Biomaterials are widely used to treat, augment, repair or replace a tissue or organ of the human body. However, implantation of biomaterials can stimulate macrophages to fuse and form foreign body giant cells (FBGCs). These FBGCs are large multinucleated cells and tend to surround and invade the implant, which can have a negative effect on the success of the treatment. Why FBGCs are formed near implants is largely unknown and moreover, whether FBGCs affect the implant remains a mystery.

FBGCs originate from the fusion of monocytes/macrophages and are exclusively related to the presence of a foreign material. In contrast herewith, osteoclasts, their multinucleated relatives, form specifically on mineralized surfaces where they specialize in mineralized tissue resorption (e.g. bone). Osteoclasts originate from the same myeloid lineage as FBGCs and have been demonstrated to share similarities with FBGCs.

The goal of this thesis was to unravel (i) if FBGCs have functional characteristics of osteoclasts, (ii) what morphological features are typical of the FBGCs, (iii) how surface structure of an implant influences the differentiation and function of osteoclasts and FBGCs, and (iv) whether different monocyte subsets can generate FBGCs.

In the first experimental chapter (Chapter 2) FBGCs and osteoclasts were differentiated in vitro from their common CD14+ monocyte precursor cells, using different sets of cytokines. Both cell types were cultured on bovine bone slices and on a hydroxyapatite coating. It was demonstrated that FBGCs expressed podosome belts, actin rings and sealing zones – a cytoskeletal organization that is considered to be osteoclast-specific. FBGCs also expressed similar levels of mRNAs of genes that are associated with the dissolution of mineral [e.g., anion exchange protein 2 (AE2), carbonic anhydrase 2 (CAII), chloride channel 7 (CIC7), and vacuolar-type H+-ATPase (v-ATPase)]. In line with these results, it was observed that FBGCs were able to dissolve the hydroxyapatite coating, a feature that is generally attributed specifically to osteoclasts. This dissolution was, however, less efficient. The inability of the FBGC to degrade the organic component of bone, the collagen and non-collagenous proteins, was possibly related to the absence of a ruffled border and the matrix degrading enzyme, cathepsin K.

In Chapter 3, it was investigated whether two different biomaterials resulted in the formation of different FBGCs. Collagen samples that were either cross-linked or non-cross-linked were subcutaneously implanted in mice for 21 days and subsequently analyzed. More FBGCs formed on and between implants of cross-linked collagen compared
to non-cross-linked material. Striking was the presence of long slender protrusions on the basolateral side of the membrane. These protrusions intermingled with protrusions from neighboring cells. The FBGCs showed signs of a clear zone on the apical side of the membrane, however, no ruffled border was observed. Signs of degradation and uptake of the collagen by the FBGCs was shown for both types of collagen. In conclusion, except from the number of FBGCs, no difference in morphology was observed between FBGCs on the two biomaterials.

In Chapter 4, the surface structure of beta-tricalcium phosphate (TCP) was changed in order to achieve and influence cellular resorption. CD14+ monocyte precursors were differentiated into osteoclasts and FBGCs and cultured on a submicron- or micron scale surface (TCPs and TCPb) consisting of beta-tricalcium phosphate. Multiple osteoclasts were observed on TCPs and contained numerous actin rings. Osteoclasts on TCPb were much smaller in size and actin rings were absent. TCPs was extensively resorbed by osteoclasts; no resorption was observed of TCPb. FBGCs did not have the capacity to resorb either TCP material. It appeared that by tuning the surface architecture, it is possible to control osteoclast resorption of calcium phosphate.

In the last experimental chapter (Chapter 5) we investigated how monocytes with a different surface expression of CD14+ and CD16+ influence the differentiation of FBGCs and osteoclasts. By differentiating CD14+ and CD16+ -monocytes into FBGCs and osteoclasts we found that FBGCs generated from CD16+ monocytes were larger and had a higher number of nuclei compared to FBGCs generated from CD14+ monocytes. For osteoclasts this difference seemed to be the opposite; cells with more nuclei per cell were generated from CD14+ monocytes.

In summary, by comparing the FBGC with the osteoclast we were able to characterize in more detail the functionality and morphology of FBGCs. We conclude that FBGCs are quite similar to osteoclasts with respect to podosome formation, actin rings, and expression of genes related to inorganic dissolution. The most important differences between the two cell types are the inability of the FBGC to form a ruffled border and the absence of cathepsin K in these cells. From the results obtained we conclude that the functionality of osteoclasts and formation of FBGCs can be influenced by surface structure. Influencing the surface structure of a biomaterial will enable the design of biomaterials which are better suited for their specific function. Furthermore, by proposing that larger FBGC form from the CD16+ subset of monocytes it might be possible to better target the source of the development of FBGCs in order to positively influence the reaction of the body to the implant.
In conclusion, the studies described in this thesis have improved our insight in the characteristic features of the FBGCs and their interaction with bone or fibrous tissue that may surround implants.