

**Gudrun Lettner*,
Jean Schmitt**

Summary

The 'stealth effect' refers to a camouflage mechanism that enables bacteria to evade the immune system. In medical research, this phenomenon is utilized to significantly increase both circulation time within the body and precision in targeting disease foci. The primary areas of application lie in targeted tumor therapy, but also include the diagnostics of infectious diseases such as cholera, as well as the treatment of chronic inflammatory bowel diseases. This dossier provides an overview of various natural and synthetic coating methods, many of which are inspired by the model of camouflaged nanoparticles. These include coatings with polymers to increase circulation time in the bloodstream, as well as the use of biomimetic cell membranes that ensure excellent biocompatibility.

Alongside the opportunities for personalized medicine, potential dangers encompass biological risks due to the inherent potential for infection, uncontrolled mutations, and the spread of antibiotic resistance, as well as the potential for misuse up to and including bioterrorism. To clarify and contextualize these anthropogenic risks, the dual-use dilemma is addressed, providing the basis for demonstrating the imperative need to establish global safety standards prior to any clinical application of coated stealth bacteria.

* Corresponding author

Coated Stealth Bacteria

Potentials and Risks of Surface-Modified Bacteria

Introduction

Bacteria are now used in a wide range of technical fields – from cellulose extraction for textile production¹ to semiconductor materials², eco-friendly composite materials for energy conversion³, wastewater treatment⁴, and even self-healing concrete⁵. Currently, various EU projects are investigating bacteria as stimulants in agriculture (AgriGel), for tumor diagnostics (DroneMTB), or for the recovery of valuable materials from electronic waste (MS-GMT). Meanwhile, medical research is intensively investigating potential applications of artificially coated bacteria for therapeutic purposes. This so-called stealth coating, also known as the "cloaking effect", has been researched for nanoparticles (NP) for decades: it prevents, for example, the body's own proteins from depositing on the particle's surface and thus alerting the immune system. The stealth effect describes the phenomenon by which NPs remain hidden from the immune system and escape premature elimination, much like a "stealth aircraft avoids detection by conventional radar".⁶ Otherwise, NPs can trigger an immune response and be rapidly excreted. Furthermore, it is worth mentioning that NPs themselves are often potentially toxic, capable of causing oxidative stress or triggering inflammation.⁷

Research is currently attempting to apply the findings, methods, and processes used for nanoparticles in medical diagnostics and therapeutics to bacteria.

Applications and Potentials

New Horizons in Oncology

Due to their unique properties, Engineered Bacteria (EB) play a vital role in the research and development of new tumor therapies. These include improving the immune response, optimizing therapeutic efficacy, and developing personalized cancer therapies. Using new genetic engineering methods such as CRISPR-Cas – the cutting and altering of DNA strands – the functionality of bacteria can be precisely controlled to identify tumor cells specifically and strengthen the body's own immune response. Another specific feature of modified bacteria is that they release thera-

peutic agents while simultaneously competing with tumor cells for nutrients and space. The therapeutic effect can be adjusted so that, for example, immunosuppressive signals emitted by the tumor cell are countered by the production of specific messenger substances (cytokines). Likewise, modified bacteria can generally trigger and improve the immune response against tumors by activating various immune cells.⁸

Furthermore, bacteria loaded with NPs are being researched as a platform for cancer vaccines. Through mineralization with manganese dioxide (MnO₂), improved tumor detection and removal have been achieved, while simultaneously curbing the recurrence of tumor cells. The injection of NP-coated *Salmonella* bacteria resulted in the accumulation of tumor antigens and subsequently led to the regression of malignant tissue due to an adapted immune response.⁹

Potential in Chronic Inflammation and Diagnostics

Beyond the treatment and prevention of tumor diseases, coated stealth bacteria are also regarded as having a great potential in the diagnosis and treatment of intestinal diseases. They offer an alternative to conventional biomarkers, because they effectively bridge systemic deficits of conventional methods, such as dietary fluctuations or delayed results. Their use in detecting inflammatory bowel diseases such as *Crohn's disease* is also being researched; however, there are no clinical studies yet, partly due to a lack of regulations.

The portfolio of diseases that can be treated with EB is broad, ranging from the diagnosis of cholera to the diagnosis and therapy of periodontitis, metabolic diseases, and many more. However, practical application has not yet been established: unlike purely medicinal administration, no modified bacterium has yet been officially approved for therapeutic or diagnostic purposes.⁹

Nanoparticle Cloaking as a Model

In medicine, NPs are used, amongst other things, as carrier systems for targeted drug delivery and for the stabilization of active ingredients. However, the body's immune defence identifies them as foreign bodies that would be immediately removed without appropriate camouflage. To ensure that the NPs reach their goal and fulfil their task, they are accordingly coated.

As early as 1977, a study¹⁰ reported successful PEGylation, an artificial coating using polyethylene glycol, which reduced immunogenicity (the ability to activate a defence reaction), and extended the circulation time of the particles. Decisive for the successful use of nanoparticles in tumor therapy is the EPR effect (Enhanced Permeability and Retention), in which the tumor's leaky vascular structure allows particles in but traps them inside. To utilize this effect, the NPs must circulate in the body for an extended period. Without a protective layer, intravenously administered particles are broken down within minutes by the body's filtering system (the reticulo-endothelial system, RES) in the liver and spleen.¹¹ During the last decades, several different coating techniques have been developed to reach this stealth effect.

Despite the so-called "PEG dilemma", the difficult balance between prolonged circulation in the blood and the necessary uptake into the target cell, PEGylation has proven to be the gold standard and is therefore being used in clinical applications in therapeutics and diagnostics. With its help, drugs are made water-soluble; it cloaks the molecule from the immune system, suppresses its response, and protects the particles from enzymatic degradation. Thereby it increases circulation time in the bloodstream, enhances the efficacy and stability of active ingredients, and simultaneously ensures better tolerability and reduced toxicity of drugs.^{11,12} In recent years, several PEGylated nanoparticles have been approved in the EU and USA for the treatment of various types of cancer (e.g., breast, pancreatic), Hepatitis B and C, and Multiple Sclerosis.¹³

In preclinical studies, Cell-Membrane-Coated Nanoparticles (CMCNPs) are utilized to prevent premature destruction by the immune system. Simultaneously, this approach equips them with the ability to adopt cellular structures and functions. Through this biomimetic functionalization of the NPs with purified cell membrane derivatives, the particles demonstrate a significantly improved capability to directly reach organs and tissues (*targeting*), and to increase therapeutic efficacy.⁷

This group includes, for example, coatings based on erythrocyte membranes (Red-Cell-Membrane-Coated Nanoparticle, RCMCNPs). These bring a variety of advantages. Since red blood cells are present in high concentrations in the body, they are easy to isolate. They also possess the capability to transport NPs across the blood-brain barrier, which is a key property for the treatment of diseases of the central nervous system. This biomimetic masking prevents RCMCNPs from being identified as foreign bodies and prematurely eliminated. Another example is tumor cell membranes, which exhibit high availability due to their straightforward *in vitro* cultivation and already possess a priori mechanism for immune evasion.

For deeper insights into the topic of nanocarriers and their diverse areas of application and potential, see NanoTrust Dossier No. 62.¹⁴

Natural Strategies: How Bacteria Protect Themselves

Bacteria naturally possess mechanisms by which they attempt to evade the body's own immune defence. One strategy is the formation of a biofilm. In doing so, they envelop themselves in a layer of complex sugars (polysaccharides), which not only complicates their identification, but also resists both the immune response and antibiotic attacks. Specifically, a bacterium's resistance to antibiotics, which increasingly poses major challenges to medicine, can be enhanced 10- to 1,000-fold through the formation of a biofilm. Promising results for getting this problem under control are shown by studies on engineered phages (viruses that attack bacteria). These explicitly attack biofilms and have the potential to destroy them.¹⁵

By enveloping the bacterium, extracellular polymeric substances (EPS), which include biofilms, provide physical camouflage. These substances form a gel-like 3D structure consisting of a multitude of biological molecules (including polysaccharides, lipids, and extracellular DNA) and play a central role in maintaining the mechanical integrity of the bacterial biofilm. Thereby, they protect the bacterium from UV radiation as well as from phagocytes, specialised cells of the immune defence.¹⁵

Artificial Protective Layers for Therapy

Many of the insights gained from the coating of therapeutic NPs can be applied to the medical use of bacteria. Current research literature likewise highlights the development of PEG coatings in this context, as well as cell membranes, nanomaterials, or materials of mineral origin.

PEG Coating

In animal testing, PEGylated bacteria were successfully utilized to build up the mucosal barrier, a mucus layer that protects organs like the digestive tract from the invasion of microorganisms and toxins. Its collapse can trigger metabolic, autoimmune, and chronic inflammatory bowel diseases. Thanks to the PEG coating, orally administered bacteria were able to penetrate the mucosal barrier, strengthen its barrier function, and thereby curb the progression of chronic inflammation as well as diabetes.¹⁶

Table 1: Artificial coatings of biological vs. non-biological origin

Category	Material	Main Function/Advantages
Biologically derived	Cell membranes [erythrocytes, tumor cells, yeast]	Maximum biocompatibility, specific tissue targeting, blood-brain barrier passage
	Proteins and lipids [silk fibroin, polyamino acids]	Increased bioavailability upon oral ingestion, mechanical integrity
	Natural polymers [other] [alginate, chitosan]	Protection against gastric acid, low toxicity, antibiotic resistance
Synthetically/minerally derived	PEG [polyethylen glycol]	Gold standard: water solubility, protection from enzymatic degradation, prolonged circulation
	Synthetic polymers [PHEA, polydopamine]	Alternative to PEG with lower accumulation risk, improved survival rate in the gastrointestinal tract
	Nanomaterials [gold NPs, ICG-loaded NPs]	Photothermal therapy [ablation/killing via heat], remote-controlled protein release via NIR light
	Minerals/Ions [calcium ions, mineral layers]	Ultra-resistance to oxygen, ethanol, and extreme environmental conditions

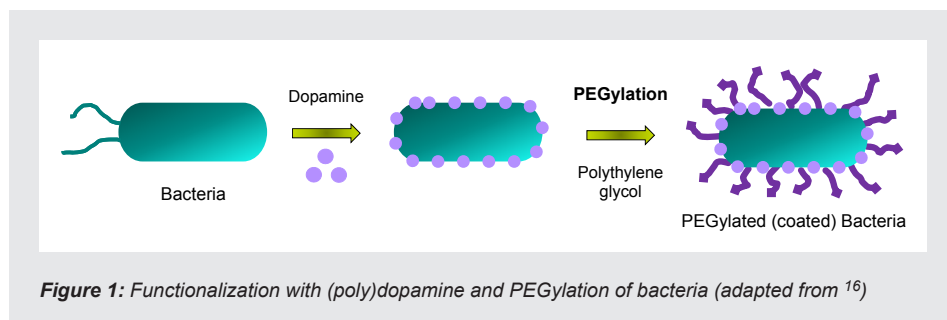


Figure 1: Functionalization with (poly)dopamine and PEGylation of bacteria (adapted from ¹⁶)

Other Polymers

Among the natural polymers that have proven promising for bacterial coating are polysaccharides, polyamino acids, proteins, and lipids. Among the polysaccharides, alginate in particular has become a focus of research. Due to their resistance to gastric acid, alginate-coated lactobacilli could be transported as far as the small intestines. Furthermore, by forming a biomimetic film, they demonstrated resistance to antibiotics. Current efforts focus on overcoming the challenges associated with coating, such as instability or uncontrollable swelling.¹⁷

Chitosan, another polysaccharide, combined with polydopamine likewise significantly improves the survival rate of EcN (*Escherichia coli* Nissle1917, a probiotic bacterial strain widely used in research) within the digestive tract. It is further characterized by low toxicity, biocompatibility, and biodegradability. Both substances are also used independently of each other as coatings for bacteria.¹⁸

Among the polyamino acids, PHEA (polyhydroxyethyl-L-asparagine) shows promising results, as it behaves very similarly to PEG but carries less accumulation potential and associated risk of toxicity.¹¹

Due to their biocompatibility, biodegradability, and low immune response, lipids and proteins are highly valued as coating materials for bacteria.¹⁷

Nanomaterials

In the field of synthetic coating materials, research is being conducted on various nanomaterials, among others. Indocyanine green-loaded nanoparticles (ICG) were successfully coupled with genetically modified *Salmonella Typhimurium* YB1. Following intravenous injection, they accumulated in the tumor tissue and, thanks to their photothermal (the conversion from light into heat) killing abilities, led to the complete eradication of large tumors. Another possibility is the use of gold nanoparticles with heat-sensitive, pro-

grammable bacteria. Upon irradiation with near-infrared (NIR) light, the gold nanoparticles can trigger bacteria to release proteins that inhibit the tumor.¹⁷

Chemical and Mineral Protective Coatings

Besides physical approaches, chemical coating methods represent another viable strategy. The latter include, for example, encapsulation with a multifunctional nanocoating made of silk fibre protein or calcium ions. Depending on the material employed, the bacteria camouflaged in this manner exhibit increased resistance to alcohol, antibiotics, or harsh environmental conditions. Silk fibroin used as a coating material provides the carriers with enhanced bioavailability of active ingredients upon oral ingestion. Another variation is mineralization: a method in which the bacteria are coated with an ultrathin inorganic layer, rendering them ultra-resistant to environmental influences (such as oxygen and UV radiation) or highly concentrated ethanol.

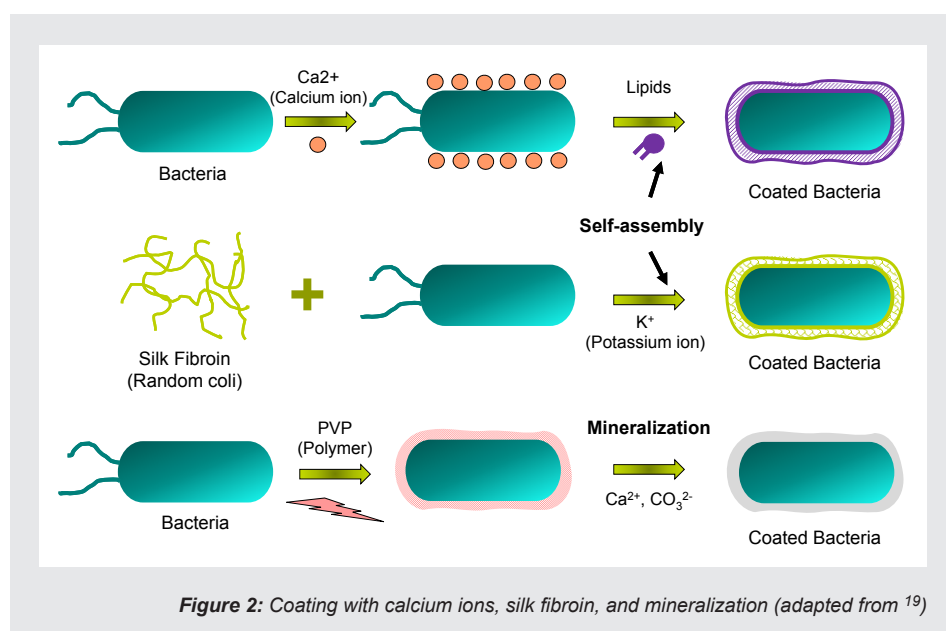


Figure 2: Coating with calcium ions, silk fibroin, and mineralization (adapted from ¹⁹)

Cell-based materials

In the case of bacteria, coating them with cell membranes derived from red blood cells leads to excellent biocompatibility and specific targeting capabilities. Furthermore, manipulating bacterial behaviour is possible through transformation into CMCB (Cell Membrane-Coated Bacteria). A significant reduction in immune response and clearance of the CMCB was observed, thereby promoting accumulation in tumors. Coating with yeast cell membranes has been shown to increase the survival rate and stability of bacteria in gastric acid, which in turn leads to their accumulation in lymph nodes.¹⁹

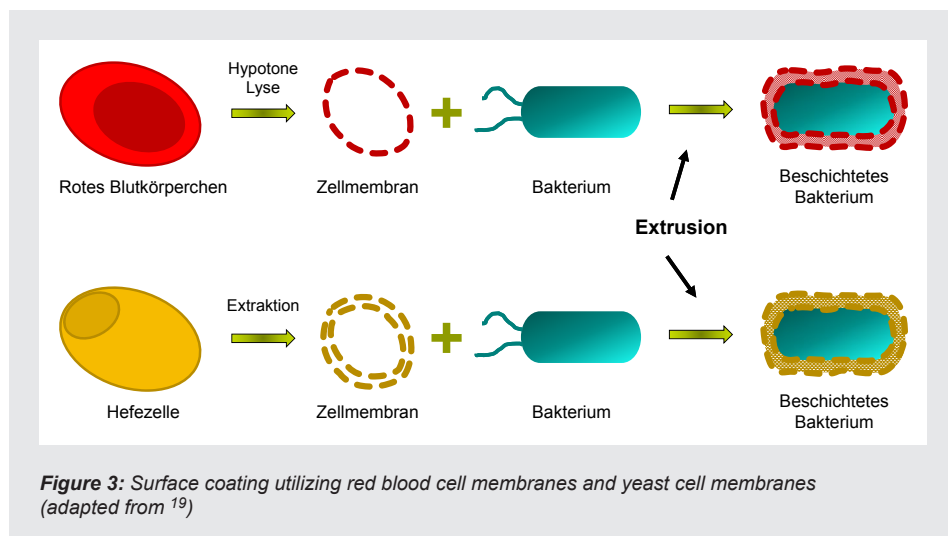
Risks and Responsibility

Safety Concerns in Application and Production

The primary concerns regarding the use of modified bacteria relate to their inherent **risk of infection** as well as their ability to trigger an **immune response** in the body (immunogenicity).⁸

Although genetically modified probiotic strains of EcN show high potential against various diseases in animal studies, they also carry the **risk of mutation**. Undesired changes could range from negative (pathogenic) effects on patients to environmental contamination.²⁰

To prevent uncontrolled dissemination, genetic “safety switches” (kill switches or suicide switches) are integrated, which are designed to ensure the safe elimination of the respective bacterium



after successful deployment. These inherent self-destruction mechanisms are based on various modes of operation. Some rely on temperature dependence²¹, while others, such as passcode or deadman kill switches, are based on the suppression or release of substances that are essential or life-threatening to the bacterium, respectively.²² However, all systems share a common vulnerability: spontaneous mutation could render their safety anchor useless. To increase the reliability of these suicide switches, research in recent years has increasingly turned to methods based on the CRISPR-Cas gene-editing tool.²⁰ In this approach, the bacteria used as therapeutics – specifically EcN – are genetically adapted to trigger cell death upon contact with a chemical inducer. Another variant combines the chemical component with a thermal one. If the temperature falls below a specified threshold, as can be expected upon excretion from the host, an inducer is no longer required to cause the bacterium to die off. This is intended to minimize the risk of **environmental contamination**.

In risk assessment, it is necessary to consider not only contamination, but also biopersistence resulting from the bacterial coating, as well as altered replication capacity and the potential development of unintended antibiotic resistance. In particular, the prevention of resistance that could be transferred to the body's own microbiome via horizontal gene transfer (see Figure 4) represents an important field of research. This process leads to the acquisition of genetic information from other microorganisms by the bacteria, which integrate the encoded traits, such as resistance, in their own genome.^{9,23}

From a production perspective, the **stability of the coating** is a crucial aspect of safety considerations. One of the greatest challenges regarding stability arises from the proliferation (multipli-

cation by cell division) of the bacteria, which rapidly leads to the shedding of chemical coatings.²⁵ Furthermore, developing efficient, stable, and cost-efficient processes to achieve **large-scale vaccine production** currently remains a veritable challenge.⁹

Misuse: The Dual-Use Dilemma

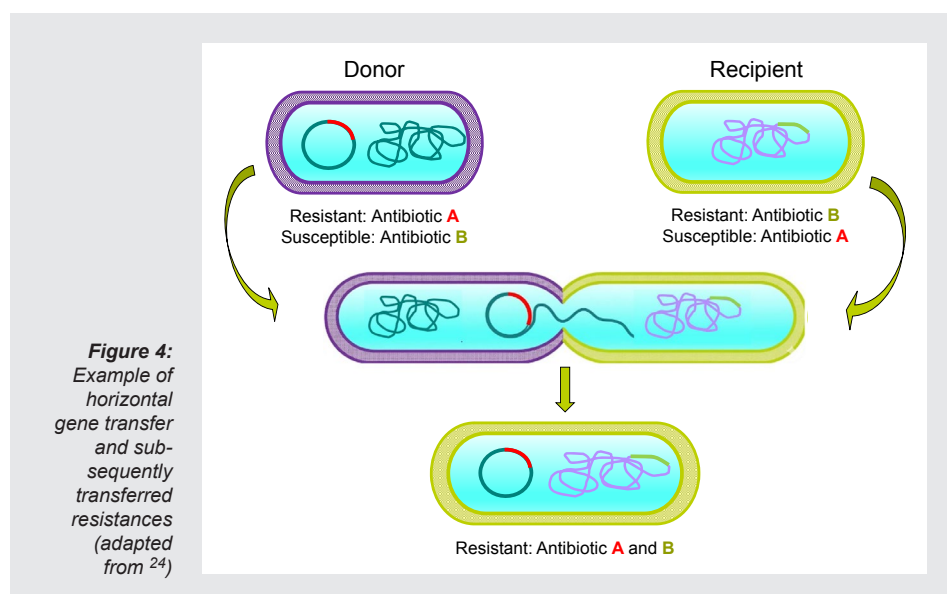
The dual-use dilemma describes the risk that findings from well-intentioned research in the natural and life sciences could be used to cause harm to humans, animals, or the environment. When little to no adaptation is required for potentially harmful applications, this is referred to as Dual-Use Research of Concern (DURC).^{26,27}

The Code of Conduct for Biosecurity, formulated in 2007 by the Royal Netherlands Academy of Arts and Sciences (KNAW)²⁸, aims to prevent

the misuse of biological agents as biochemical weapons. It addresses various stages along the lifecycle, ranging from raising awareness about dual-use potentials, through internal and external communication and the publication of research findings, to transport and shipping.

The terminology DURC can be found, for example, in publications by the WHO²⁹, directly linking dual-use to malicious applications. This raises questions that are objectively difficult to answer, particularly regarding the evaluation result of "of concern". Who decides on this, how is this decision made, and who bears the responsibility if necessary?³⁰ EU regulations differentiate dual-use according to various aspects. Fundamentally, the focus is on awarding funding only to research projects that explicitly exclude potential military applications. Further regulations address the issue of misuse, as well as the potential export of dual-use items from the EU and their possible application in chemical, biological, radiological, or nuclear (CBRN) weapons.³¹

Synthetic Biology (SynBio) is an emerging field that enables, for example, the production of synthetic viruses and bacteria. Consequently, however, it also represents one of its greatest uncertainties: this "democratization" of technology, namely the combination of simplicity, availability, and affordability, creates an increased risk of bioterrorism. The production of multi-resistant strains of bacteria has already been carried out successfully. The danger of a biological attack using lethal multi-drug-resistant pathogens can no less be disregarded than the potential escalation of this threat through the integration of AI (artificial intelligence) and machine learning.^{32,33}



Bioweapons

Through additive manufacturing, the production of tissue using 3D printing has become possible. For instance, *E. coli* bacteria have already been “printed” successfully, as have oncolytic viruses or viable bacteria embedded in clothing. It is therefore easily conceivable that in the future, tailor-made microbes, viruses, and toxins incorporated into appropriate carrier substances could be produced via biological 3D printing. Furthermore, this technology potentially facilitates the cost-effective testing of bioactive agents, such as biological weapons (bioweapons), while simultaneously complicating detection if highly infectious agents are produced in small quantities.³⁴

Additionally, a real threat potential exists through the exploitation of private service providers and manufacturers by criminal forces. The commercialisation of services and particularly products in the field of SynBio would need to be regulated (more) strictly to prevent misuse. In China, where a Biosecurity Law was implemented in 2021 as a framework for, among other things, the safe handling of SynBio research, the establishment of formal, open community laboratories is being considered.³⁵ Actors from the “do-it-yourself biology” scene (biohackers), who are credited with great potential in China’s high-tech sector, are to be given the opportunity to pursue their (amateur) research in a safe and regulated environment. Such public research facilities would not only serve to prevent accidents, but also raise awareness among hobby researchers regarding the necessity of appropriate regulations that are promptly adapted to the fast-moving field of SynBio. New standards are urgently needed, especially for the synthesis of bacteria, viruses, and other pathogens that could be used for the production of bioweapons or by bioterrorists.

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Conclusion

Medical research on coated stealth bacteria – engineered bacteria with the ability to evade the body’s immune response – has made remarkable achievements. The diversity of coating possibilities extends from polymers (in particular PEGylation using polyethylene glycol) to cell-based materials such as membranes of red blood cells, all the way to the use of gold nanoparticles. The fields of application are no less diverse – targeting metabolic diseases as well as cholera or periodontitis – with the primary focus on tumor diagnosis, prevention, and treatment. Despite impressive laboratory results, there are currently no clinical trials on immune-camouflaged bacteria. In addition to practical hurdles³⁶ such as sterilizability, storage, or coating stability, the primary reasons for this lie in safety concerns regarding these medical ‘Trojan horses’: Undesired mutations could not only pose health risks to treated patients but could also trigger antibiotic resistance and environmental contamination. Integrated self-destruction mechanisms, whose safe and reliable deployment is likewise a subject of current research, are intended to prevent these unintended modifications.

A completely different threat arises from the inherent dual-use potential of synthetic biology: technologies developed with the best of intentions can cause enormous harm if misused. The deployment of coated stealth bacteria as a bioweapon represents one such case. Existing EU-wide and national regulations attempt to cover individual fields of application. In view of this rapidly changing field of research, continuous regulatory adaptation involving the numerous stakeholders is required. As promising as the results in the respective fields of application may be, in terms of risk assessment, establishing comprehensive and, ideally, global standards prior to *in vivo* applications is indispensable to prevent the worst-case scenarios associated with the misuse of SynBio research, as themed in cinematic and literary dystopias, from becoming a reality.

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