

In addition, the cytotoxicity and biodegradability of magnetic hydrogels and the long-term fate of embedded MNPs *in vivo* also need to be considered. Even though there are no universal criteria to predict this important aspect of magnetic hydrogels due to their different physicochemical properties, two steps should take place during the clearance of the embedded MNPs, they include:

1. The release of MNPs embedded in hydrogels can be achieved as the hydrogels biodegrade and the cells secrete their own ECM (Xu et al. 2012).
2. The elimination of MNPs out of the body is also required.

Up to now there is little knowledge or discussion on the effect of nanoparticles on organs such as the liver, kidneys, spleen, etc. However, one can speculate that as long as there is translocation to and accumulation of nanoparticles in these organs, potentially adverse reactions and cytotoxicity may lead to disease. For instance, particle debris has been found in the liver of patients with worn orthopedic prosthesis (Milosev et al. 2006) and the injection of magnetic nanoparticles smaller than 100 nm into the tongue and facial muscles of mice resulted in synaptic uptake (Oberdörster et al. 2005). Therefore nanoparticles used by themselves or as crosslinkers of polymers, exploited as beneficial to destroy cancer cells may cause harmful effects elsewhere in the body.

The United States Food and Drug Administration (FDA) has approved the use of MNPs in several clinical applications such as the magnetic resonance imaging (MRI), and these should be rapidly eliminated through the known pathways for Fe metabolism by the reticuloendothelial system (RES), particularly by the liver (LaConte et al. 2005). However, further studies of the biodistribution and elimination of metallic and bimetallic MNPs *in vivo* are needed for more clinical applications. In the case of magnetic hydrogels with MNP as crosslinkers, the MNP will never be found naked but they will appear more frequently wrapped by pieces of polymers, which have not undergone a complete degradation. Thus the process becomes more complicated to study. Surface coatings can render noxious particles nontoxic, while less harmful particles can be made highly toxic. Nickel-ferrite particles, with and without surface oleic acid, show different cytotoxicity (Yin et al. 2005). Spherical gold nanoparticles with various surface coatings are not toxic to human cells, despite the fact that they are internalized (Connor et al. 2005; Goodman et al. 2004). Quantum dots of CdSe can be rendered nontoxic when appropriately coated (Derfus et al. 2004).

The viability and functions of various cell types (stromal cells such as fibroblasts and potential target cells such as endothelial or tumor cells) in the presence of the MNP hybrid hydrogels and the *in vivo* biocompatibility of the hydrogels when implanted subcutaneously in mice were studied, considering the potential use of delivery system for antitumor and vascular targeting drugs (Finetti et al. Unpublished results). On the whole, the results for CMC gel alone, CMC gel + Fe<sub>3</sub>O<sub>4</sub> NPs (50%), CMC gel + CoFe<sub>2</sub>O<sub>4</sub> NPs (50%) and CMC gel + CoFe<sub>2</sub>O<sub>4</sub> NPs (70%), documented a high biocompatibility of the biomaterials tested with the appearance of toxic effect only by gels containing the higher concentration of nanoparticles which, at the end of the incubation, were retrieved attached on and inside the cells (Fig. 24). In addition tumour cells were shown to be more sensitive, when compared to the other cell lines, to higher concentrations of NPs, thus indicating a potential selective effect toward cancer cells. In the subcutaneous implants (0.5 mg/sample) all the biomaterials were well tolerated.