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**Proceedings Paper:**

Feichtinger, GA [orcid.org/0000-0002-7724-3006](https://orcid.org/0000-0002-7724-3006), Nomikou, N, Saha, S et al. (4 more authors) (2016) Ultrasound-responsive gene-activated matrices (GAMs) for osteogenic gene therapy using matrix-assisted sonoporation (MAS). In: Human Gene Therapy. Changing the Face of Modern Medicine: Stem Cells and Gene Therapy, 18-21 Oct 2016, Florence, Italy. Mary Ann Liebert , A151-A152.

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## **Ultrasound-responsive gene-activated matrices (GAMs) for osteogenic gene therapy using matrix-assisted sonoporation (MAS)**

G A Feichtinger<sup>1,2,7</sup> N Nomikou<sup>3,7</sup> S Saha<sup>2</sup> S Nuernberger<sup>4,5</sup> P Heimel<sup>1</sup> H Redl<sup>1</sup> A P McHale<sup>6</sup>

<sup>1</sup>Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Centre, Austrian Cluster for Tissue Regeneration, European Institute of Excellence on Tissue Engineering and Regenerative Medicine Research (Expertissues EEIG), Vienna-Branch, Vienna, Austria <sup>2</sup>Department of Oral Biology, School of Dentistry, University of Leeds, Leeds, UK <sup>3</sup>Research Department of General Surgery, Division of Surgery & Interventional Science, Faculty of Medical Sciences, University College London, London, UK <sup>4</sup>Medical University of Vienna, Department of Traumatology, Vienna, Austria <sup>5</sup>Bernhard Gottlieb University Clinic of Dentistry, Vienna, Austria <sup>6</sup>School of Pharmacy and Pharmaceutical Sciences, University of Ulster, Coleraine, UK <sup>7</sup>both authors contributed equally.

Gene-activated matrix (GAM)-based therapeutics for tissue re-generation are limited by efficacy, the lack of spatiotemporal control and availability of target cells, all of which impact negatively on their translation to the clinic. Here we describe an advanced ultrasound-responsive GAM containing target cells that facilitates matrix-assisted sonoporation (MAS) to induce osteogenic differentiation. Ultrasound-responsive GAMs consisting of fibrin/collagen hybrid-matrices containing microbubbles, bone morphogenetic protein BMP2/7 co-expression plasmids together with C2C12 cells were treated with ultrasound either in vitro or following parenteral intramuscular implantation in vivo. Using direct measurement for alkaline phosphatase activity, von Kossa staining and immuno-histochemical analysis for osteocalcin expression, MAS-stimulated osteogenic differentiation was confirmed in the GAMs in vitro 7 days post treatment with ultrasound. At day 30 post-treatment with ultrasound, ectopic osteogenic differentiation was confirmed in vivo using X-ray microcomputed tomography ( $\mu$ CT) and histological analysis. Osteogenic differentiation was indicated by the presence of ectopic bone structures in all animals treated with MAS when compared with controls. In addition, bone volumes in this group were statistically greater than those in the control groups. This novel approach of incorporating a MAS capability into GAMs could provide a minimally invasive means of stimulating in situ transgene delivery with enhanced spatiotemporal control for osteoinductive gene-based therapies.