**Part 1 Final publishable summary report**

The health sector is one of the most promising areas for nanotechnology applications. Nanoparticles are already widely used for medical diagnostics and therapeutics, notably for in vitro diagnostic tests and new imaging tools. Metallic and magnetic nanoparticles occupy a prominent place among these multipotent nanosystems, especially for the development of anticancer nanotherapies. Indeed, when excited by a remote energy source, these nanoparticles generate physical effects such as heat, which can destroy cancer cells without damaging healthy tissues.

The project DUALNANOTHER was designed to study and understand the mechanisms of hyperthermic cancer therapies based on the activation of nanomaterials embedded within tumor cells. The originality of the approach lies in the combination of in-depth physical studies (magnetic, optical) of nanomaterials in biological media with fundamental investigations of the intracellular environment and in vivo studies in small animals.

The main objectives of the project lay in its originality and multidisplinarity by testing the therapeutic potential of nanomaterials in their intended biological environment, while at the same time exploring new therapeutic modalities. The aim of the project has been focused on two main issues:

1) The influence of magnetic or plasmonic nanoparticle confinement inside cells on heat generating potential: when nanomaterials are uptaken by cells in endosomal compartments, their local organization is modified, and thus, their heating response. While the heating efficiency of magnetic nanoparticles systematically decreases[1, 2] in cellular conditions, cell internalization in plasmonic nanoparticles (gold nanostars)[3] can either increase or decrease the photothermal efficiency depending on size and laser excitation.

2. Therapeutic synergism between magnetic and optical hyperthermia, with a view to combined therapy, and their cumulative efficacy in solution, in vitro cell models, and in vivo tumor models: the simultaneous application of magnetic hyperthermia (MHT) and photothermia (PTT) in innovative magneto-plasmonic platforms[4] and in iron oxide nanocubes[1] allows to efficiently increase the local delivered heating at very low therapeutic doses and overcoming the poor magnetic heating efficiency in cells. The application of dual treatment using iron oxide nanocubes totally eradicated solid tumors in mice[1] (Figure 1).

DUALNANOTHER project results aim to contribute to the understanding of physical mechanisms associated to nanoparticle-based treatments in order to improve their efficacy though the optimization and synergistic combination of cancer therapeutic modalities. These actions can lead to reduction of nanomaterial concentration and administered doses with a positive impact in the patient's healing and comfort.

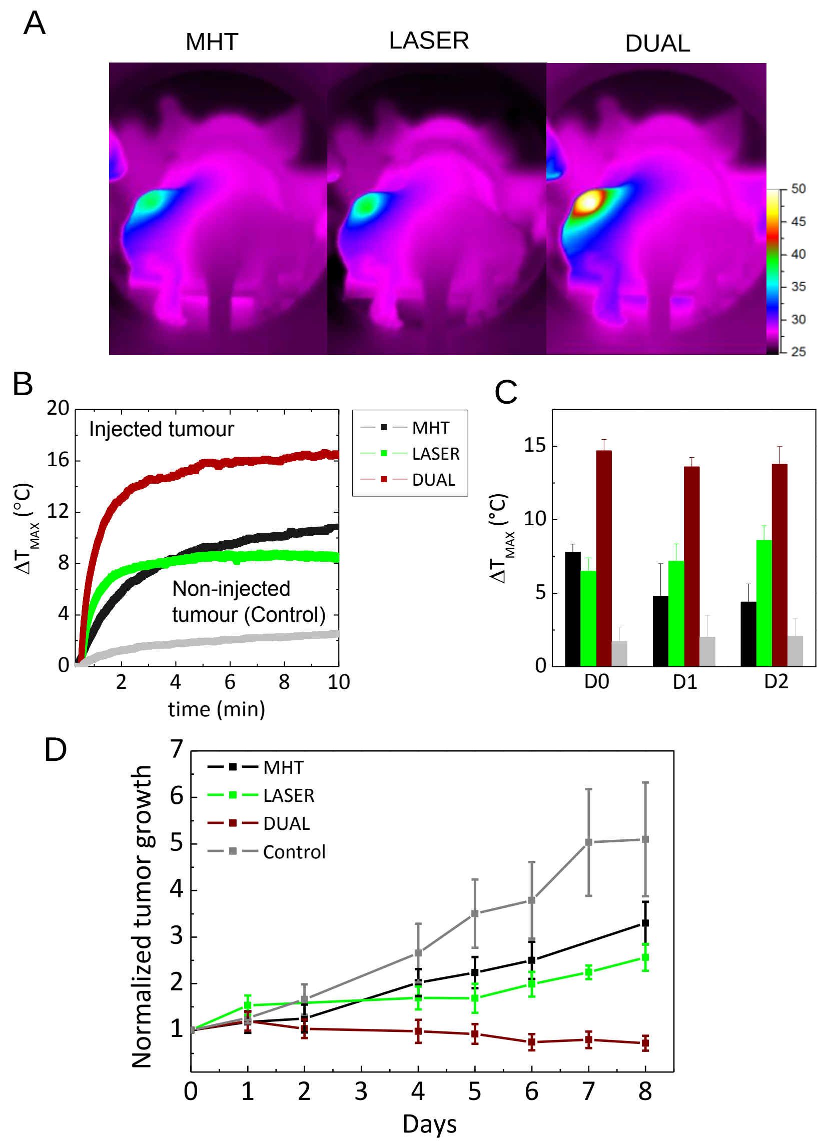


Figure 1. In vivo heat therapy. (A) Thermal images obtained with the IR camera in mice, after intratumoral injection of nanocubes and after 10 min application of magnetic hyperthermia (MHT, 110 kHz, 12 mT), NIR-laser irradiation (LASER, 808 nm at 0.3 W/cm2), or DUAL (both effects). (B) Thermal elevation curves for all treatments and for the noninjected tumor in the DUAL condition. (C) Average final temperature increase obtained on day 0 (1h after injection) and one and two days after injection for non-injected tumors; and (D) average tumor growth in nanocube-injected mice.

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3. Espinosa, A.; Silva, A. K.; Sánchez-Iglesias, A.; Grzelczak, M.; Péchoux, C.; Desboeufs, K.; Liz-Marzán, L. M.; Wilhelm, C. Cancer Cell Internalization of Gold Nanostars Impacts Their Photothermal Efficiency in Vitro and in Vivo: Toward a Plasmonic Thermal Fingerprint in Tumoral Environment. *Advanced Healthcare Materials* **2016**, 5, 1040-1048.

4. Espinosa, A.; Bugnet, M.; Radke, G.; Neveu, S.; Botton, G.; Wilhelm, C.; Abou-Hassan, A. Can Magneto-Plasmonic Nanohybrids Efficiently Combine Photothermia with Magnetic Hyperthermia? *Nanoscale* **2015**, 7, 18872-18877.