

Functionalized medical implants in the era of personalized medicine



Mathias Wilhelmi^{*1,2} & Axel Haverich^{1,2}

“...medical implants in the era of personalized medicine have to be tailored and individualized, these ... implants should be manufactured/finally functionalized directly on-site within the operating theater and at the time of implantation.”

Today, the common availability and application of medical prostheses and implants is taken for granted by doctors and patients alike. The original thought behind the development of these devices was to facilitate or even substitute compromised, mostly single functions within a defined area of the body. Typical examples are joint prostheses to re-establish motivity, dental prostheses to support chewing and degestation, or vascular prostheses to improve or re-establish tissue nutrition and oxygenation. The conception and technical realization, as well as the clinical transfer and subsequent surgical implantation, often required the bundling of complex knowledge originating from various scientific areas such as engineering, material sciences, chemistry and physics, as well as surgical disciplines. However, although hundreds of thousands of patients worldwide regained health, quality of life and workability, which have some important implications on

the discharge of socioeconomic systems, some essential limitations must not be ignored.

Beside individual- (e.g., allergies and intolerances), device- (e.g., fragility or other technical shortcomings) and implant site-specific (e.g., osteoporosis or atherosclerosis) problems, three superordinate limiting aspects should be noted: failing or at least incomplete device integration due to suboptimal hemo- and bio-compatibility; due to implant site-specific problems the incidence of implant infections is elevated; and a missing ability of almost all devices to react and thus, modulate and adjust its shape/function towards changed biometric parameters (e.g., an ongoing osteoporosis with perishing bone and changing joint angles or an infectious disease with accumulation of bacteria and the creation of a biofilm). Most of these limitations (i.e., infectious complications) can often not be or not sufficiently be treated by the administration of drugs, many scientific

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¹Division for Cardiothoracic-, Transplantation- & Vascular Surgery, Hannover Medical School, Hannover, Germany

²Center of Competence for Cardiovascular Implants – Medimplant, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany

*Author for correspondence: Tel.: +49 511 532 6592; Fax: +49 511 532 5404; wilhelmi.mathias@mh-hannover.de

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approaches focus on the development of optimized and thus, more bio-/hemo-compatible implant base materials. Another more expansive approach to enhance the intracorporal behavior and performance of medical devices is to ‘functionalize’ them by adding auxiliary substances. Already existing and clinically available examples for such functionalized implants include vascular prostheses and stents coated with silver or antibiotic agents to protect them from infections [1–3]; anticoagulant agents (e.g., heparin) to improve its hemocompatibility and thus, to reduce thromboembolic complications [4–6]; or cytotoxic agents (e.g., sirolimus) to prevent cellular hyperplasia and thus, graft (re-)stenosis/occlusion [6,7]. Other more basic science-orientated approaches comprise nanoscale surface modifications, for example, to facilitate osteointegration of bone implants [8–11] or to selectively promote or suppress the growth and expansion of specific cells or pathogens [5,12–14]. The list could be continued *ad libitum*, but nevertheless, even most of these functionalizations have important restrictions so that they either act only transiently (e.g., those drugs mentioned above or surface modifications that are masked over time by proteins) or are durable with defined fixed functions unable to respond and adapt dynamically to changed biometric parameters. Existing functionalized devices, and those currently under construction, amend and enhance implant performances but are still limited in their ability to actively respond to a specific problem.

Future perspective

Research and development are dynamic and fast-expanding processes that warrant the discovery of multiple additive implant functions and base materials in the near future. However, for several reasons we believe that most will never find their way into broad clinical use and will not account for considerable improvement of medical prostheses and implants. In this regard, we hold the view that, to date, the following issues have not been sufficiently addressed and considered:

- Currently, due to production costs, the availability of commercial medical products, whether functionalized or not, is often limited to a small spectrum of alternatives. Thus, the operator is not able to implant the optimal

prosthesis into an individual patient, but only that, which is the most optimal out of the available spectrum of industrial prostheses. Obviously, a personalized treatment according to individual needs of a certain patient is almost impossible for this reason;

- The combination of a medical standard product with an active locally or systemically acting component as is in pharmacologically functionalized implants, entails a regulatory shift of its admission and certification. Thus, a standard medical product turns into a medicinal product, a process that often requires the completion of extensive and protracted protocols and is associated with high financial expenditures;
- Another aggravating aspect is that prospective serial productions of these hybrid products may be constrained and complicated by the fact that conventional sterilization processes (e.g., in the case of protein-based functionalization) and other industrial engineering techniques are not applicable;
- The generation and clinical application of individual and patient-specific functionalized medical implants in the era of personalized medicine demands the supply of not only single patients but broader levels of the population.

As mentioned above, the more complex hybrid products are getting, the more expensive and extensive the legal requirements for its certification and admission and thus, the resulting product costs. Furthermore, the generation of specific, individual need-adapted functionalized implants manufactured to supply broader levels of the population, necessitates the establishment of a huge organizational apparatus to manufacture small product series or even customized single prostheses. From the view of the healthcare market and the socioeconomic system in general, the financing of such products will obviously not be feasible anymore. From the manufacturer’s view, a cost reduction will not be profitable and thus, the idea of personalized medicine is not alluring. In conclusion, the individual patient is and will always be the most important person in terms of medical treatment. However, he or she will not benefit at all from these approaches and prospective refinements, heroic and sophisticated as they may.

Acting in both areas, basic sciences and clinical practice, we believe that the only realistic and feasible answer to this problem is to integrate and involve the operator into the manufacturing process. They are the only ones who:

- Know about the individual and specific needs of a patient;
- Are able to recognize and estimate (acute) alterations of the clinical status;
- Are able to spontaneously react in response to these changes.

Thus, medical implants in the era of personalized medicine have to be tailored and individualized, these highly specific functionalized implants should be manufactured/finally functionalized directly on-site within the operating theater and at the time of implantation. Following this route, single components could still be manufactured in larger and thus, economically attractive series and potentially technically challenging features such as difficult sterilization processes, among

others, could be facilitated or even avoided for that the implant remains within the highly clean environment of the operating theater and within a single institutional unit. Additionally, the latter provides essential advantages with respect to legal aspects of product admission and certification. Should it be prospectively possible to further generate implants that are able to autonomously and dynamically modulate their multiple functions in direct response to changing biometric parameters or which can at least be switched and modulated from outside the body, the vast majority of medical conflicts associated with implants could be solved.

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