# An *In vivo* Study On Cobalt Ferrite Nanoparticles As Multi-Modal Cancer Therapy Combining Intrinsic Toxicity and Hyperthermia

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Magnetic nanoparticles under alternating magnetic field can convert the electromagnetic energy into thermal energy which, in turn can be exploited for hyperthermia (HT) therapy[1]. Besides Iron Oxide nanoparticles (IONPs) which are commonly used as heat hubs in magnetic hyperthermia, mixed ferrites of these IONPs with Manganese (Mn), Cobalt (Co) or Zinc (Zn) ions are also promising candidates for such magnetic HT treatment due to their improved magnetic properties. Cobalt ferrite nanocubes have shown very high specific adsorption rate (SAR) values (a measure of their heat performances) at clinically acceptable frequency and field conditions [2]. However, the use of Co-based nanoparticles for biomedical applications is still under debate. There are numerous evidences of intrinsic toxicity of $CoFe_2O_4$ NPs in cellular studies, with a toxicity profile being highly dependent on the cell types and concentration tested[3]. Due to the proven cytotoxicity, not much exploration has been made on cobalt-based nanoparticles in in-vivo conditions. We synthesized 17nm cobalt ferrite nanocubes by thermal decomposition method, which showed improved SAR values at lower field and frequency conditions compared to standard IONPs of similar size and shape[2]. Here, on a xenograft murine mice model, we demonstrate the synergic effects of cobalt ferrite nanocubes as magnetic hyperthermia inducing agents and intrinsic toxic agent with controlled Co ion release. The intra-tumoral injection gave us the control, by specifically inducing toxicity only at to tumor mass, avoiding uncontrolled toxicity to other vital organs. The animals treated with the combination of cobalt-ferrite injection and magnetic hyperthermia showed complete reduction in tumor volume as compared to untreated control and other groups studied (without HT, IONPs with and without HT). Furthermore, the same group showed the longest survival of up to 200 days post treatment. The survived animals showed no signs of distress throughout the study. Histopathological, TEM and elemental analysis were performed on tumor and organs such as kidney, liver and spleen to study in detail the fate of these nanoparticles in vivo. With the results obtained in our study, we demonstrated that the intrinsic toxicity of the Co ions in the cobalt ferrite nanocubes, when exploited in a controlled environment, can replace the usage of other chemotherapeutic drugs and act as a self-standing multi-modal therapy, all working under lower dosage and acceptable hyperthermia limits.

## References

[1] Klaus Maier-Hauff et al., Journal of Neuro-Oncology, 2007, 81 (1), pp 53–60.
[2] Ayyappan Sathya et al., *Chem. Mater.*, 2016, 28 (6), pp 1769–1780.
[3] Limor Horev-Azaria et al., *Particle and Fibre Toxicology* 2013, 10:32.

## Figures

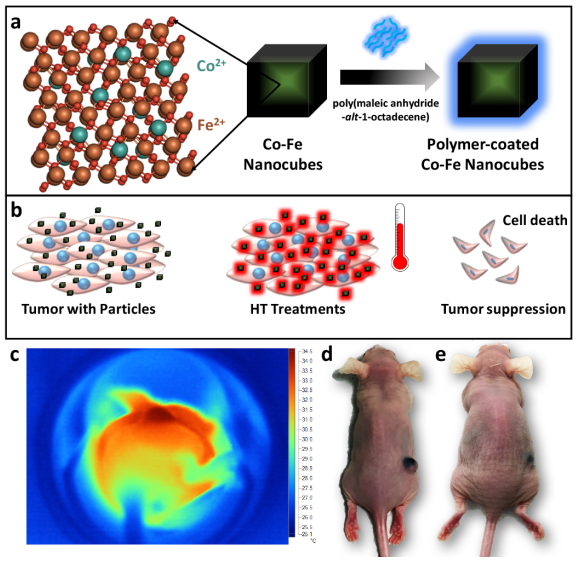


**Figure 1. Schematic representation of preparation of cobalt ferrite NPs for biomedical application (a) and their function as HT inducing agents (b). IR image of animal injected with Cobalt ferrite and subjected to HT(c). Image of animal before and after treatment.**