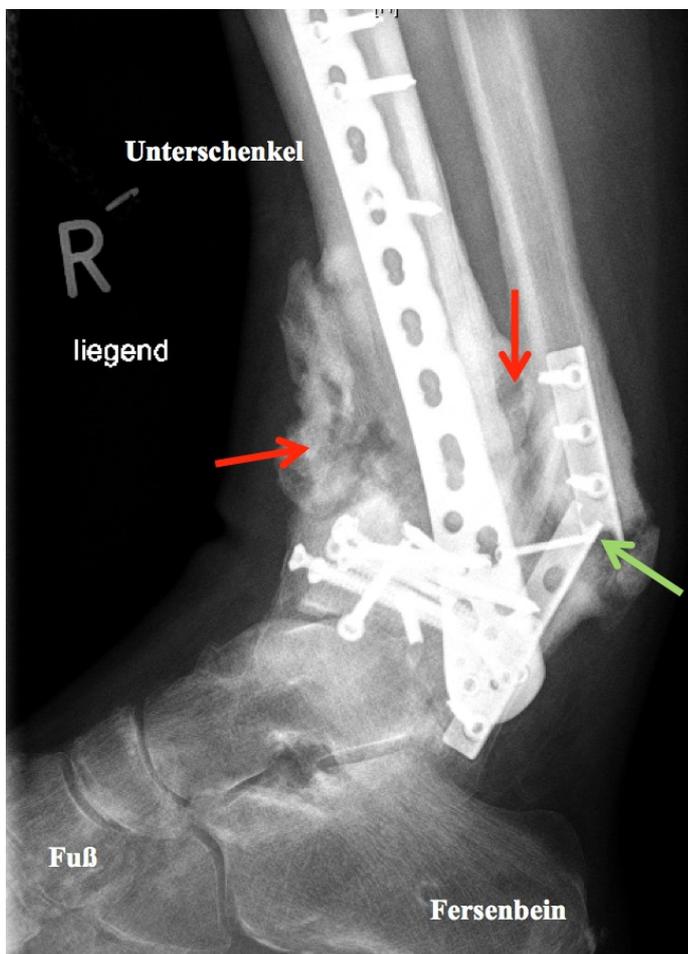


## The body's immune system loosens artificial joints

**The implantation of artificial joints has long become routine orthopaedic practice and is one of the most successful orthopaedic interventions. However, hip and knee endoprostheses are not nearly as long-lasting as their natural counterparts. This can be down to bacterial infections that degrade the bone, resulting in the loosening of the implants. Dr. Ulrike Dapunt from the University Hospital Heidelberg's Department of Orthopaedics and Traumatology has now discovered that it is not the bacterial activity or secretions that lead to the degradation of bone during chronic inflammation, but rather local host defence mechanisms. The researchers will now use these findings to develop new therapies with the aim of curbing excessive immune reactions and preventing the loosening of the implants.**



In Germany, more than 300.000 patients are given an artificial joint, a so-called endoprosthesis, every year. Most endoprostheses are implanted into the hip or knee. Although these artificial joints are a huge relief for patients who are in a great deal of pain and have limited mobility due to injury or degenerative joint disease, they are nowhere near as long-lasting as their natural counterparts. Around one to two percent of all implants loosen very quickly after implantation, and the majority of artificial joints have to be replaced due to wear and tear after around 15 to 20 years. Implant replacement surgery is more complex and time-consuming than the initial implantation of a prosthesis, and also causes major psychological stress for patients, especially those who are elderly and weak.

The loosening of a prosthesis shortly after implantation is, in most cases, down to joint inflammation. It is assumed that bacteria on the patient's skin get into the body during surgery or that they are transferred from other infection sites, e.g. infected teeth, to the implant by way of the bloodstream. These

X-ray image of an implant infection in the area of the lower leg/ankle. Bacterial infection prevents the bone from healing (red arrows), resulting in the loosening (break) of the implant (green arrow).

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pathogens are normally harmless and the body's immune system usually destroys them. However, in a few cases, the bacteria manage to colonise the surface of the artificial joint, resulting in inflammation of the surrounding tissue, which is difficult to treat. When severe bone loss occurs, the implant loosens. The

only remedies are antibiotics, cleaning of the open wound or replacement of the endoprosthesis with a new one.

## Bone degradation signal comes from the body's own immune system

The orthopaedist Dr. Ulrike Dapunt from the Department of Orthopaedics and Traumatology at Heidelberg University Hospital and her team of researchers have spent quite some time focussing on the inflammatory processes around artificial joints in order to find out the reasons why the bone tissue degrades and the prostheses loosen. With the help of cell cultures and the examination of tissue samples, the researchers found that during chronic inflammation the body's own immune cells are responsible for the degradation of bone around the artificial joint and that this results in the loosening of the implant. The researchers discovered that during a persistent immune response, the patient's immune system produces messenger substances, i.e. cytokines, that make normally harmless cells (monocytes) differentiate into bone-degrading cells (osteoclasts). Although osteoclasts also play a key role in normal bone remodelling processes, the signal that induces increased bone loss comes from the body's immune cells as well as cells of the bone tissue itself. "We were able to identify the cytokines involved in these processes," says Dapunt. "We found that the longer the inflammation lasted, the more osteoclasts were produced. This leads to a collateral damage of the joint – the degradation of the bone – which worsens as the fight between the immune system and the bacteria continues."

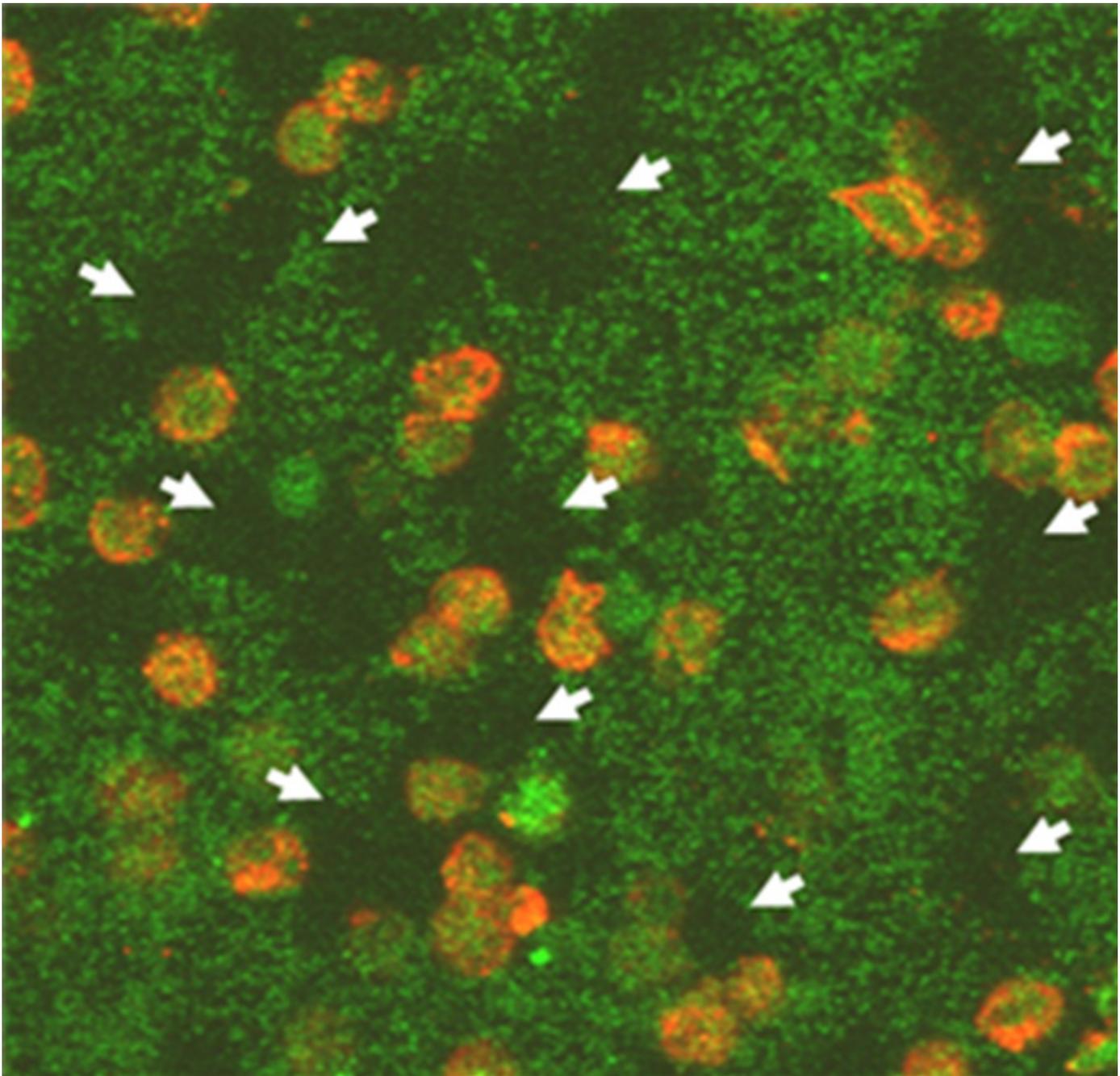


Dr. Ulrike Dapunt from the University Hospital in Heidelberg investigates why artificial joints loosen. She was awarded the Anita and Friedrich Reutner Prize for Medical Research for her achievements in April 2016.

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Based on these findings, the researchers came up with the idea of targeting both fronts, bacteria and degrading bone. Dapunt comments: "We want to destroy the bacteria with a suitable antibiotic. But we also want to inhibit the immune system, so that the body does not degrade its own bones."

In addition to bacteria, wear particles released from implanted material have also been shown to



Neutrophilic granulocytes (immune cells, red) recognise and phagocytose bacterial biofilms (green), as seen by the holes in the biofilm.

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have a similar effect. They activate local host defence mechanisms, causing a persistent inflammatory response which leads to the destruction of the bone followed by loosening of the implant. "We assume that the reaction is similar to the one that occurs when bacteria colonise an artificial joint, but less pronounced," says Dapunt. "This is due to the fact that metal implants have been optimised in recent years in order to reduce wear as much as possible."

## Bacterial protein induces immune system attack

After it had become clear that the immune system recognises and responds to biofilms, the physicians from Heidelberg then went on to find out how it recognises the bacteria hidden away in the protective slimy layer on the implant surface. "The prevailing assumption was that the immune system is unable to recognise the bacteria within a biofilm, which protects them against host defences," said the orthopaedist. "But this is not true. We discovered, however, that it was not the

bacteria themselves that are recognised by the immune system, but another constituent of the biofilm." Further studies on isolated biofilms led to the identification of GroEL, a protein that induces an immune response. The immune cells then fight against the biofilm. GroEL is a bacterial heat shock protein of the chaperonin group that is essential for the correct folding of the majority of newly synthesised proteins into active structures. "As GroEL is a vital component of the bacterial organism, it makes sense in evolutionary terms that our immune system recognises such a protein," says Dapunt.

After identifying the responsible protein, the researchers recently joined forces with colleagues from the Institute of Immunology and the Institute of Pathology in Heidelberg to look for a GroEL receptor on the immune cells. "We have already found one potential candidate. This receptor, which is called TLR4 (TLR: Toll-like receptor), is part of the innate immune system which recognises many pathogens," says Dapunt. "However, blocking the receptor only led to an incomplete reaction. We therefore assume that other receptors must also be involved in the immune reactions that occur in inflamed joints. And we are now looking for them. If we are able to block the receptors with drugs, we would be able to inhibit the self-destructive immune reaction."

## Therapeutic protein to block destructive immune response



Example of an implant infection in the lower leg area. Chronic infection leads to the exposure of the implant.  
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Existing treatment strategies exclusively target the bacteria involved. Antibiotics and repeated surgical interventions are used to contain the inflammation. However, the researchers from Heidelberg aim to develop as quickly as possible proteins that specifically block the immune system's

recognition mechanism. If they succeed, a complementary therapeutic concept would be available that, in addition to fighting the infection, would curb the excessive immune reaction, and thus prevent the bone from degrading.

In April 2016, the physician was awarded the University of Heidelberg Medical Faculty Anita and Friedrich Reutner Prize with a purse of 7,000 euros for up-and-coming researchers without established positions.

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## Article

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