

Recombinant Plasmid DNA Construct Encoding Combination of vegf165 and bmp2 cDNAs Stimulates Osteogenesis and Angiogenesis In Vitro

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Abstract

© 2016, Springer Science+Business Media New York. Though normally bone regenerates well, non-union, delayed union, or defective bone formation can occur. Since impaired healing is often caused by local trophic disorders, standard fracture management is often ineffective. Gene therapy is a promising field for bone engineering. We have created a recombinant plasmid construct encoding the genes for pro-angiogenic vascular endothelial growth factor 165A (VEGF165A) and pro-osteogenic bone morphogenetic protein 2 (BMP2) with kanamycin resistance (pBudKan-VEGF165A-BMP2). This plasmid has the potential for use in treatment of trauma and skeletal system disorders, especially in cases of low trophicity.

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Keywords

Angiogenesis, Bone morphogenetic protein 2 (BMP2), Osteogenesis, Plasmid, Vascular endothelial growth factor (VEGF165)

References

- [1] Kayal, R. A., Tsatsas, D., Bauer, M. A., Allen, B., Al-Sebaei, M. O., Kakar, S., et al. (2014). Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity. *Journal of Bone and Mineral Research*, 22(4), 560-568.
- [2] Morshed, S. (2014). Current options for determining fracture union. *Advances in Medicine*. doi:10.1155/2014/708574.
- [3] Perlman, M. H., & Thordarson, D. B. (1999). Ankle fusion in a high risk population: an assessment of nonunion risk factors. *Foot and Ankle International*, 20(8), 491-496.
- [4] Murphey, M. D., Foreman, K. L., Klassen-Fischer, M. K., Fox, M. G., Chung, E. M., Kransdorf, M. J. (2014). From the radiologic pathology archives imaging of osteonecrosis: radiologic-pathologic correlation. *Radiographics*, 34(4), 1003-1028.
- [5] Reddi, A. H. (1994). Bone and cartilage differentiation. *Current Opinion in Genetics and Development*, 4, 737-744.
- [6] Lo, K. W.-H., Ulery, B. D., Ashe, K. M., Laurencin, C. T. (2016). Studies of bone morphogenetic protein based surgical repair. *Advanced Drug Delivery Reviews*, 64(12), 1277-1291.
- [7] Xiao, C., Zhou, H., Liu, G., Zhang, P., Fu, Y., Gu, P., et al. (2011). Bone marrow stromal cells with a combined expression of BMP-2 and VEGF-165 enhanced bone regeneration. *Biomedical Materials*, 6(1), 015013.
- [8] Bao, P., Kodra, A., Tomic-Canic, M., Golinko, M. S., Ehrlich, H. P., Brem, H. (2009). The role of vascular endothelial growth factor in wound healing. *The Journal of Surgical Research*, 153(2), 347-358.

- [9] Kanczler, J. M., & Oreffo, R. O. (2008). Osteogenesis and angiogenesis: the potential for engineering bone. *European Cells & Materials*, 15, 100-114.
- [10] Masgutov RF, Bozo IY, Rizvanov AA, Isaev AA, Bogov AA, Bogov AA J, Deev RV, Salafutdinov II, Plaksa IL (2014) Codon-optimized recombinant plasmid, method of peripheral nerve regeneration, method of treatment of human injured nerve. Russian Federation patent RU 2 558 294 C1.
- [11] Declercq, H., Van den Vreken, N., De Maeyer, E., Verbeeck, R., Schacht, E., De Ridder, L., et al. (2004). Isolation, proliferation and differentiation of osteoblastic cells to study cell/biomaterial interactions: comparison of different isolation techniques and source. *Biomaterials*, 25(5), 757-768.
- [12] Katina, M. N., Gaifullina, R. F., Hayatova, Z. G., Emene, C. C., Rizvanov, A. A. (2012). Isolation, culture and differentiation of rat (*Rattus norvegicus*) and hamster (*Mesocricetus auratus*) adipose derived multipotent stem cells. *Genes and Cells*, 7(3), 82-87.
- [13] Chen, S. M., Ward, S. I., Olutoye, O. O., Diegelmann, R. F., Kelman Cohen, I. (1997). Ability of chronic wound fluids to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. *Wound Repair and Regeneration*, 5(1), 23-32.
- [14] Chira, S., Jackson, C. S., Oprea, I., et al. (2015). Progresses towards safe and efficient gene therapy vectors. *Oncotarget*, 6(31), 30675-30703.
- [15] Kempen, D. H., Lu, L., Heijink, A., Hefferan, T. E., Creemers, L. B., Maran, A., et al. (2009). Effect of local sequential VEGF and BMP-2 delivery on ectopic and orthotopic bone regeneration. *Biomaterials*, 30(14), 2816-2825.
- [16] Peng, H., Usas, A., Olshanski, A., Ho, A. M., Gearhart, B., Cooper, G. M., et al. (2005). VEGF improves, whereas sFlt1 inhibits, BMP2-induced bone formation and bone healing through modulation of angiogenesis. *Journal of Bone and Mineral Research*, 20(11), 2017-2027.
- [17] Zelzer, E., & Olsen, B. R. (2005). Multiple roles of vascular endothelial growth factor (VEGF) in skeletal development, growth, and repair. *Current Topics in Developmental Biology*, 65, 169-187.
- [18] Seamon, J., Wang, X., Cui, F., et al. (2013). Adenoviral delivery of the genes to rat mesenchymal stem cells potentiates osteogenesis. *Bone Marrow Research*. doi:10.1155/2013/737580.
- [19] Lin, Z., Wang, J.-S., Lin, L., et al. (2014). Effects of BMP2 and VEGF165 on the osteogenic differentiation of rat bone marrow-derived mesenchymal stem cells. *Experimental and Therapeutic Medicine*, 7(3), 625-629.
- [20] Stoll, S. M., & Calos, M. P. (2002). Extrachromosomal plasmid vectors for gene therapy. *Current Opinion in Molecular Therapeutics*, 4, 299-305.
- [21] Herweijer, H., Zhang, G., Subbotin, V. M., Budker, V., Williams, P., Wolff, J. A. (2001). Time course of gene expression after plasmid DNA gene transfer to the liver. *The Journal of Gene Medicine*, 3(3), 280-291.
- [22] Herweijer, H., & Wolff, J. A. (2003). Progress and prospects: naked DNA gene transfer and therapy. *Gene Therapy*, 10(6), 453-458.
- [23] Morrissey, D., Collins, S. A., Rajenderan, S., Casey, G., O'Sullivan, G. C., Tangney, M. (2013). Plasmid transgene expression in vivo: promoter and tissue variables (pp. 35-47). Rijeka: InTech.
- [24] Ghodadra, N., & Singh, K. (2008). Recombinant human bone morphogenetic protein-2 in the treatment of bone fractures. *Biologics: Targets and Therapy*, 2(3), 345-354.
- [25] Deev, R. V., Drobyshev, A. Y., Bozo, I. Y., Isaev, A. A. (2015). Ordinary and activated bone grafts: applied classification and the main features. *BioMed Research International*. doi:10.1155/2015/365050.
- [26] Huber, P. E., & Pfisterer, P. (2000). In vitro and in vivo transfection of plasmid DNA in the Dunning prostate tumor R3327-AT1 is enhanced by focused ultrasound. *Gene Therapy*, 7(17), 1516-1525.
- [27] DiFranco, M., Quinonez, M., Capote, J., Vergara, J. (2009). DNA transfection of mammalian skeletal muscles using in vivo electroporation. *Journal of Visualized Experiments*, 32, 1520.