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## Bio-optical imaging of host–bacteria interactions in biomaterial-associated infection

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# **Chapter 1**

**General introduction and aims of this thesis**

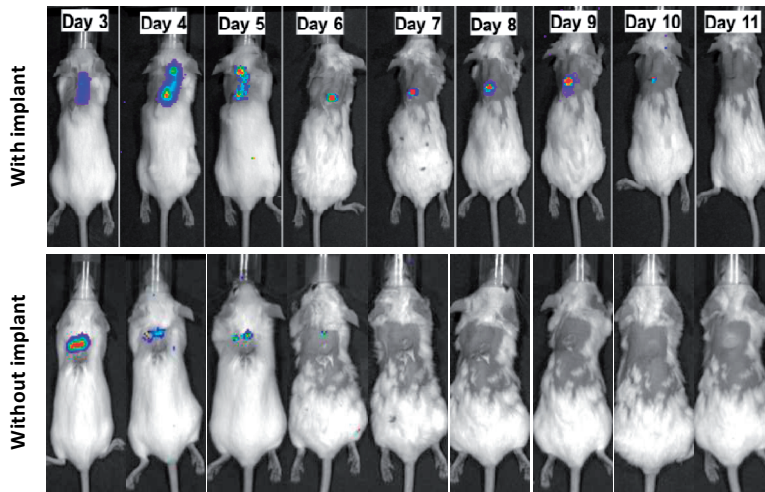
Biomaterials-Associated Infections (BAI) occur across all permanent and temporary implants and devices, used to restore human body function (1). The consequences of BAI are enormous: a patient with an infected implant starts a series of hospital visits and antibiotic use, with the almost certain outcome that the infected implant or device will have to be replaced at high costs and great discomfort for the patient (2). Infections associated with temporary devices, such as intravenous catheters used for administration of chemotherapeutics, are seemingly less complicated to solve as they can be easily removed, but yet often pose a clinical dilemma: its removal, necessary to cure the infection, will disrupt the chemotherapy, while maintaining the catheter in place may yield the risk of death due to sepsis of an already weakened patient.

Sterile implantation of a biomaterial may be considered a myth and it is safe to assume that implants are always inserted in an infected state (“peri-operative contamination”). Moreover, the surgical site is at risk of infection after surgery during hospitalization (“early post-operative contamination” of the wound site) (3). Bacteria can also be attracted to the surface of a biomaterial implant or device surface by haematogenous spreading of bacteria from an infection elsewhere in the body (4), a process that can occur any time after implantation. BAI does not necessarily develop at the time of bacterial contamination of an implant or device, but frequently manifests itself later, as bacteria can remain dormant on implant or device surfaces for many years (5).

Microorganisms adhering on a biomaterial implant or device surface protect themselves against the host immune system and antimicrobial challenges by embedding themselves in a complex matrix of extracellular polymeric substances to form a so-called “biofilm” (6). Apart from the fact that the biofilm mode of growth protects the organisms against antibiotic treatment, the number of microbial strains and species that have become resistant to currently available antibiotics is rapidly increasing (5,7), making it more difficult to eradicate a BAI.

In case of BAI, the host immune system is triggered by bacterial cell surface molecules, designated as “Pathogen-Associated Molecular Patterns” recognized by specific receptors on the professional phagocytes, e.g. “Toll-Like Receptors (8). Parallel to activation of the host immune system by bacteria in BAI, implantation of a biomaterial itself provokes host immune reactions to initiate a dynamic inflammatory process in which a variety of innate and adaptive immune cells are involved, known as the foreign body reaction. The onset of a foreign body reaction is accompanied by migration of neutrophils and granulocytes to the tissue adjacent to implanted materials. This acute inflammation resolves during a few hours to days and progresses to chronic inflammation, characterized by dense infiltration of monocytes derived macrophages. This process is followed by fusion of macrophages to multi-nucleated foreign body giant cells lining the biomaterial, novel fibroblast formation and deposition of fibrin, leading to fibrosis/encapsulation of the foreign body (9). The sterile inflammation due to the presence of the foreign body, together with the simultaneous activation of the host immune system induced by bacteria, may promote a prolonged inflammatory response towards BAI at the site of implantation. Eventually, an implanted biomaterial may compromise the local inflammatory response, and bacterial presence develops into BAI when a patient becomes (temporarily) immuno-compromised due to illness, fatigue, etc. (5).

Different strategies have been developed to prevent the incidence of BAI. Antimicrobial coatings are considered as a most promising solution, as they sandwich an infectious biofilm between a “killing” surface and an unfriendly environment, i.e. the local host immune system and/or systemically administered antibiotics. At the same time, antimicrobial coatings should also possess the ability to allow non-disturbed functioning of the local immune system, or even enhance its functioning in order to prevent microbial colonization and infection.



**Figure 1.** Visualization of BAI using bioluminescence imaging in mice, after deliberate early, post-operative contamination by a bioluminescent *S. aureus* strain in presence (upper panel) and absence (lower panel) of a biomaterial implant. Note that after 11 days, the bioluminescence signal becomes too low to detect in both mice.

The interplay between antimicrobial strategies applied either locally in the form of coatings or otherwise and the host immune response to BAI is difficult, if not impossible, to mimic in *in vitro* assays. Therefore, the use of animal models is indispensable for assessing the immune-compatibility and antimicrobial efficacy of antimicrobial strategies applied on biomaterials. *In vivo* bioluminescence systems, extensively used in cancer research (10), have recently been used successfully to monitor the course of BAI in murine models (11). Bacterial bioluminescence based *in vivo* models, mimicking infection developed from peri- or post-operative contamination of a biomaterial implant or device, allow to monitor pathogen presence longitudinally and non-destructively in one and the same animal (Fig. 1). Bio-optical imaging can either be based on the use of bioluminescent or fluorescent bacterial strains or on the application of fluorescent

probes, which can be activated by inflammatory mediators such as matrix metalloproteases or cathepsins expressed by host immune cells (12).

A first aim of this thesis is to gain a better understanding of the biological events that take place during the interaction of the host immune system with bacteria and implant surfaces during the course of BAI, in order to assist the development of new antimicrobial biomaterial coatings. As the second aim of this thesis, *in vivo* implant BAI models based on bioluminescence and fluorescence imaging of BAI will be developed and validated.

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