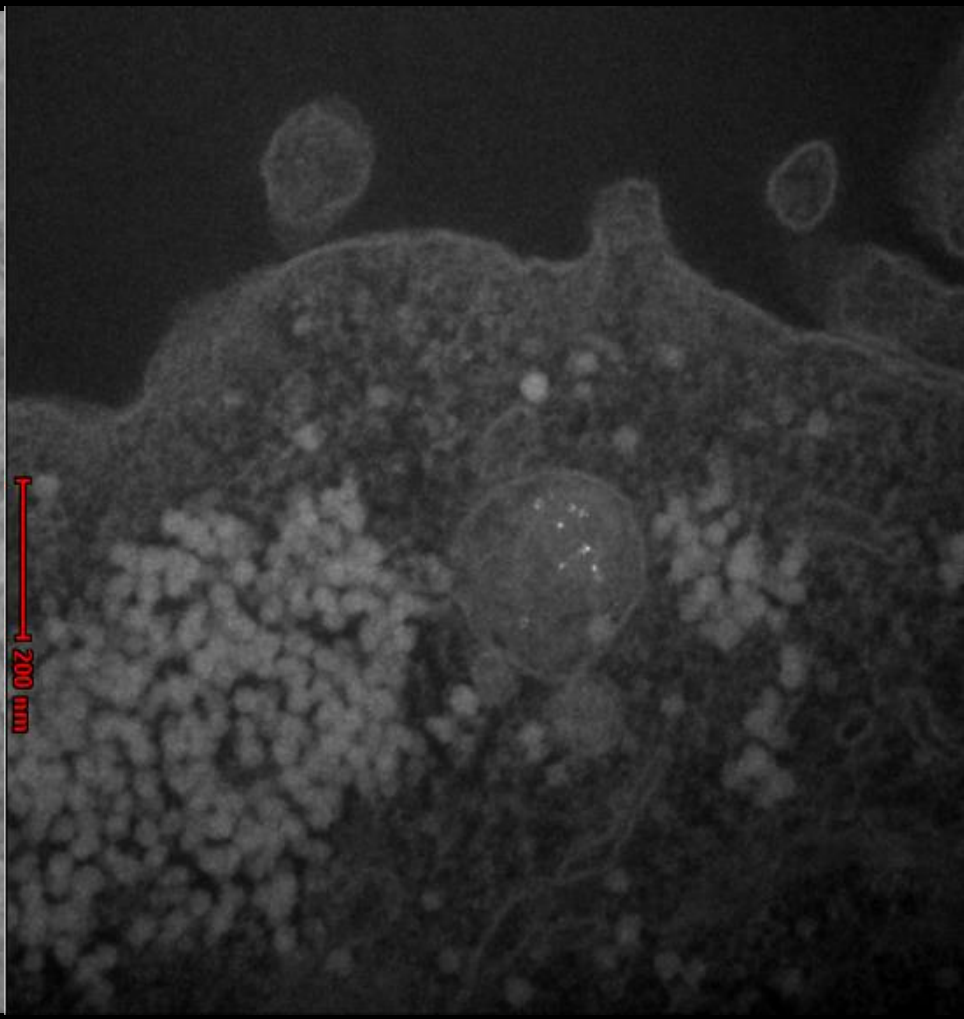
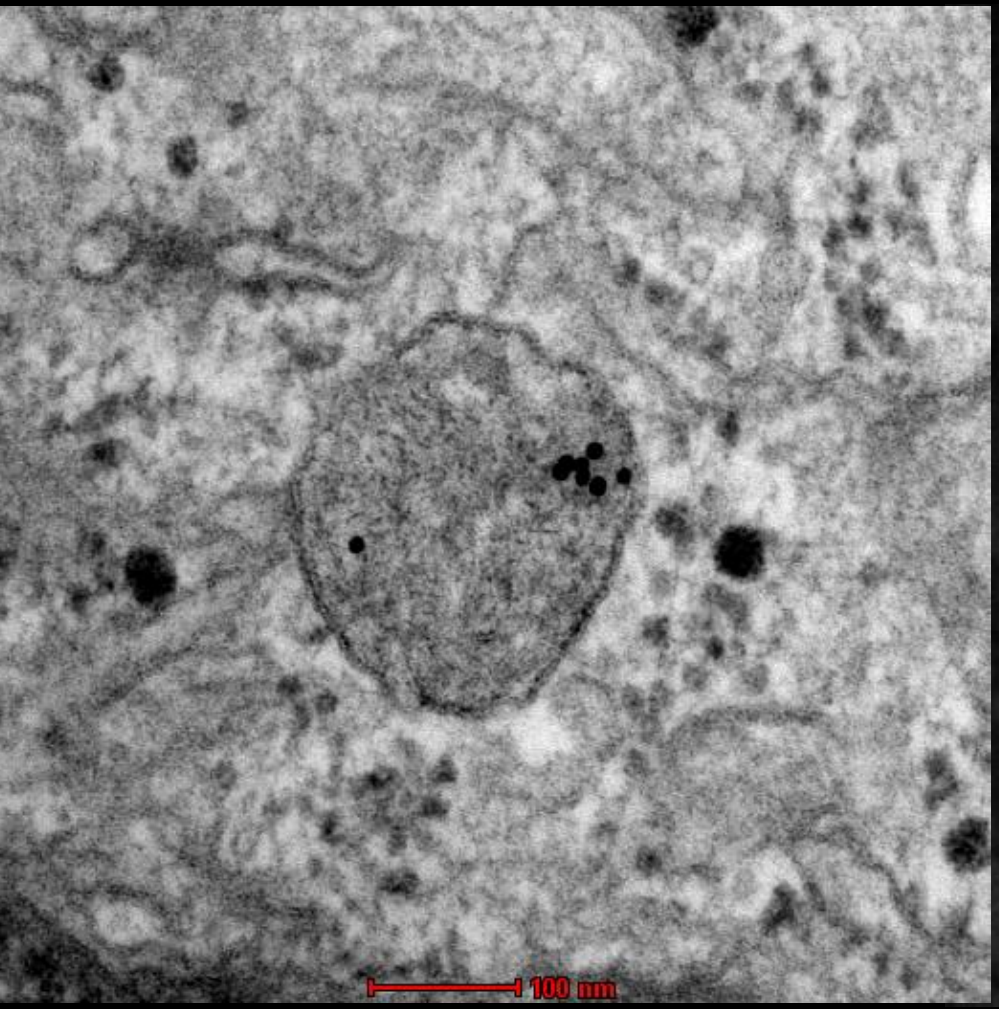
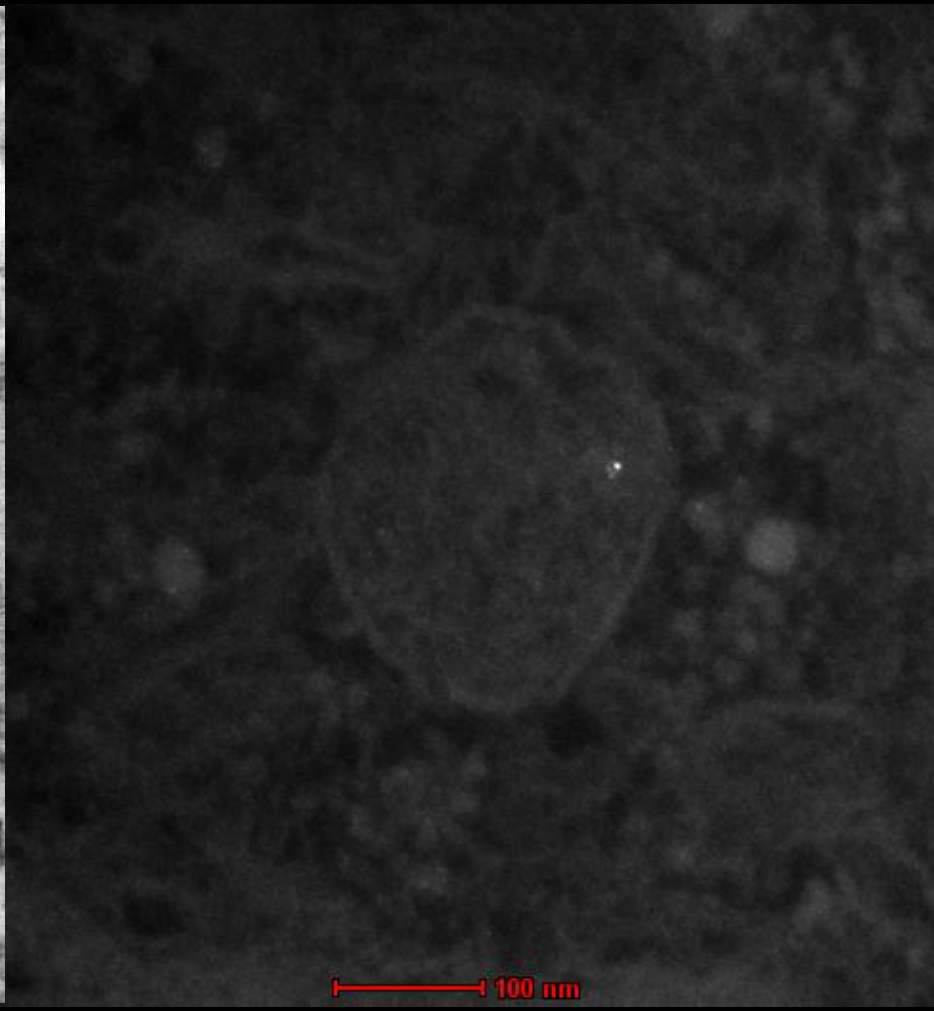


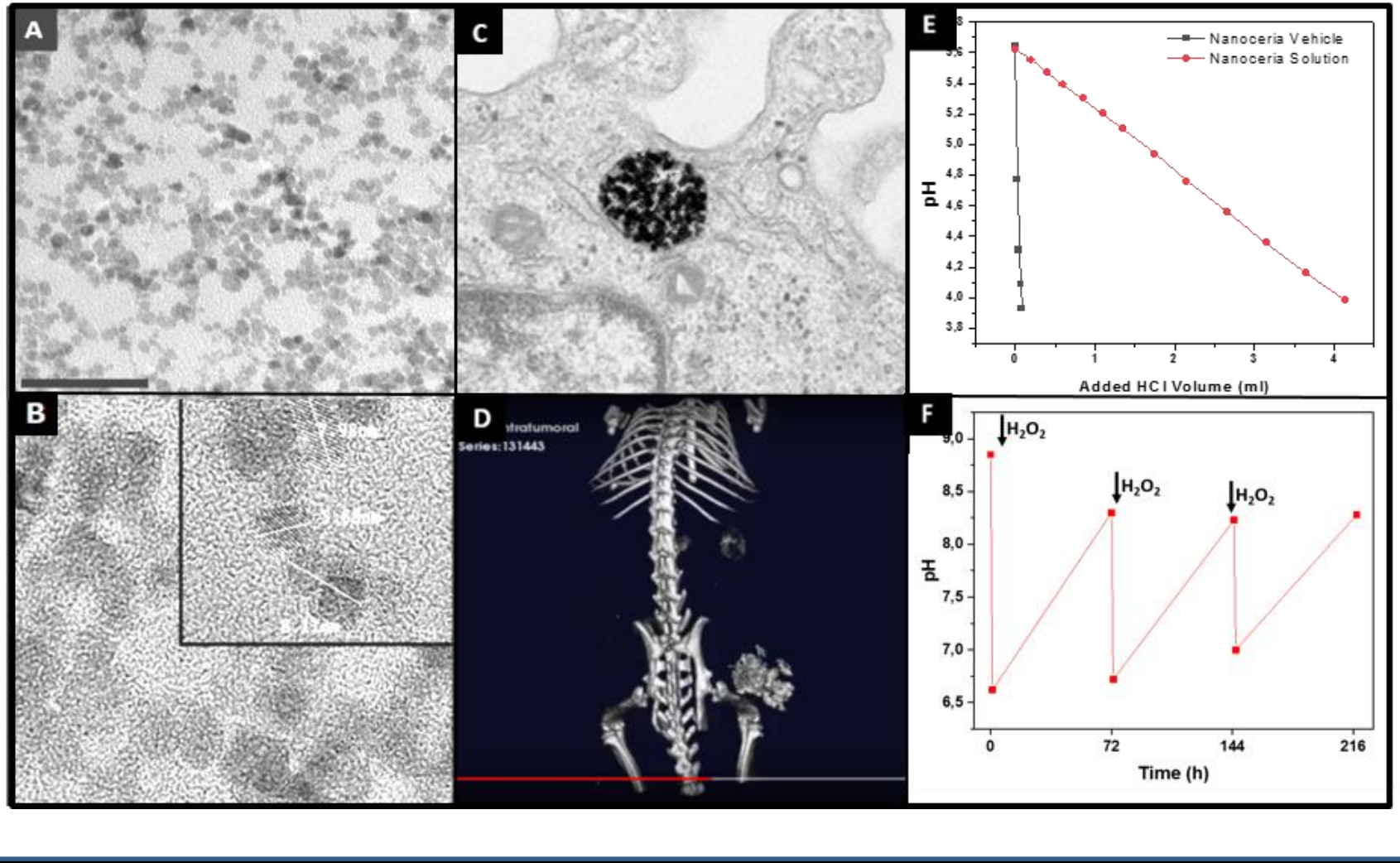


THE CERIASOME

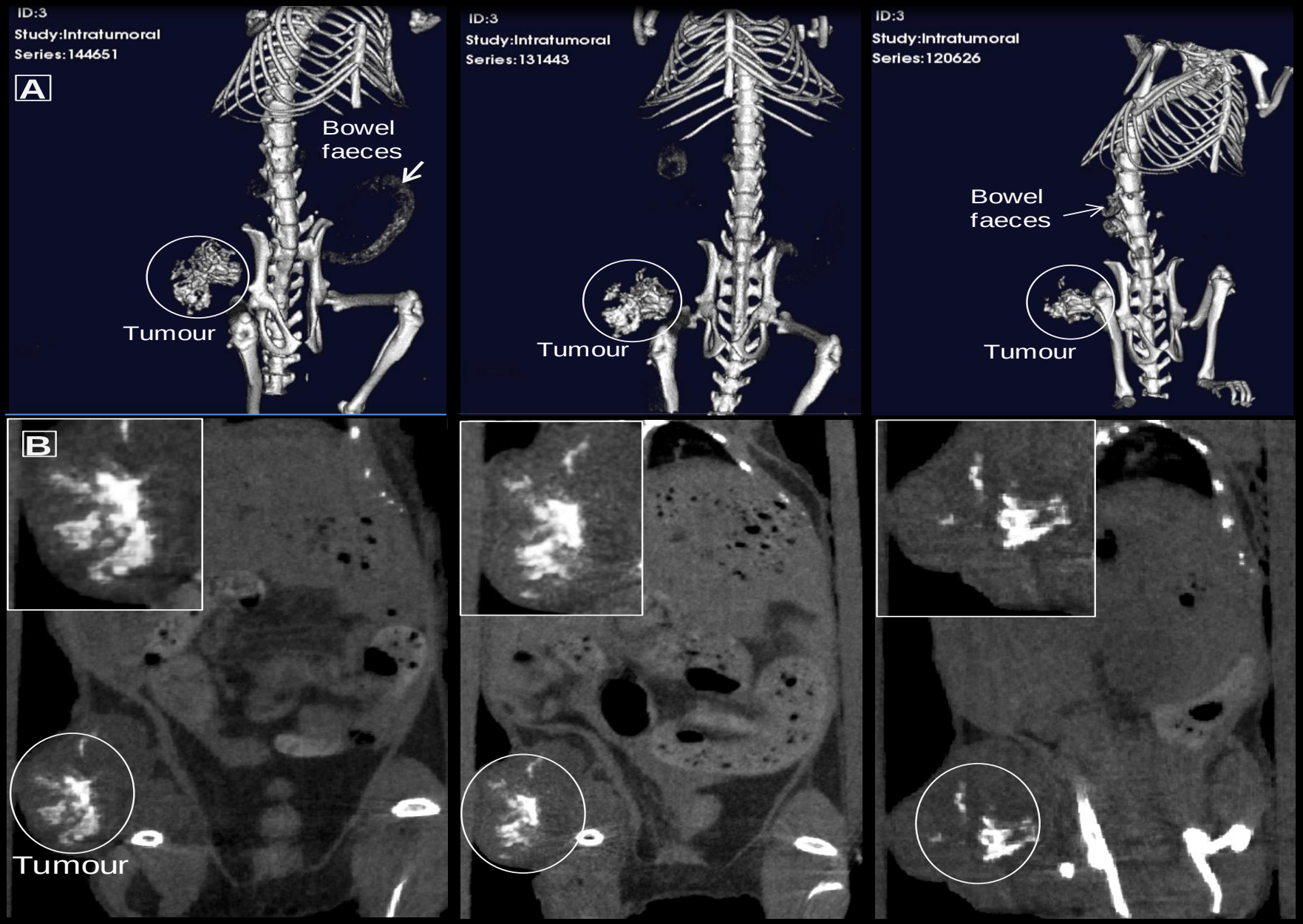




NANOCERIA CHARACTERIZATION



AS X-RAY SAFE CONTRAST AGENT



RESPONSIBLE RESEARCH AND INNOVATION. HOW?

APPLIED NANOPARTICLES
BIOGAS

i.- Anticipation. Safety and sustainability (nanosafety by design)

ii.- Communication with the stakeholders.
Two ways –transforming- dialogue.

iii.- Including stakeholders, consumer associations, worker safety, ecotoxicity

iv.- Creat Nanosafety Experts in our working environment.

v.- Education. “The case of sun screens.”

RESPONSIBLE RESEARCH AND INNOVATION. HOW?

APPLIED NANOPARTICLES

BIOGAS

SUSTAINABILITY. Following the list of 12 Principles of Green Chemistry developed by Paul Anastas and John Warner on 1998, a list of requirements that an ideal "green" or environmentally friendly chemical, process or product would follow or accomplish:

1.- Prevention.
2.- Atom (matter) Economy.
3.- Less Hazardous Chemical Syntheses.
4.- Designing Safer Chemicals.
5.- Safer Solvents and Auxiliaries.
6.-Design for Energy Efficiency.
7.- Use of Renewable Feedstocks.
8.- Reduce Derivatives.
9.- Catalysis.
10.- Design for Degradation.
11.- Real-time analysis for Pollution Prevention.
12.- Inherently Safer Chemistry for Accident Prevention.

TARGET APPLICATIONS:THE FUTURE USE OF NANOCERIA.

Chronic and acute inflammation, from Septic shock to ageing

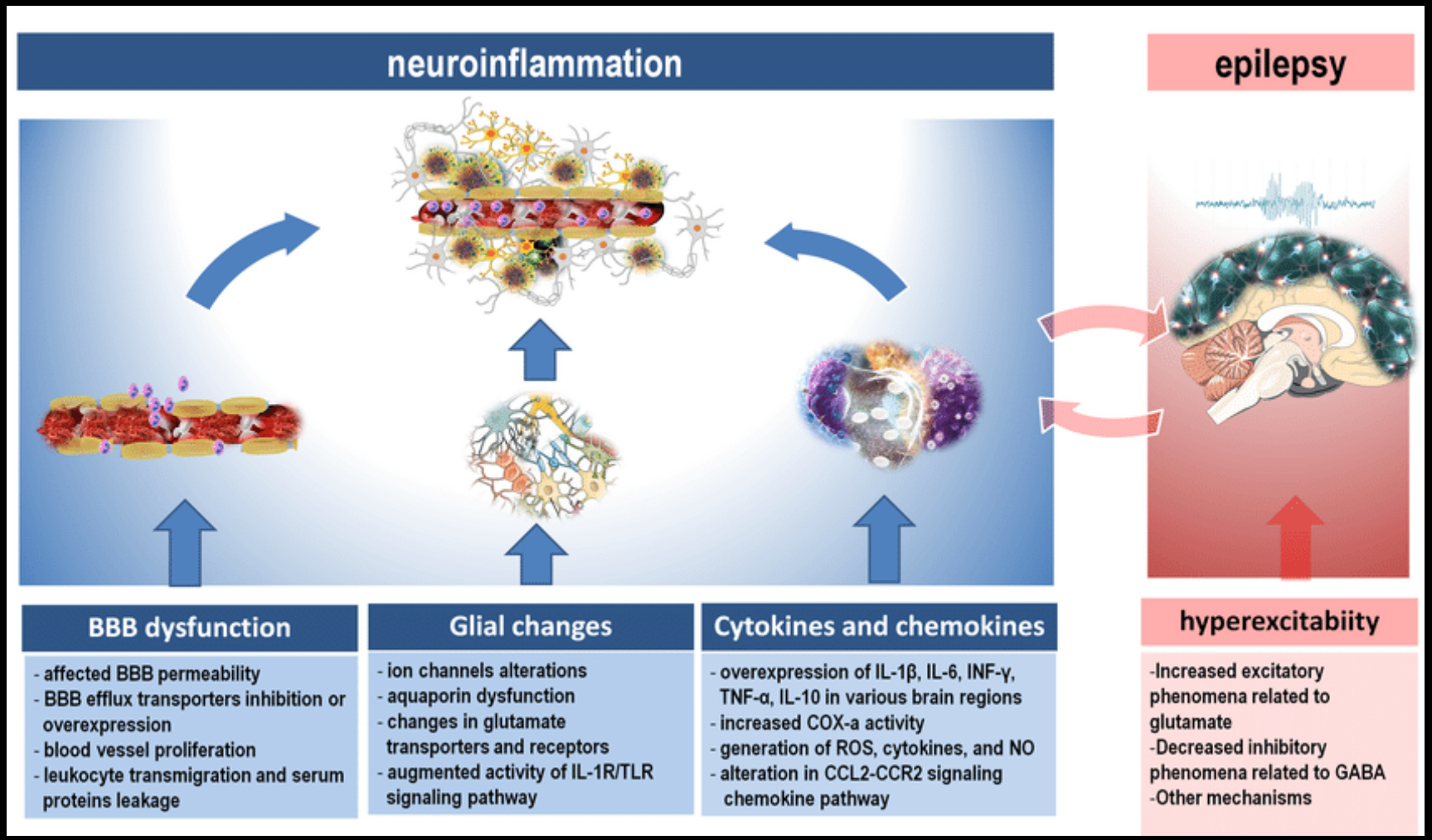
Also it will be interesting in **METABOLIC DISEASES**

The previous theoretical considerations apply well to Cancer where the immune activation is at the origin and the progression of the disease and the warburg effect.

TISSUE REGENERATION, transplants.

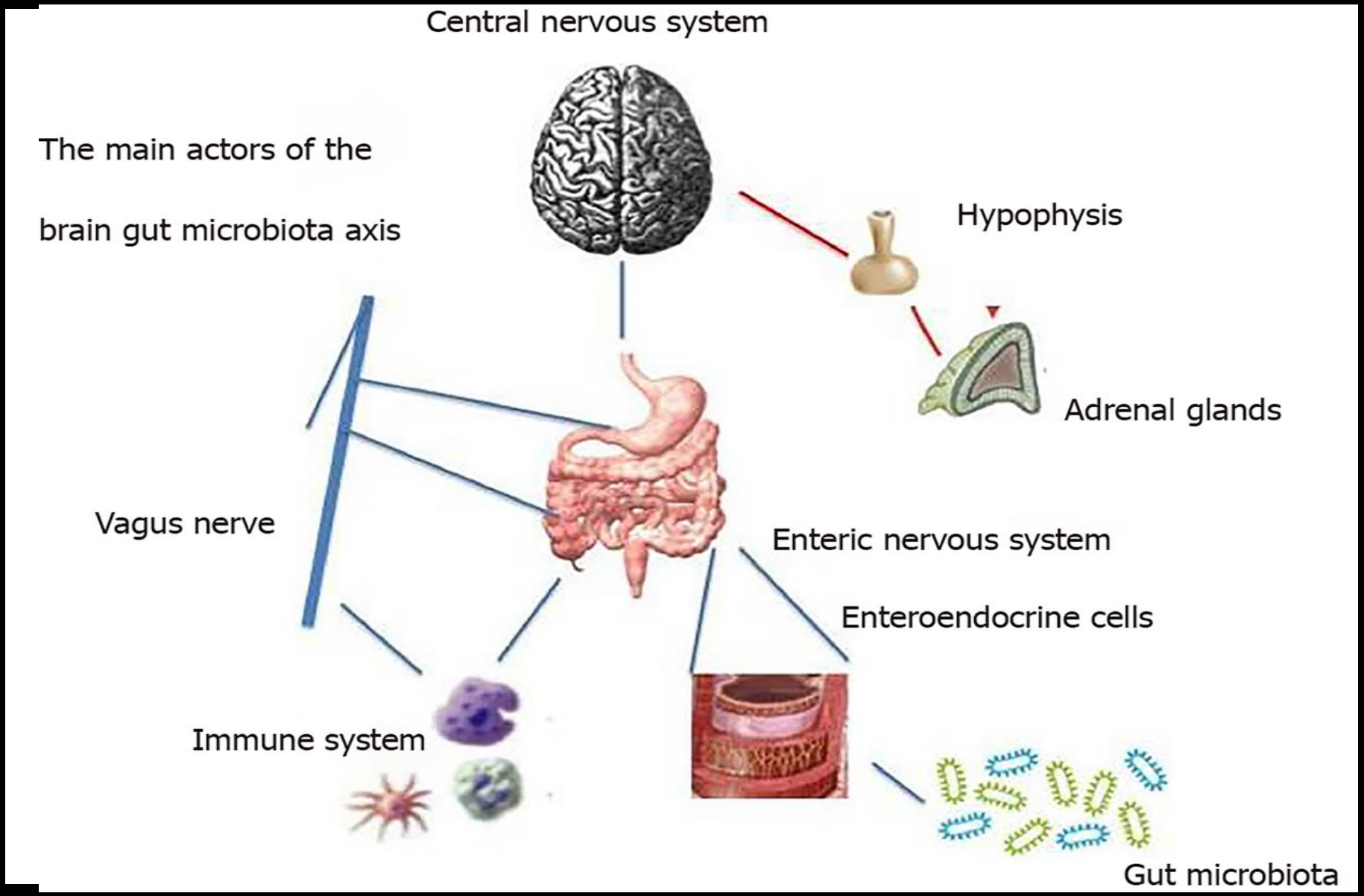
Other disease where nanoceria is showing promising result is in those related to **neuroinflammation and epilepsy.**

HYPEREXCITABILITY AND NEUROINFLAMMATION



https://www.researchgate.net/figure/Contributors-of-neuroinflammation-and-its-relation-with-epileptogenesis_fig1_328689945

THE GUT BRAIN AXIS



CONCLUSIONS

1. Traditionally, nanotechnology has been presented as an adjuvant for drug delivery, radiotherapy, or medical imaging. In this case, it is a new paradigm. It is the nanoparticle itself, thanks to its nanometric form and a high concentration of oxygen vacancies at its surface, the active principle, radically different from the previous pharmacologic antioxidants substances.

2. Nanoceria is a potent anti-inflammatory agent contributing to treating inflammation-related diseases.

3. Cerium is a rare earth element that, in its nano-oxide form, has clear biomedical potential as it is capable to efficiently remove excess ROS in situations of metabolic imbalance, showing biological activities similar to the SOD and catalase enzymes.

4. Ceria is highly soluble; its action is catalytic (does not intervene in the reaction) and does not get consumed.

CONCLUSIONS

5. Its ROS scavenging capacity decreases as the concentration of ROS decreases, becoming inert at healthy homeostatic conditions. Indeed, nanoceria act as a redox buffer: only in the case of an abnormally high concentration of free radicals is nanoceria active. Otherwise, it is rather inert and slowly dissolves at healthy physiological conditions into Ce^{3+} ions which are excreted through the urine in a matter of weeks.

6. The mechanism responsible for these actions is their state of dual oxidation (+3/+4).

7. Nanoceria competing advantages are multifold: It is oxidative-stress selective (only degrades ROS in excess) but not ROS selective (degrades any kind of ROS and free radicals), i.e., it is only active in oxidative stress conditions.

8. As a robust catalyst, it performs well at low doses and for extended periods of time.

9. When adequately formulated (endotoxin-free, stable, soluble), no toxic effects have been observed in vitro or in vivo at applicable doses.

10. All these advantages make us think about new increased population health by controlling metabolism and immune metabolism with severe implications for aging, cancer, and inflammation.


THANKS
2 µm