INTRODUCTION
Gold salts have been used for a long time as an effective drug against rheumatoid arthritis due to the anti-inflammatory effects of gold ions. Experimental studies have shown that gold ions are effective in inhibiting antigen processing in macrophage lysosomes and also in suppressing NF-kappa B binding activity and the activation of the I-kappa B-kinase. These mechanisms result in a subsequently reduced production of pro-inflammatory cytokines, most notably TNF-alpha, IL-1, and IL-6. Gold ions bio-released from metallic gold particles have recently been shown to have pronounced anti-inflammatory and neuron-protective capacities in mouse subjected to focal brain injury.

The use of allograft bone in revision arthroplasty has been shown to have inflammatory and foreign body immune response and implants are often found to be encapsulated in fibrous tissue resulting in reduced implant stability and longevity. We hypothesized that allograft containing gold particles would reduce fibrous tissue production by suppressing inflammation and give rise to increased biocompatibility, better osseointegration and a following improved implant fixation.

MATERIALS
We included 10 skeletally mature sheep into the study. Additional 2 sheep were used as allograft donors. Spherical gold particles sized 45 – 63 µm were used. We inserted cylindrical plasma sprayed porous titanium implants (L 10 mm/Ø 6 mm) with endcaps and top screws (Ø 11 mm), leaving a 2.5 mm circumferential defect around each implant. Allograft was harvested the day before surgery. The proximal part of the humerus, distal femur and proximal tibia were prepared and morselized in a bone mill.

METHODS
The study was conducted as a block randomized, paired animal experiment approved by the Institute’s Animal Care and Use Committee. Each sheep received two implants in the proximal humerus. One implant was surrounded by impacted allograft with gold particles (129 mg) and the contralateral implant was surrounded by allograft only.

By sterile technique and under general anaesthesia we drilled 11.0 mm wide and 10.0 mm deep holes in the cancellous bone of the proximal part of the humerus. First the implant with premounted endcap was inserted into the drill hole. One mL bone graft +/- gold was impacted into the 2.5 mm circumferential defect around the implant and the hole was closed by the top washer. The study design was paired with gold graft on one side and identical control graft on the contra-lateral side.

The sheep were sacrificed after 12 weeks. The bone-implant specimens were cut perpendicular to the long axis of the implant. The section closest to the surface was used for biomechanical push-out test. The other section was used for histomorphometrical analysis.

A MTS Bionics Test Machine was used to push the implant out of the surrounding bone (5 mm/min), measuring load and implant displacement. The mechanical parameters were determined from these data.

Histomorphometry was performed with the Olympus CAST grid stereological software. Tissue fractions were quantified on the implant surface, in an inner zone 0 – 500 µm and an outer zone 500 – 2500 µm.
All data were normally distributed and we used Student’s paired t-test to test the differences between pairs. Two-tailed p-values less than 0.05 were considered statistically significant.

RESULTS
One animal was lost under surgery, a second animal was excluded due to problems in specimen preparations and in a third animal biomechanical data was lost.

Biomechanical fixation: The results are shown in table 1.

<table>
<thead>
<tr>
<th></th>
<th>Max Shear Strength (MPa)</th>
<th>Max Shear Stiffness (MPa/mm)</th>
<th>Total Energy Absorption (kJ/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.16 (5.02 - 9.30)</td>
<td>34.04 (14.52 - 53.56)</td>
<td>1.35 (0.74 - 1.96)</td>
</tr>
<tr>
<td>Gold</td>
<td>9.17 (6.77 - 11.56)</td>
<td>32.4 (23.70 - 41.09)</td>
<td>2.08 (1.16 - 3.01)</td>
</tr>
<tr>
<td>Gold / Control</td>
<td>1.27 (0.94 - 1.71)</td>
<td>1.05 (0.68 - 1.61)</td>
<td>1.47 (0.85 - 2.53)</td>
</tr>
<tr>
<td>P values</td>
<td>P = 0.098</td>
<td>P = 0.803</td>
<td>P = 0.134</td>
</tr>
</tbody>
</table>

Table 1 Data are presented as mean for each treatment group or median for the relative paired increases (Gold/Control). 95% CI in parentheses.

DISCUSSION
We hypothesized that gold particles could modulate the foreign-body inflammations associated with the use of allograft to fill defects around orthopedic implants. This study was designed to evaluate the effect of allograft with gold particles on implant fixation, bone remodeling and fibrous tissue formation. We found that when particulate gold was added to the bone graft, mechanical fixation was improved in all parameters and formation of new bone was increased. However, none of these differences were statistically significant. The histological sections confirmed the presence of spherical gold particles in the peri-implant tissue.

Previous studies have shown that metallic gold inserted in tissue liberate gold ions in the surrounding tissue and can be found in immune cells such as macrophages. Although the anti-inflammatory effects of gold are well established, we found in a previous study that gilding of a titanium surface does not improve osseointegration. This was believed to be due to excessive inhibition of the primary inflammatory response post-operatively.

In the present study we failed to demonstrate any statistical significant improvement in early mechanical strength and implant stability by changing the dose, form of administration and the observation period. The power of the study may have been insufficient, and it was further reduced with the loss of three out of ten included animals. However the consistent (but statistically non-significant) trend that the gold particles improve biomechanical strength and stability, new bone formation and graft remodeling is noticeable and warrants further experiments.

Aseptic implant loosening is the main long-term complication in orthopedic surgery. This is thought to be due to the continuous inflammatory process that takes place in the peri-prosthetic tissue causing formation of fibrous tissue that finally leads to a degree of osteolysis that causes implant loosening. The presence of gold particles in peri-implant tissue could be an adequate way to deliver an inflammatory modulator. This would delay or inhibit osteolysis and fibrous encapsulation leading to implant loosening without disturbing the important early implant fixation and osseointegration. Long-term studies are needed to clarify this perspective.

REFERENCES