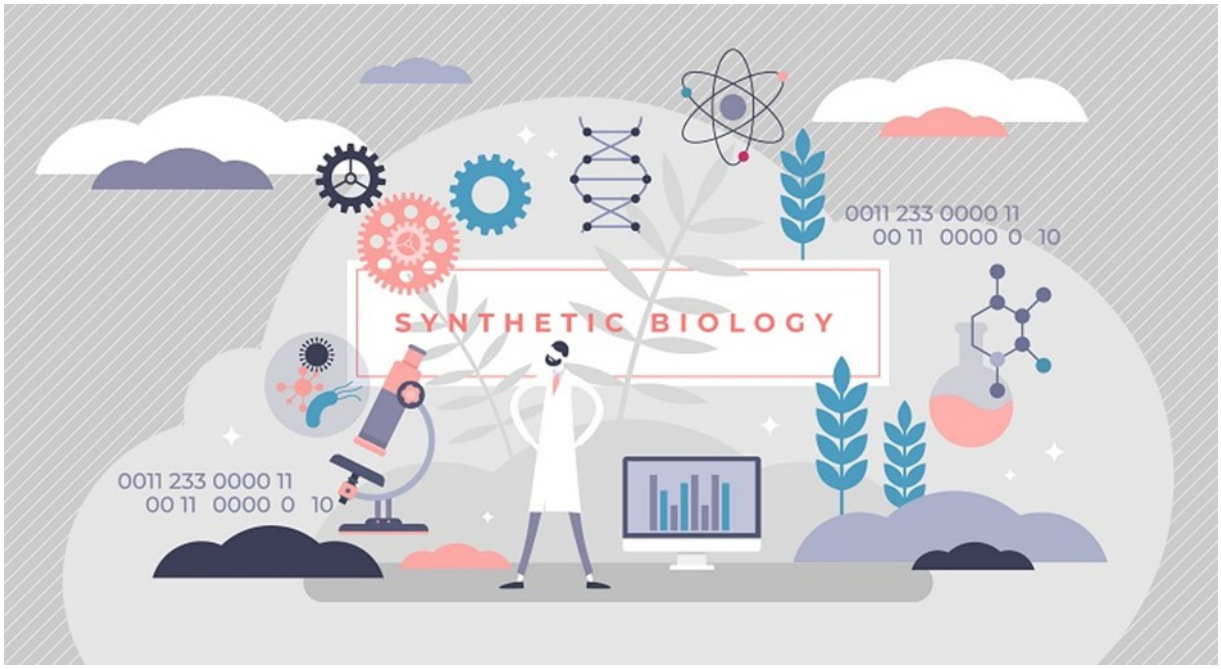
Synthetic Biology



4th Report of the Central Committee on Biogical Safety (ZKBS)

Period: 2022–2025

ZKBS
Zentrale Kommission für die Biologische Sicherheit

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Contents

1 Introduction

The Central Committee on Biological Safety (ZKBS) has been monitoring advancements in synthetic biology for more than 15 years in order to provide expert and critical oversight and comprehensive biosafety assessments of ongoing scientific developments. The resulting reports were published in 2012, 2018 and 2022. While the first report focused on research activities within Germany, subsequent reports expanded their scope to examine global scientific developments.

Since 2018, the ZKBS website has also featured an annual selection of publications deemed particularly representative and relevant to the research fields defined by the ZKBS as synthetic biology (https://zkbs-online.de/en/synthetic-biology/current-developments).

This fourth report presents developments across various research areas within synthetic biology, based on publications from 2022 to 2025 that were selected by the ZKBS for its website. Furthermore, the ZKBS assesses whether these advances fall within the scope of the German Genetic Engineering Act (GenTG) or the relevant European Directives regarding potential risks to biosafety.

Research into the creation of mirror life currently poses no risk to biosafety, as the generation of self-replicating mirror organisms is not yet technically feasible. The potential risk that could arise from such a future development cannot, at present, be conclusively assessed.

For a comprehensive introduction to synthetic biology, please refer to the reports published previously (https://zkbs-online.de/en/synthetic-biology/overview).

2 Developments in the research fields of synthetic biology and evaluation by the ZKBS

To date, no generally accepted definition of synthetic biology exists, as it does not constitute a distinct, clearly delineated scientific discipline. Instead, it represents a convergence of many specialist fields with differing objectives. In its monitoring activities, the ZKBS focuses on seven defined categories of research areas within synthetic biology. These are:

- Synthesis of genes and genomes
- Synthesis of molecular switches and genetic circuits
- Synthesis of customised metabolic pathways
- Generation of proto-, minimal and synthetic cells
- Xenobiology
- Methods with impact on synthetic biology
- Synthetic biology with application perspectives

The seventh category was newly introduced in the previous monitoring report. This research field presents and evaluates work which, based on the fundamentals of synthetic biology, demonstrates significant potential for practical applications.

The results of the ongoing monitoring from 2022 to 2025 are briefly summarised below. More detailed summaries of the majority of the publications can be found on the ZKBS website (https://zkbs-online.de/en/synthetic-biology/current-developments).

2.1 Synthesis of genes and genomes

As already described in the previous reports, the development of synthetic genomes has continued in recent years. For example, progress has been made on the Synthetic Yeast Genome Project (Sc2.0), which has now synthetically produced all 16 yeast chromosomes as well as a 17th *de novo* neochromosome [1]. New approaches to the construction of synthetic chromosomes also enable the assembly of large DNA fragments, the step-by-step replacement of genome segments, and the transfer of artificial chromosomes into new hosts [2–4]. Among other applications, a *de novo* designed synthetic accessory chromosome was successfully introduced into yeast strains to expand their metabolic network [4]. For the first time, a synthetically designed chromosome segment was successfully integrated into the natural genome of a multicellular organism, the terrestrial moss *Physcomitrium patens* [5]. Furthermore, methods for genome recoding in human cells were established, in which stop codons were replaced by multiplex base editing [6]. A DNA recorder (peCHYRON) was presented, capable of recording a transient biological event in mammalian cells through targeted, permanent genome edits that can subsequently be read out via DNA sequencing [7]. Furthermore, the AI-supported language model for genomics, Evo 1.5, enables the generation of novel (new-to-nature) functional genes and biological systems [8]. Generative DNA language models increasingly enable the function-guided design of genes without requiring significant sequence similarity to natural genes with the same function. Consequently, biological function can increasingly be decoupled from an association with known donor sequences at the protein and DNA levels [9].

Assessment by the ZKBS:

As detailed in the preceding three reports, capabilities for synthesising complete genomes continue to advance. However, no *de novo* design of complete genomes has been realized yet; the *in vitro* synthesised genomes are still strongly based on their natural counterparts. Consequently, a comparative risk assessment remains possible. Meanwhile, however, novel genes have been designed that lack a traceable donor organism. As the performance of generative AI models continues to improve, the predicted or experimentally determined function of synthetic nucleic acid segments will therefore become increasingly important for the risk assessment in the future, alongside sequence similarity.

The ZKBS considers that the risk assessment of genetically modified organisms (GMOs) produced using nucleic acid segments that are novel in nature is possible under current genetic engineering legislation, even if these nucleic acid segments cannot be attributed to a donor organism (see Section 4, sentence 1, no. 1, point d of the German Genetic Engineering Safety Ordinance (GenTSV)). The risk assessment is then carried out on the

basis of Section 5 of the GenTSV in conjunction with Annex 1, taking particular account of the known and predictable information regarding the transferred nucleic acid segment (see Section 5(1), no. 2 of the GenTSV in conjunction with Annex 1, no. 2.1(b)). Accordingly, the GMO may also be assigned to a higher risk group if it cannot be ruled out that an introduced nucleic acid segment increases the GMO's hazard potential.

The mere *in vitro* synthesis of genes and genomes does not fall within the scope of the GenTG, provided the resulting nucleic acid segments are not introduced into living organisms. If newly synthesised and modified genes or genomes are introduced into living organisms, this constitutes a genetic engineering operation according to the GenTG, unless these modifications could occur naturally by mating or natural recombination.

2.2 Synthesis of molecular switches and genetic circuits

Advanced approaches to the control of CAR-T cell therapies were presented, including logic-controlled LINK-CARs [10], off-switch adaptors for universal CARs [11] and CARs with a synthetic intramembrane proteolysis receptor (SNIPR), which can guide CAR-T cells to solid tumours [12]. Further new synthetic receptor systems include a photoreceptor established in plants, which is activated by blue-green light and is also applicable in prokaryotes and other eukaryotes [13], as well as a system based on two receptor domains (a protease and a releasable transcription factor) that is sensitive to adaptable extracellular protein signals with a customised output, e.g. a fluorescence signal [14]. In the field of biosensor technology, proteins have been developed whose fluorescence changes in response to an external magnetic field [15], as well as bacteria that respond to specific environmental stimuli by forming characteristic swarm patterns [16]. Artificial gene regulation has been expanded by a novel class of riboregulators, known as split-intron-enabled trans-splicing riboregulators (SENTRs) [17], as well as by small RNAs that dynamically modulate gene expression in genetic circuits with a broad spectrum of repression (high, medium and low) [18]. Furthermore, Cas proteins have been engineered into translational modulators in mammalian cells [19].

A new modular system enables contact-dependent communication between cells (mating-peptide anchored response system, MARS) as well as specific cell-cell adhesion (*Saccharomyces* Adhesion Toolkit for mUlticellular patteRNing, SATURN) in yeast cell clusters [20].

The so-called synpoptosis circuit triggers targeted cell death in mammals via modified apoptosis and pyroptosis proteins [21].

An enzyme functions as a UV-light-sensitive switch through the incorporation of a non-canonical amino acid, which prevents it from being inhibited through a feedback loop by its natural inhibitor. UV light removes a bulky o-nitrobenzyl group, allowing the inhibitor to bind to the enzyme once again [22]. Genetic circuits have been developed for plants that enable the specific gene expression in different tissues. These circuits have been used to modify the lateral growth of the lateral roots of *Arabidopsis thaliana* [23]. Orthogonal synthetic promoters have also been developed for use in plants, regulated by the endogenous signalling molecule ethylene [24].

In cancer therapy, research has been conducted regarding genetic circuits in bacteria which, following a temperature increase induced by ultrasound, lead to the targeted release of cytokines [25]. Furthermore, miRNAs are used in artificial logic circuits capable of performing various computational operations within cells. In artificial DNA circuits, miRNAs act as input signals that specifically activate or inhibit subsequent DNA reactions via strand displacement processes [26].

Neural networks have been developed *in silico* for bacteria to programme their behaviour to solve optimisation problems or to respond to changing environmental conditions [27]. In mammalian cells, logic gates have been constructed based on the incorporation of two different non-canonical amino acids. These circuits are active only in the presence of one or both of the non-canonical amino acids [28]. So-called bactoneurons have been constructed in *Escherichia coli*, each with three inputs and three outputs, together they form five artificial neurosynapses. They are used for cellular computational operations [29]. Multistability was achieved in mammalian cells using a circuit consisting of transcription factors. This process allows a cell to transition into a specific state in response to external stimuli in combination with the built-in circuit [30]. In addition, a wirelessly controllable electronic system was developed for minimally invasive biomedical applications. In this system, nanoparticles respond to an electromagnetic field by generating reactive oxygen species, which in turn serve as a signal for the expression of a transgene. The system was validated for the control of blood glucose levels in mice with type 1 diabetes [31].

Assessment by the ZKBS:

The design of genetic circuits involves combining precisely defined and usually functionally well characterized DNA segments. The circuits are often introduced into well-established model organisms, using a biosafety measure. As already stated in the last two interim reports, such processes generate GMOs that fall within the scope of the GenTG.

2.3 Synthesis of customized metabolic pathways

The publications address the optimisation of the CO_2 metabolism, the production of synthetic active substances, energy conversion and artificial photosynthesis.

The yeast *Komagataella phaffii* has been modified to utilise CO_2 as its sole carbon source whilst simultaneously producing organic acids such as itaconic acid or lactic acid [32]. Furthermore, the THETA cycle – a new-to-nature CO_2 fixation pathway – has been developed, which efficiently converts gaseous CO_2 into acetyl-CoA [33]. The lactyl-CoA mutase module has also been described, which efficiently converts acetyl-CoA into pyruvate without releasing CO_2 [34]. Another newly developed metabolic pathway is the artificial phosphoketolase pathway, which, unlike glycolysis, breaks down simple sugars (monosaccharides) into acetyl-CoA without any losses [35].

The newly developed BIOPOLYMER platform utilises genetically modified *Streptomyces coelicolor* strains to produce novel anthracycline analogues [36]. A yeast cell factory enables the scalable production of 24-Epi-ergosterol, which occurs extremely rarely in nature and is a precursor to a plant hormone that plays an important role in agriculture by

increasing crop yields and the quality of harvested produce [37]. The abiological carbene transfer reaction has been incorporated into a bacterial biosynthetic pathway for the first time, expanding the range of organic substances that can be produced by cellular metabolism [38]. A newly developed metabolic pathway can reduce formate to formaldehyde both *in vitro* as well as *in vivo* in *E. coli* using just two enzymes and inorganic phosphate (P_i) [39].

The acid/aldehyde-ATP cycle, a new-to-nature electrobiological module, enables a cell to convert electrical energy directly into ATP and can be coupled to other *in vitro* processes such as transcription/translation systems [40]. A C2-symmetric designer protein has been engineered which functionally binds excitonically coupled chlorophyll pairs (special pairs) and enables artificial light excitation and energy transfer [41]. By inserting genetic components of the α-carboxysome from a proteobacterium, morphologically correct carboxysomes were generated in tobacco chloroplasts. This work paves the way for improving photosynthesis and the productivity of crop plants [42]. A new method has been developed to transfer the genes required for specific metabolic pathways across species using iModulons (groups of co-expressed but potentially independently regulated genes) [43].

Assessment by the ZKBS:

For the development of novel customised metabolic pathways, existing genes are modified or genes from another organism are introduced into an already existing organism. This could enable the specific formation of hazardous substances. However, the production and handling of these organisms are fully covered by the GenTG.

2.4 Proto-, minimal and synthetic cells

During this reporting period, no publications were identified that offer significant new developments in the *top-down* production of minimal cells compared to the work covered in previous reports.

In *bottom-up* protocell engineering, the use of giant unilamellar vesicles (GUVs) remains predominant, complemented by giant unilamellar niosomes [44], protein vesicles [45] and nucleated cells in the form of vesicle-in-vesicle structures with genetically controlled communication between compartments [46]. Polymerisation-induced self-assembly has been proposed as a new synthesis method for GUVs [47]. Complete plant cell walls [48] and cell scaffolds based on DNA, RNA or bacterial fragments [49–51] have been engineered. Artificial compartments were created from DNA, dipeptide or protein coacervates, RNA nanostructures and silicon dioxide [52–54]. These compartments, among other functions, spatially separate two chemically incompatible processes within GUVs [55], mimic mitochondria [56], or facilitate metabolically controlled transcription [57]. A synthetic bacterial microcompartment has been established in chloroplasts [58]. Using DNA origami, a rotary motor comparable to an ATPase that can self-assemble has been encoded [59], and DNA origami tweezers have been produced for the targeted control of GUV morphology [60]. Furthermore, the intracellular transport system, consisting of a colloidal motor and self-assembling lipid tubes, has been replicated [61]. Artificial cells that

respond to stimuli via sensors and regulate mammalian cells [62] have been created. Following subcutaneous administration in mice, these cells trigger neovascularisation through the production of pro-angiogenic factors [63]. Other artificial cells control protein expression via a temperature-sensitive mRNA element [64]. A cell division machinery for artificial cells was presented [65, 66], and the artificial reconstruction of endosymbiotic processes in eukaryotic cells was described [67–69]. For the first time, a complete viral infection cycle of a T7 phage was recreated within artificial cells [70]. Furthermore, it was demonstrated that synthetic cells can interact with one another in a synthetic mating system, thereby activating various genetic circuits [71].

Assessment by the ZKBS:

In the case of minimal organisms created by the targeted reduction of the genome, the potential risk can be accurately assessed – as provided for in the GenTG – by comparing the organisms with the parent organisms. Organisms designed 'from scratch' using the *bottom-up* approach do not fall within the scope of the GenTG, which applies to organisms whose 'genetic material has been modified in a way that does not occur under natural conditions by mating or natural recombination' (Section 3 GenTG). Under the GenTG, the risk assessment is based on the known risk potential of the donor and recipient organisms. Protocells that are not based on a natural organism are therefore not covered by the GenTG.

To date, no protocell has been described that replicates autonomously and can be regarded as an organism.

2.5 Xenobiology

In the field of xenobiology, a number of studies have been published on the expansion of the genetic code and the incorporation of non-canonical monomers into proteins. These included, for example, the development of a pyrrolysyl-tRNA synthetase with an expanded substrate range, capable of accepting α-thioacids and α-carboxylic acids, thereby enabling the incorporation of additional non-canonical monomers into proteins [72]. In addition, a method for identifying orthogonal tRNA synthetases was developed, which was used to identify variants capable of incorporating further non-canonical amino acids, such as β-amino acids, α,α-disubstituted amino acids and β-hydroxy acids [73]. In a further study, a strategy for the efficient use of a four-base codon was described, which allowed the incorporation of several non-canonical amino acids without modification of the host genome [74]. Furthermore, fluorescent, non-canonical amino acids were developed and used for the production of artificial fluorescent proteins and biosensors, which serve for molecular investigations in mammalian cells [75]. Finally, a method was described that combines the *in situ* biosynthesis of non-canonical amino acids with an expansion of the genetic code, thereby enabling the production of artificial enzymes with novel catalytic properties within cells [76].

Assessment by the ZKBS:

The approaches pursued in the field of xenobiology are used to produce organisms whose genetic material has been altered in a way that does not occur under natural conditions through mating or natural recombination. In this context, non-natural bases are also regarded as genetic material. Such organisms are therefore subject to the GenTG.

Many applications in the field of xenobiology also aim for orthogonality and require very specific compounds that often do not occur in nature. This can lead to an increase in biosafety.

2.6 Methods with impact on synthetic biology

In recent years, new methods for the design, construction and optimisation of genetic circuits, metabolic pathways, molecular components (such as proteins, ribosomes [77] and synthetic receptors [78]) and cellular systems (such as programmed cell-cell interactions [79] and synthetic sensor systems [80]) have been developed. These include publicly accessible, computer-aided design platforms such as Galaxy-SynBioCAD for planning genetic constructs and metabolic pathways [81], strategies for the heterologous and cross-host expression of biosynthetic gene clusters [82], methods for the controlled expression of multiple genes in fungi [83], and CRAPs, an *in vivo* method in yeast in which CRISPR-based DNA repair is used to generate and functionally compare numerous different combinations of metabolic pathways [84].

In addition, tools have been developed for the targeted manipulation of DNA sequences, extending even to chromosomes, including orthogonal replication systems for the accelerated evolution of synthetic DNA elements [85], RNA-controlled bridge recombinases for precise genomic rearrangements such as insertions, excisions and inversions [86], and methods for the transfer and targeted modification of human chromosomes [87]. These new molecular tools extend programmable genome engineering from local sequence changes in individual genes to the targeted reorganisation of chromosomes and genomes. As a result, large-scale modifications such as the construction and reorganisation of entire genomic regions can be significantly simplified and accelerated in the future.

Another key focus was on the development and application of AI-based models for the design and optimisation of proteins, nucleic acid sequences and genetic circuits. For example, machine learning enabled the optimisation of genetic circuits and complex expression systems [88], whilst generative AI models such as Chroma and ESM3 enabled the design of new proteins and protein structures [89, 90]. Furthermore, the aforementioned AI-powered language model for genomics, Evo, enables the prediction and generation of DNA, RNA and protein sequences [91]. High-throughput methods for analysing large genetic design spaces have been combined with machine learning to predict and optimise genetic circuits [92]. AI-supported predictive models, in conjunction with automated laboratory platforms, are increasingly enabling autonomous ‘design-build-test-learn’ cycles for the iterative optimisation of enzymes [93]. Consequently, biological engineering is increasingly shifting from the manual selection of individual designs by researchers towards

AI-supported and automated design processes capable of independently generating, testing and optimising designs at high throughput.

Assessment by the ZKBS:

The methods listed here involve the targeted modification or recombination of genetic elements, metabolic pathways, molecular components or cellular systems. Where organisms are genetically modified in this process and the resulting genetic changes cannot arise under natural conditions through cross-breeding or natural recombination, the GenTG applies.

In the AI-based methods described, the generated or optimised designs are implemented experimentally and validated in organisms or cell cultures. Even though novel DNA sequences are introduced into organisms in some cases, the resulting GMOs are subject to the provisions of the GenTG (see also the assessment under 2.1 Synthesis of genes and genomes).

Generative AI and laboratory automation are increasingly changing the fundamentals of comparative risk assessment, as biological functions can be designed and optimised independently of natural sequence templates. The further development of generative AI and automated 'design-build-test-learn' approaches remains the subject of ongoing monitoring.

2.7 Synthetic biology with application perspectives

Since the third report, published in 2022, the ZKBS has also included publications on the prospective applications of synthetic biology in its ongoing monitoring. The innovations presented utilise artificial genetic circuits, bio-electronic interfaces, nanotechnology and generative AI for new medical and biotechnological applications.

In the field of AI-assisted protein design, a cell-free biosynthesis platform was presented that can generate and validate antimicrobial peptides *de novo* within a single day [94]. MCNet is a model for predicting protein-glycan interactions, including the complete stereochemistry of glycan structures [95]. RoseTTAFold Diffusion (RFdiffusion, [96]) enables the design of novel therapeutic binding proteins against medically relevant target structures and could reduce development times and costs compared with traditional methods such as animal immunisation or extensive screening approaches [97, 98].

In the field of new therapies, the DNA-encoded ARCT model has been developed, which mimics cytotoxic T lymphocytes that destroy tumour cells by releasing a pore-forming protein [99]. In the future, the generation of tissues or organs for clinical applications could be supported by programmed fibroblasts (organiser cell line), which, when arranged alongside mouse embryonic stem cells, enable embryonic development that closely resembles natural processes [100]. A bioelectronic capsule that can be ingested by humans measures inflammatory markers in the gastrointestinal tract in real time and transmits the data wirelessly to a smartphone [101]. The direct current-actuated regulation technology (DART) interface connects wearable electronic devices with medical interventions, thereby enabling the expression of a foreign gene in human cells to be programmed and promising a wide range of applications for gene- and cell-based therapies, real-time dosing and the

remote monitoring of patients by medical staff [102]. To further the development of interspecies organogenesis, nanobodies have been developed that artificially enhance adhesion between human and mouse cells [103]. An oscillating circuit controlled by two inductors in *E. coli* can vary both its period and amplitude and can be used for pulsed drug delivery [104].

DUEC (dueling competent) is a highly selective platform for protein delivery and is based on the tit-for-tat response of the H1-T6 secretion system of *Pseudomonas aeruginosa* [105]. A synthetic transcription system has been developed that controls the expression level of a target gene via guide RNAs, their complementary binding sites and an inactivated CRISPR protein [106].

Artificial photosynthesis increases the light-dependent production of ATP and malate using CdS semiconductor nanoclusters in the periplasm of *E. coli* [107]. A nanoscale DNA origami turbine operates autonomously under physical conditions and converts energy from naturally abundant electrochemical potentials into mechanical work [108].

For the first time, fully functional mirror-image nanopores made from D-amino acids (DpPorA) have been developed; these are based on a natural bacterial porin (PorACj) and exert a selective cytotoxic effect on breast cancer cells [109]. A novel nanostructure based on mirror-image RNA (L-RNA) has been designed for the stable and targeted delivery of therapeutics [110].

Assessment by the ZKBS:

The potential applications of synthetic biology described here encompass a broad spectrum of different approaches and methods.

When organisms are genetically modified, for instance, through the introduction of synthetic circuits or novel expression systems, the work is subject to the GenTG.

By contrast, other approaches listed do not inherently involve GMOs. These include AI-assisted protein design carried out *in silico*, cell-free systems, or molecular structures such as DNA origami and mirror-image protein or RNA structures. Provided that their production or use does not involve genetic engineering operations on living organisms, these approaches do not fall within the scope of the GenTG.

From the ZKBS's perspective, this does not currently give rise to any fundamentally new issues regarding biosafety.

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