Beyond drug delivery: bioactive nanoceria targets lipid inflammation to overcome cancer resistance

Francesca Corsi[1,2], S. Briganti[3], A. Pelliccia[1,4], G. Deidda Tarquini[1,2], M. Urbani[2,4], F. Torino[1], C. Montesano[4], E. Traversa[2], L. Ghibelli[4]

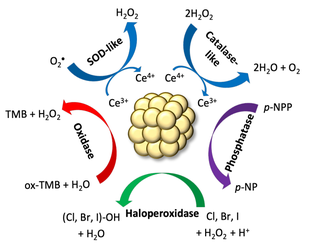
[1] Dept. Chemical Science and Technologies, University of Rome "Tor Vergata", Rome, Italy; [2] Fondazione PTV – Policlinico Tor Vergata, Rome, Italy;
[3] Laboratory of Skin Pathophysiology, IRCCS Istituti Fisioterapici Ospitalieri, Rome, Italy; [4] Dept. Biology, University of Rome "Tor Vergata", Rome, Italy.

francesca.corsi@uniroma2.it

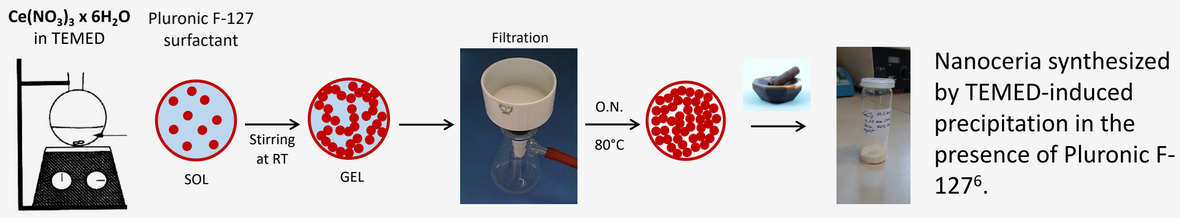
BACKGROUND

The prevailing paradigm in nanomedicine has largely framed nanoparticles as carriers for the targeted delivery of molecular drugs. In contrast, the intrinsic therapeutic activity of nanomaterials, central to the emerging concept of nanotherapeutics, remains comparatively underexplored. **At the nanoscale, metal oxides can acquire unconventional enzyme-like functions, acting as nanozymes**, thereby **opening new avenues for therapeutic intervention[1]**.

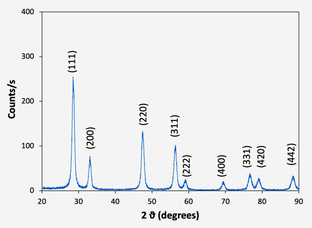
Cerium oxide nanoparticles (**nanoceria**) emerge as **biocompatible antioxidant, anti-inflammatory and anticancer nanozymes[2,3]**. Their Ce^{3+}/Ce^{4+} surface redox cycling underlies SOD/catalase-mimetic activities, protecting cells and organisms from oxidative stress. However, growing evidence indicates that nanoceria also **catalyze non-redox reactions**, **revealing a broader potential beyond ROS regulation[4,5]**.



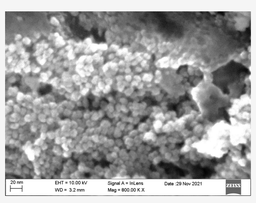
(1) Materials Synthesis and Characterization



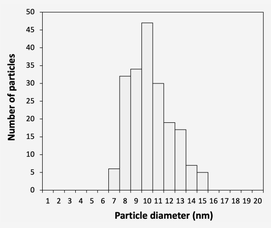
Nanoceria synthesized by TEMED-induced precipitation in the presence of Pluronic F-127[6].



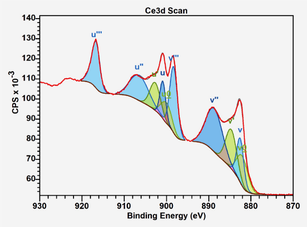
XRD pattern of nanoceria with the corresponding Miller indices



FE-SEM image of nanoceria



Size distribution of nanoceria determined by SEM analysis

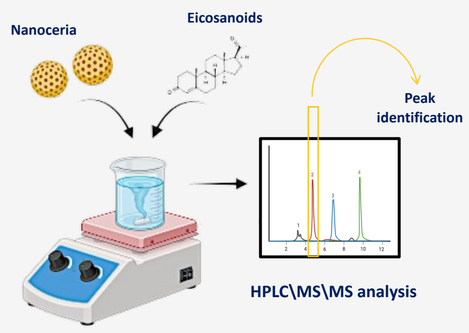


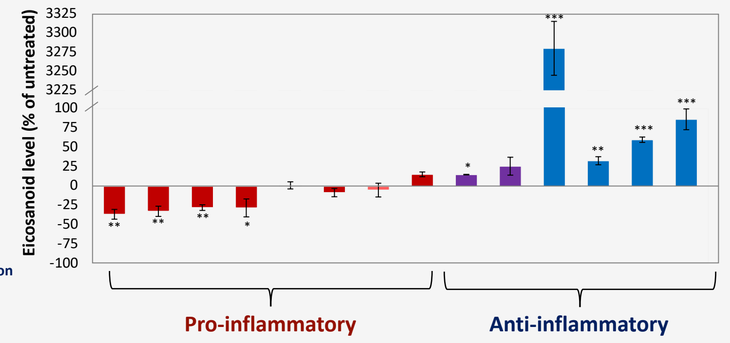
Ce 3d XPS spectrum of nanoceria

Crystallite size (nm)	Particle size (nm)	Particle Morphology	Ce^{3+} (%)	Ce^{4+} (%)	Z-average (nm)	Polydispersity Index	ζ-potential (mV)
11	7 - 15	Quasi-spherical	32	68	106	0.27	+ 46.3

(2) A New Nanozymatic Activity of Nanoceria

Incubation of nanoceria with arachidonic acid-derived lipid mediators in a controlled environment for 24 h

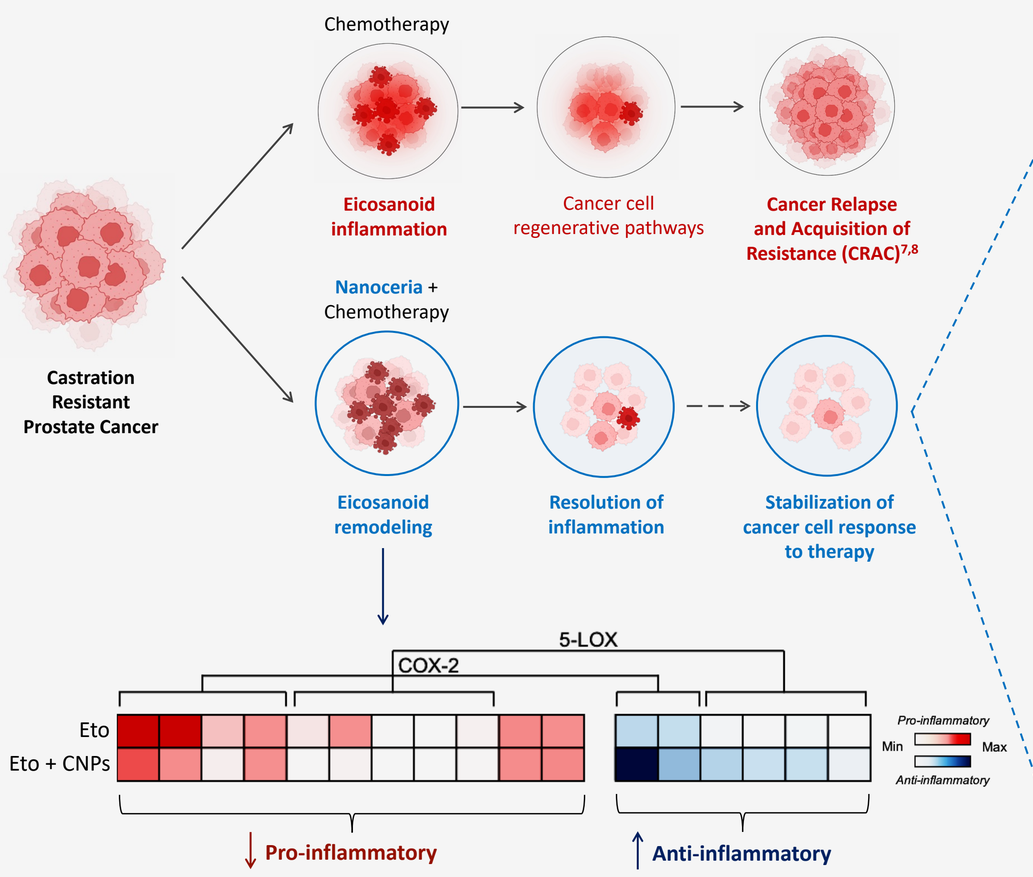




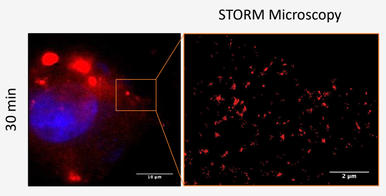
Nanoceria catalyze the conversion of pro-inflammatory (tumorigenic) eicosanoids into pro-resolving (anticancer) lipid mediators

Could this new catalytic activity be exploited to sensitize cancer cells to therapy?

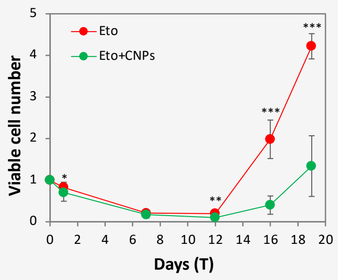
(3) Chemo-sensitizing Effect of Nanoceria on Castration Resistant Prostate Cancer Cells



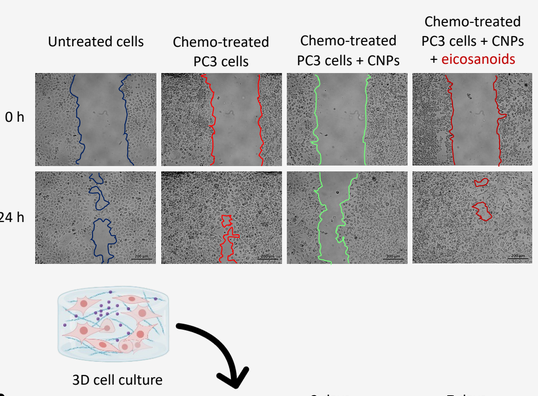
A single treatment with nanoceria abates chemotherapy (etoposide)-induced release of pro-inflammatory eicosanoids (red) and increases that of anti-inflammatory eicosanoids (blue)



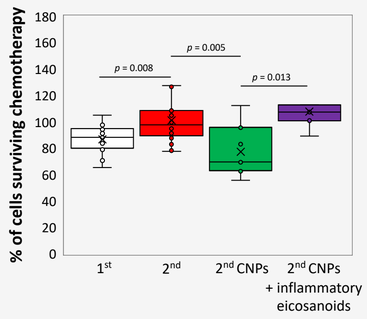
Nanoceria enter PC3 prostate cancer cells forming nanoclusters



Nanoceria reduce post-therapy cancer cell repopulation

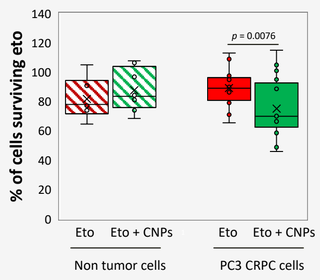


Nanoceria block post-therapy epithelial-to-mesenchymal transition and restrain cancer cell motility and invasion in 3D extracellular matrix



Nanoceria abrogate etoposide-induced resistance through the depletion of inflammatory eicosanoids

But protect non-tumor cells from chemotoxicity



Nanoceria sensitize selectively cancer cells

TAKE HOME MESSAGES

TEMED-induced precipitation yielded 7-15 nm, biocompatible **cerium oxide nanoparticles** able to:

- **Sensitize cancer cells** to chemotherapy by **catalytically redirecting** their dysregulated **lipid metabolism toward an anticancer, anti-inflammatory state** through an unprecedented non-redox mechanism.
- **Protect non-tumor cells** from chemotherapy-induced damage through a redox mechanism

Nanoceria may represent an unprecedented pharmacological tool to achieve a CRAC-free chemotherapy, combining durable and stable cancer remission with normal tissue protection.

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