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XXXII Cycle

Study of a new ultrasound-based device in combination with smart nanoparticles for the treatment of cancer

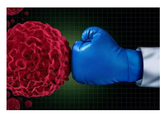
Luisa Racca

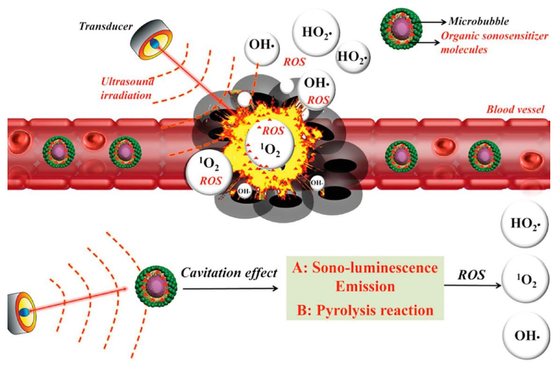
Supervisors: Prof. V. Cauda and Prof. F. C. Pirri

Research context and motivation

Cancer incidence is expected to increase wordwide, staining resources even in countries with advaced healthcare systems. Traditional approaches are associated with severe side effects, poor selectivity and the develop of multidrug resistances.

Request of new therapeutic strategies

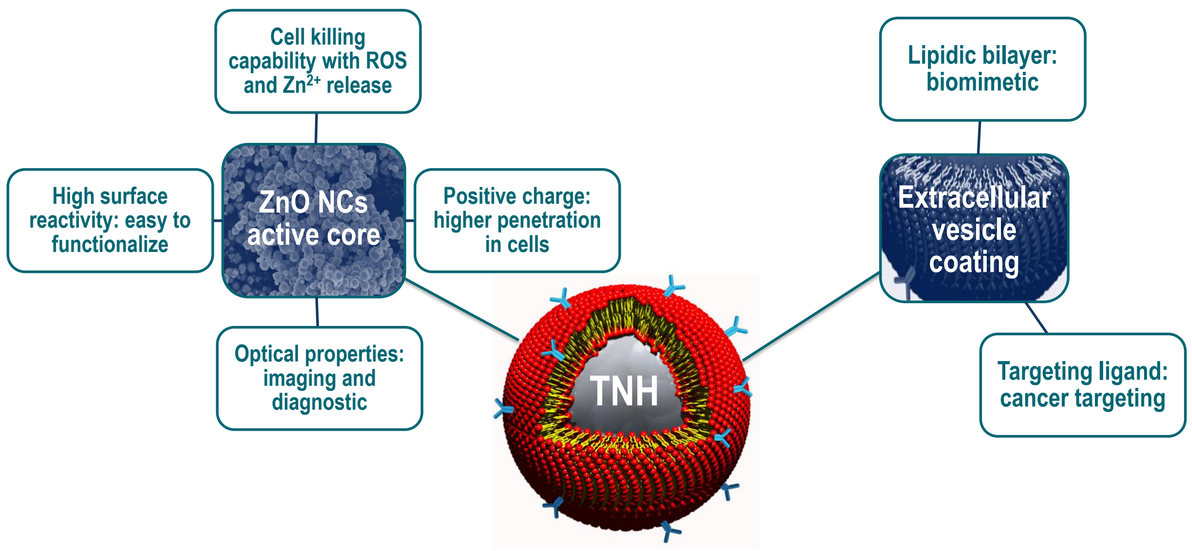




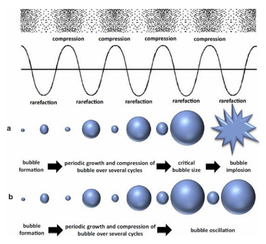
The idea of the **multimodal approach:** conjugate two different stimuli in order to maximize their effects and obtain complete tumor ablation.

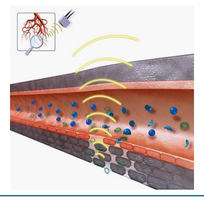
Addressed research questions/problems

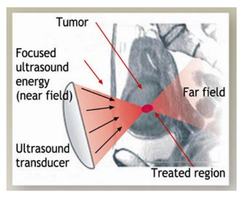
The TrojanNanoHorse (TNH) project

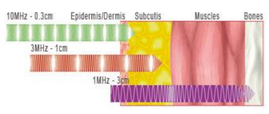


Remotely activated by









Cell killing with mechanical and thermal effects

High selectivity

US

Sonoporation: increase uptake

Deeper tissue penetration

Submitted and published works

Papers

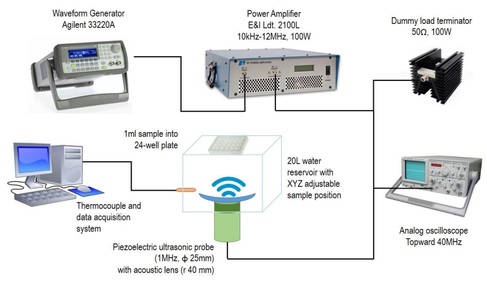
- **Racca L.**, Dumontel B., Miccoli B., Canta M., Serpe L., Canaparo R., Di Benedetto C., Falqui A., Cauda V., *Investigation of cytotoxic effects of different ZnO nanostructures on living cancer cells*, In: 16th edition of the Merck Young Chemists Symposium, Rimini, 25-27th October, 2016, pp. 158 [ISBN: 978-88-86208-92-5].
- Dumontel B., Canta M., Engelke H., Chiodoni A., **Racca L.**, Ancona A., Limongi T., Canavese G., Cauda V., *Enhanced Biostability and Cellular Uptake of Zinc Oxide Nanocrystals Shielded with Phospholipid Bilayer*. J. Mater. Chem B, Vol 5, 2017, pp. 8799-8813
- Canavese G., Ancona A., **Racca L.**, Canta M., Dumontel B., Barbaresco F., Limongi T., Cauda V., *Nanoparticle-assisted ultrasound: A special focus on sonodynamic therapy against cancer*, The Chemical Engineering Journal, Vol 340, 2018, pp. 155-172
- **Racca L.**, Canta M., Dumontel B., Ancona A., Limongi T., Garino N., Laurenti M., Canavese G., Cauda V., *Zinc Oxide Nanostructures in biomedicine*, in: Ciofani G. Micro and Nano Technologies, Smart Nanoparticles for biomedicine, Elsevier,, 2018, pp. 171-187
- Garino N., Limongi T., Dumontel B., Canta M., **Racca L.**, Laurenti M., Castellino M., Casu A., Falqui A. and Cauda V. *A Microwave-Assisted Synthesis of Zinc Oxide Nanocrystals Finely Tuned for Biological Applications*, Nanomaterials 2019, 9(2), 212; DOI: 10.3390/nano9020212
- Limongi T. Canta M., **Racca L.**, Ancona A., Vighetto V., Tritta S and Cauda V. *Improving dispersal of therapeutic nanoparticles in the human body*, Nanomedicine, Vol 14, n.7, 2019, doi: 10.2217/nnm-2019-0070.

Patents

- "Biomimetic Non-Immunogenic Nanoassembly for the Antitumor Therapy" (Original title:"Nanocostrutto Biomimetico Non Immunogenico per la Terapia Antitumorale") Italian Patent N. 102017000129243 of 13th Nov. 2017, Inventors: Cauda V., Canavese G., Limongi T., Garino N., Laurenti M., Dumontel B., Canta M., **Racca L.**, Ancona A.
- "Sonosensitizing agent and its method of activation" (Original title:"Agente sonosensibilizzante e suo metodo di attivazione") application n.P3008IT00, Inventors: Cauda V., Cicero G., Canavese G., Limongi T., Garino N., **Racca L.**, Ancona A., Dumontel B., Canta M., Serpe L., Canaparo R., Foglietta F., Francovich A., Durando G., *pending evaluation.*
- "A biomimetic nanoporous carrier comprising an inhibitor directed towards the native form of IDH2 protein" (Original title: "Vettore nanoporoso biomimetico comprendente un inibitore diretto verso la forma nativa della proteina IDH2" Italian Patent N. IT102019000001009 of 23rd January 2019, Inventors: Cauda V., Limongi T., **Racca L.**, Canta M., Susa F., Piva R., Bergaggio E., Vitale N., Mereu E.

Novel contributions

Comparisons of the bio-effects of three different US devides



Customized home-made device

Lipozero G39 (Globus)

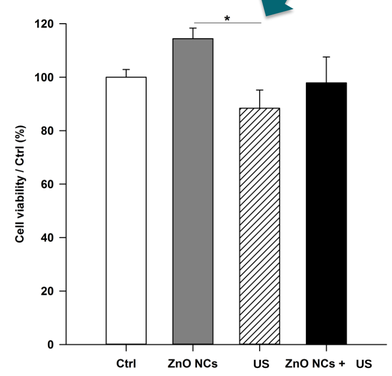
PiezoWave 2 (Richard Wolf)

Adopted methodologies

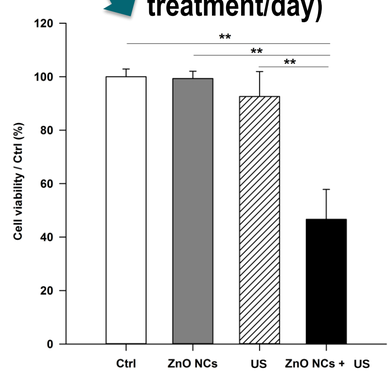
- Cell line: KB cells – cervix adenocarcinoma cell line.
- ZnO NCs biocompatibility: cytotoxicity evaluation with the WST-1 and the Trypan Blue assay. Cell internalization with cytofluorimetric assay and TEM imaging.
- US biocompatibility: cytotoxicity evaluation with the WST-1 and the Trypan Blue assay. Comparing three US setups changing various parameters: acoustic pressure expressed ad Peak Positive Pressure (PPP) (Mpa), duty cycle (DC), time of exposure, **single and multiple treatments.** Investigation on the synergistic effects of ZnO NCs and US.
- Investigation on the mechanism of the synergistic effect: ROS scavenging assays (N-acetyl-cysteine, Mannitol), real time evaluation of apoptosis and necrosis (RealTime Annexin V Apoptosis and Necrosis Assay).
- TNH building, cytotoxicity evaluation with the WST-1 assay. Cell internalization with cytofluorimetric assay

Investigating a possible synergistic effect of ZnO NCs and US: single toward multiple treatments with the same parameters.

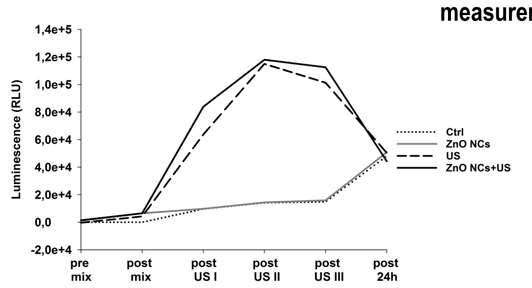
SINGLE | **MULTIPLE (3 treatment/day)**

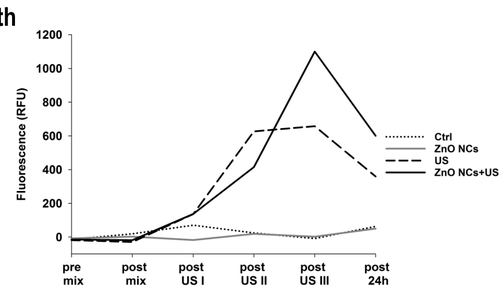


US: Piezowave, US PPP 50.3 Mpa, 500 shots, 4 shots/s



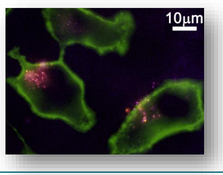
Investigating the mechanism: Real-time kinetic measurement of cell death





At least three US treatments are required to achieve a synergic effect between ZnO NCs and US!

Now ready for TNH + US investigations!



Future work

- TNH constituted by ZnO NCs and B lymphocytes extracellular vesicles building, cytotoxicity and internalization assays in lymphoma cancer cells
- Evaluate TNH in combination with US treatment in cancer cells.
- Improve the customized setup: add a specific automatic adjustable XYZ position controller

List of attended classes

- 01LXBRW - Life Cycle Assessment (LCA) (03/07/2017, 5 cfu)
- 01NUWKI - Chimica-fisica dei materiali per le nanotecnologie (16/02/2018, 7 cfu)
- 01QORRV - Writing Scientific Papers in English (08/06/2017, 3 cfu)
- 01QQXRW - Descrizione modellistica dei meccanismi ambientali nell'ambito dell'LCIA (25/07/2017, 4 cfu)
- 01QZTRR - Progettazione di dispositivi medici per la chirurgia (20/07/2017, 4 cfu)
- 01REIRR – Terapie avanzate (nanomedicina, terapia genica e cellulare) in chirurgia (29/06/2018, 4 cfu)
- 02LWHRP - Communication (19/9/2017, 1 cfu)
- 03LCLRO - Epistemologia della macchina (05/04/2017, 4 cfu)

POLITECNICO DI TORINO

PhD program in
Electrical, Electronics and Communications Engineering