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TRACKING THE *IN VIVO* RELEASE OF BIOACTIVE NRG FROM PLGA AND PEG-PLGA MICROPARTICLES IN INFARCTED HEARTS

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ABSTRACT:
The growth factor neuregulin (NRG) is one of the most promising candidates in protein therapy as potential treatment for myocardial infarction (MI). In the last few years, biomaterial based delivery systems, such as polymeric microparticles (MPs) made of poly (lactic co glycolic acid) and poly ethylene glycol (PLGA and PEG-PLGA MPs), have improved the efficacy of protein therapy in preclinical studies. However, no cardiac treatment based on MPs has yet been commercialized since this is a relatively new field and total characterization of polymeric MPs remains mandatory before they reach the clinical arena. Therefore, the objective of this study was to characterize the *in vivo* release, bioactivity and biodegradation of PLGA and PEG-PLGA MPs loaded with biotinylated NRG in a rat model of MI. The effect of PEGylation in the clearance of the particles from the cardiac tissue was also evaluated. Interestingly, MPs were detected in the cardiac tissue for up to 12 weeks after administration. *In vivo* release analysis showed that bNRG was released in a controlled manner throughout the twelve week study. Moreover, the biological cardiomyocyte receptor (ErbB4) for NRG was detected in its activated form only in those animals treated with bNRG loaded MPs. On the other hand, the PEGylation strategy was effective in diminishing phagocytosis of these MPs compared to non coated MPs in the long term (12 weeks after injection). Taking all this together, we report new evidence in favor of the use of polymeric PLGA and PEG-PLGA MPs as delivery systems for treating MI, which could be soon included in clinical trials.

Key words: myocardial infarction, microparticles, protein therapy, phagocytosis, bioactivity, biotinylation.