Recently, it has been demonstrated that the ionic dissolution products of bioactive glasses can promote angiogenesis (Miguez-Pacheco et al., 2015; Hench, 2009; Hoppe et al., 2011), both for hard and soft tissue applications. The neovascularization of an implant site or a wound is a critical aspect for the success of an implantable device for tissue engineering. It can facilitate the transport of appropriate nutrients and growth factors into the affected area, removal of waste products in the newly formed tissue, and survival of newly seeded cells (Miguez-Pacheco et al., 2015). The angiogenic effect of bioactive glasses can be generally ascribed to their ionic dissolution or to the release of specific ions having an explicit role in angiogenesis (e.g., copper and cobalt ions).

In 2004, Day et al. showed for the first time that the ionic dissolution of 45S5 bioactive glass particles was effective in promoting an angiogenic effect (Day et al., 2004; Day, 2005). They performed in vitro studies using endothelial cells and demonstrated that an appropriate amount of Bioglass can stimulate the secretion of angiogenic growth factors, such as VEGF, increasing angiogenesis in vitro. This study was confirmed by Leu and Leach (2008) and Gorustovich et al. (2010) who confirmed the dose-dependent effect of 45S5 in promoting angiogenesis.

The ability of sol-gel bioactive glasses (58S and 80S), in particular nanosized formulations (58S-NBG and 80S-NBG), to increase the new blood vessel formation was also tested (Lin et al., 2012; Mao et al., 2015). These studies demonstrated that the ionic extracts of sol-gel 58S-NBG and 80S-NBG stimulate the expression of VEGF, bFGF (basic fibroblast growth factor), and their receptors, and can activate nitric oxide (a major regulator of vascular cell migration and angiogenesis) synthase, promoting the formation of capillary tube in vitro. The angiogenetic effect may be caused by increased levels of released Ca and predominantly Si (up to 50 times more in respect to the control). In fact, several studies have demonstrated the role of Si in stimulating the angiogenic process both in vitro and in vivo (Zhai et al., 2012). Thus, it can be assumed that Si ions play a major role in stimulating angiogenesis, while Ca ions have a supporting role.

Cu-containing glasses were studied for their potential angiogenic properties in 2013. Wu et al. (2013d) showed that Cu-doped mesoporous bioactive glass scaffolds (Cu-MBG scaffolds) possess enhanced angiogenic effects compared with undoped samples. They showed that Cu-MBG scaffolds improved hypoxia-inducible factor (HIF-1α) stabilization and VEGF secretion of human bone marrow stromal cells (hBMSCs), indicating that copper ions play a crucial role in inducing hypoxic effects on hBMSCs.

As previously reported, VEGF was identified as a mediator of angiogenesis. It activates endothelial cells in the surrounding tissue by regulating their proliferation, migration, and the formation of tubular structures (Miguez-Pacheco et al., 2015). Moreover, Wu et al. have discovered an important link between hypoxia and angiogenesis, mediated by copper ions, showing that the expression of VEGF was induced in the hypoxic microenvironment. Rath et al. (2014)