SUPPLEMENTARY MATERIAL 1

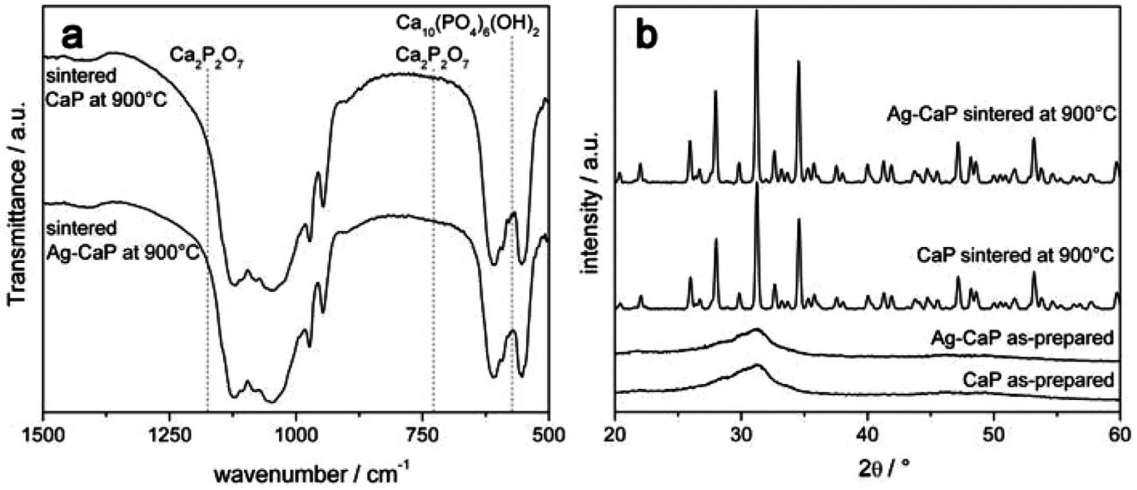
Preparation and Characterisation of Cotton Wool Like PLGA/CaP Nanocomposites

Calcium Phosphate Nanoparticles Preparation and Characterisation

X-ray diffraction (XRD)-amorphous calcium phosphate (CaP, $Ca_3(PO_4)_2$) and silver calcium phosphate (Ag-CaP, 1 wt% Ag on CaP) nanoparticles were prepared using flame spray synthesis. Briefly, tributyl phosphate (Fluka, puriss), calcium- and silver carboxylates were mixed in the corresponding ratio (Ca/P = 1.5) and fed into a methane/oxygen flame. The nanopowders were collected on glass fibre filters, sieved (250 µm mesh) and thoroughly investigated. XRD-spectra were collected on X'Pert PRO-MPD (PANalytical, CuKα radiation, X'Celerator linear detector system, step size of 0.0338, ambient conditions). Fourier transform infrared (FTIR) spectroscopy (Tensor 27, Bruker Optics, 4 cm^{-1} resolution, 1 wt% powder in KBr) was routinely used to confirm the phase purity. The specific surface area (SSA) of the as-prepared particles was determined by BET (Brunauer-Emmet-Teller) measurement (Tristar 3000, Micromeritics). For TEM (transmission electron microscopy) investigation, the material was deposited onto a holey carbon foil supported on a carbon grid. TEM images were recorded on a CM30ST microscope (LaB_6 cathode, operated at 300 kV, point resolution ~4Å) to study the morphology and to confirm the particle size. The silver content in the Ag-CaP nanopowder was analysed by flame atomic-absorption spectroscopy (AAS) on a Varian SpectrAA 220FS at a flame composition of 13.5 l/min air (PanGas) and 2.1 l/min acetylene (PanGas) and measuring the adsorption at a wavelength of 328.1 nm.

Bone Cotton Wool Preparation and Characterization

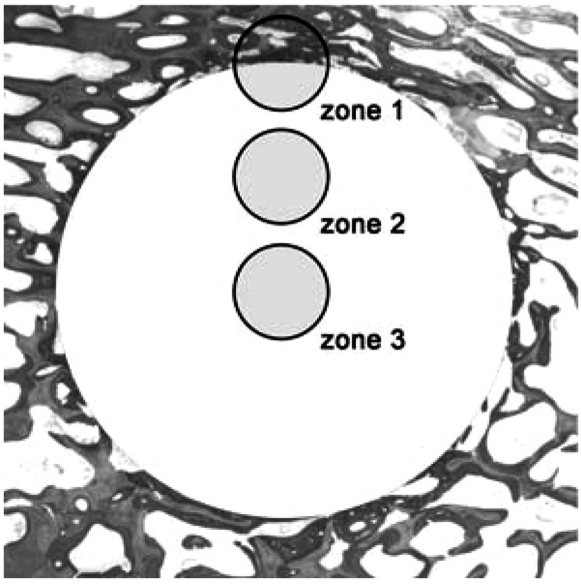
Clinically approved poly(lactide-co-glycolide) (PLGA) was purchased from Boehringer Ingelheim with a copolymer ratio of 85:15 (Resomer® Sample MD Type RG) and with a weight and number average molecular weight of 305'440 g/mol and 110'500 g/mol, respectively. PLGA/CaP 60:40 and PLGA/Ag-CaP 60:40 (total silver concentration in scaffold = 0.4 wt%) scaffolds were fabricated by low-temperature electrospinning. Briefly, the nanoparticles were dispersed in chloroform (Riedel de Haen, Ph. Eur.) using an ultrasonic processor (320 W, 5 min) and by the addition of 8 wt% surfactant (Polysorbate20, Fluka, Ph. Eur.) with respect to the particles. PLGA was subsequently added and dissolved under magnetic stirring (15 h) to a concentration of 8 wt% in chloroform. The electrospinning solutions were pumped with a flow rate of 2 ml/h (KD Scientific syringe pump) through a capillary (inner diameter = 1.0 mm) connected to a DC high voltage supply (Glassman, EL Series) operated at 20 kV. To prevent the exit from clogging, the needle tip was kept in a chloroform saturated air stream by using a concentrically mounted sheath tube. The fibres were sprayed for 45 min onto a rotating (130 rpm), hollow and grounded tube (diameter = 8 cm) covered with an aluminium foil. This collector was previously loaded with dry ice (frozen CO_2, average temperature 195 K) which resulted in rapid deposition of ice crystals at the cold (200-220 K) external surface. The relative humidity during electrospinning was 35 % and the distance between the needle tip (transversal movement = 5 cm) and the collector was maintained at 10 cm. Directly after low-temperature electrospinning the as-prepared scaffolds were dried in a vacuum oven (20 mbar, room temperature, 12 h). Scanning electron microscopy (SEM, LEO 1530 Gemini) was routinely used to investigate the morphology of the electrospun fibres after coating with a 4 nm platinum layer.



(Suppl. Fig. 1). Characterisation of flame spray synthesized nanoparticles*:* (**a**) Fourier transform infrared spectra of as-prepared CaP and Ag-CaP nanoparticles. Distinct peaks characteristic for β-TCP after sintering and the absence of impurities such as hydroxyapatite (575 cm^{-1}) and calcium pyrophosphate (727 cm^{-1} and 1140-1215 cm^{-1}) confirm the purity of the material. (**b**) Broad XRD pattern of as-prepared amorphous CaP/Ag-CaP nanoparticles and peaks characteristic for β-TCP after sintering at 900°C.

SUPPLEMENTARY MATERIAL 2

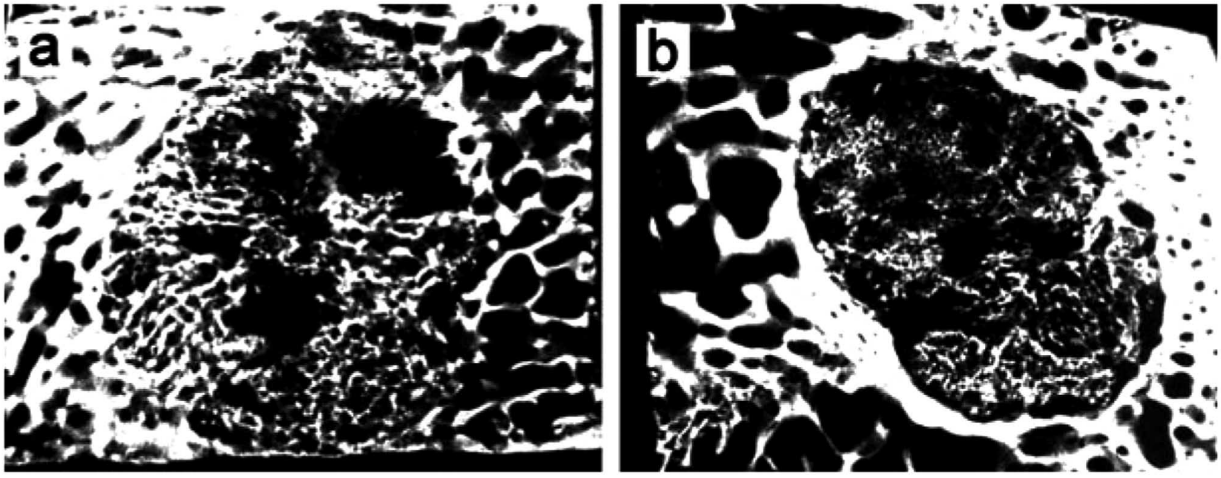
Evaluated Zones in the Former Defect for Semi-Quantitative Histological Evaluation



Schematic description of the three different zones investigated in the semi-quantitative histological evaluation applying a score system.

SUPPLEMENTARY MATERIAL 3

Microradiographs



Microradiographs after eight weeks implantation of bone cotton wool-like PLGA/CaP. (**a**) sheep 3118 femur left proximal and (**b**) sheep 3119 humerus left proximal.

SUPPLEMENTARY MATERIAL 4

Semi-Quantitative Analysis of the Cellular Content After 8 Weeks Implantation

Suppl. Table 1. Semi-Quantitative Analysis of the Cellular Content After 8 Weeks Implantation of PLGA/CaP and PLGA/Ag-CaP Applying a Score System in Three Different Zones from Border to Centre of the Former Defect: Scores (0 for 0%, 1 for 1-25%, 2 for 26-50%, 3 for > 50%) for Percentage Fraction of the Cells Per Power Field and the Corresponding Sum for Each Defect

Sheep	Defect	Ag	Lymphocytes/Plasma Cells				Macrophages				Fibroblasts/Fibrocytes			
			1	2	3	Sum	1	2	3	Sum	1	2	3	Sum
3118	hu r di		0	0	1	1	1	2	2	5	0	0	0	0
	hu r pr	x	0	0	0	0	1	1	1	3	0	0	0	0
	hu l di	x	1	0	0	1	2	1	1	4	0	0	0	0
	fe r di		0	1	0	1	1	1	1	3	0	0	0	0
	fe r pr	x	0	0	0	0	1	0	0	1	0	0	0	0
	fe l di	x	0	0	0	0	1	1	1	3	0	0	0	0
	fe l pr		1	0	0	1	1	1	1	3	0	0	0	0
3119	hu r di		1	0	0	1	1	1	1	3	0	1	0	1
	hu r pr	x	1	1	0	2	1	1	1	3	0	0	0	0
	hu l di	x	0	0	0	0	1	1	1	3	0	0	0	0
	hu l pr		0	1	0	1	1	1	1	3	0	0	0	0
	fe r di		0	0	0	0	1	1	1	3	0	0	0	0
	fe r pr	x	0	0	0	0	1	1	1	3	0	0	0	0
	fe l di	x	0	0	0	0	1	1	1	3	0	0	0	0
	fe l pr		0	0	0	0	1	1	1	3	0	0	0	0

Suppl. Table 2. Semi-Quantitative Analysis of the Cellular Content After 8 Weeks Implantation of PLGA/CaP and PLGA/Ag-CaP Applying a Score System in Three Different Zones from Border to Centre of the Former Defect: Scores (0 for None, 1 for 1-5, 2 for 6-10, 3 for > 11) for the Absolute Number of the Cells Per Power Field and the Corresponding Sum for Each Defect

Sheep	Defect	Ag	Foreign Body Giant Cells				Macrophages Circles				Bone Islands				Osteoclasts			
			1	2	3	Sum	1	2	3	Sum	1	2	3	Sum	1	2	3	Sum
3118	hu r di		0	1	0	1	0	1	0	1	0	1	0	1	0	0	0	0
	hu r pr	x	1	1	0	2	2	1	1	4	1	1	1	3	1	0	0	1
	hu l di	x	0	0	1	1	1	1	1	3	0	1	0	1	1	1	0	2
	fe r di		0	0	0	0	1	1	1	3	0	1	1	2	1	0	1	2
	fe r pr	x	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1
	fe l di	x	0	1	0	1	0	0	1	1	1	1	1	3	1	0	0	1
	fe l pr		0	1	1	2	0	1	0	1	1	1	1	3	1	1	0	2
3119	hu r di		0	0	0	0	0	1	1	2	0	1	0	1	0	0	0	0
	hu r pr	x	1	1	0	2	1	1	0	2	0	1	0	1	0	0	0	0
	hu l di	x	0	1	0	1	0	1	1	2	0	1	0	1	0	0	0	0
	hu l pr		0	0	0	0	0	1	1	2	0	1	1	2	1	0	0	1
	fe r di		0	0	1	1	1	1	1	3	1	0	0	1	0	0	0	0
	fe r pr	x	0	0	0	0	0	0	1	1	1	0	0	1	1	0	0	1
	fe l di	x	0	0	1	1	1	2	1	4	1	1	0	2	1	1	0	2
	fe l pr		0	0	0	0	0	0	1	1	0	1	0	1	0	0	0	0