TAB

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AT THE GERMAN BUNDESTAG

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Synthetic biology – the next phase of biotechnology and genetic engineering

Summary

November 2015
Working report no. 164

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2017

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The complete Working report no. 164 is available as PDF file in German language on http://www.tab-beim-bundestag.de/de/untersuchungen/u9800.html

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Introduction 1.

For more than ten years now, the term »synthetic biology« (synbio for short) refers to research projects, methods and procedures dealing with the »redesign of natural organisms« that goes far beyond what has been possible so far by »traditional« genetic engineering. The approaches involved are envisioned to ultimately give rise to the creation of (completely) artificial »biological« systems. The significance in the short and medium term as well as the longer-term potential of this very heterogeneous field are assessed quite differently by actors from science, economy and politics which is also due to the fact that a stringent definition is still missing. Nevertheless, such a stringent definition would be indispensable for a differentiated examination of the possible consequences involved. So far, none of the many bodies that have made an attempt has succeeded in to define a scientifically reasonable demarcation to genetic engineering that is also (easily) understandable to non-experts. Thus, it is not surprising that – despite sporadic media coverage – the subject has hardly reached society's awareness yet.

In the TAB report, a basic differentiation is made between synbio in the narrow sense and synbio in the broad sense which is used for impact analysis and the associated debate:

- *Synbio in the narrow sense* refers to the production of cells or organisms developed from scratch and designed »de novo« (or of cell-free biological or biochemical systems). These organisms are intended for the production of any, even completely novel substances or visionary applications in the fields of health, energy or the environment. In this context, the production of entire synthetic genomes, the construction of so-called »minimal cells« (either »top down« by reducing natural cells or »bottom up« or »from scratch« from basic biochemical components) as well as the use of non-natural molecules (»xenobiology«) are characteristic research approaches and methods. Synbio in the narrow sense is promoted by a rather small number of scientists and shall also provide knowledge on the emergence of life (and its chemistry) on Earth.
- In contrast, *synbio in the broad sense* refers to all currently pursued approaches regarding the molecular-biological modification of known organisms which are mostly application-oriented and increasingly based on digital information. These approaches aim at producing chemicals by means of new ways of bio-synthesis or at designing genetic circuits for new sensory and regulatory cell functions in existing organisms. Synbio in the broad sense goes beyond simple approaches for genetically modifying metabolic pathways of organisms (so-called metabolic engineering). For

this, computer-assisted design and modelling processes are used increasingly.

From the perspective of the present investigation, synbio in the broad sense also includes genome editing techniques which have not been dealt with under the label »synbio« so far. In spring 2015, the rapid development of these techniques as well as their application in plants, animals and even humans sparked an intensified debate on genetic engineering both at the national and international level – that will also involve synbio as a research area and funding object.

Mission and focus of the study 1.1

The project of the Office of Technology Assessment at the German Bundestag (TAB) was commissioned by the Committee on Education, Research and Technology Assessment (»ABFTA«) and started in spring 2011. Besides adressing natural-scientific and technological aspects, the project was intended to particularly focus on issues regarding ethics, biosafety and biosecurity, intellectual property, regulation (or governance), public perception as well as on an adequate and early communication of the opportunities and risks involved. In the course of the project and in view of TAB's primary task of advising the German Bundestag, the following project design has been chosen:

- The question regarding the nature of synbio shall not be dealt with too academically;
- No in-depth presentation of primarily speculative visions or scenarios of future applications and impacts of synbio;
- Instead: aligning as comprehensively as possible the debates on potentials and perspectives of synbio with wider contexts of science, research and innovation policies –
- With the objective to work out and characterize major topics and fields of action – which are interconnected and relevant for the future – to be pursued by the German Bundestag and particularly by the »ABFTA«.

This results in the following main chapters of the report: current state of research, development and application (chapter III) safety issues of synthetic biology (chapter IV), public discourse as a governance perspective of synbio (chapter V), actors and perspectives of DIY bio(techno)logy (chapter VI) as well as future issues and fields of action (chapter VII).

Current state of research, development and application 2.

Many research and development approaches of synbio focus on the use of renewable instead of fossil raw materials in chemical and energy production, and thus on the core notion of a (future) »bioeconomy«. Furthermore, there are potential applications in medicine as well as in the field of environmental sensing and remediation. The objective of all these approaches is to use synbio in order to overcome, or at least extend, some of the limitations inherent in biological processes.

Chemical and energy production 2.1

Meanwhile, a whole series of new bio-based production processes for chemical substances has been successfully established on a laboratory scale by means of synbio in the broad sense. For this, genes from various organisms typically are combined and the native genes of the recipient organism are optimized. Particularly high-value ingredients (including flavouring substances and fragrances) for the food, cosmetics and detergents industry are increasingly produced this way. In some cases – at least on a pre-commercial scale – such new production processes are also used to synthesize important basic chemicals for the production of plastics (1,3-Propanediol, 1,4-Butanediol, or to generate biodegradable polymers (polylactides, polyhydroxyalkanoates).
The production of 1,4-Butanediol by means of Escherichia coli strains represents an exemplary step towards synbio in the narrow sense: 1,4-Butanediol is a non-natural chemical which is not produced by any known organism. Thus, its »bio-based« production requires a biosynthesis pathway without having any »natural« model. The corresponding biosynthesis pathway has been modeled 'in silico' based on knowledge about metabolic pathways and enzymatic activities of E. coli and several other organisms, and thus has been »rationally designed« to a large extent.

In the energy sector, approaches of synbio for modifying metabolic pathways are mainly used in micro-organisms (such as yeasts or micro-algae) aiming at optimizing or redesigning the provision of raw materials (i. a. for the production of butanol, biodiesel and farnesenes). With regard to the conversion of raw materials, efforts focus on the use of lignocellulosic biomass – the material which represents the largest part of plant biomass and which is not edible (e. g. corn stalks and leaves) – in order to avoid direct competition with food production and, at the same time, to tap a source of raw materials which is available in large quantities.

Medicine 2.2

Synthetic biology offers a number of approaches for innovative therapeutic strategies as well as for novel development and production processes for pharmaceuticals and vaccines. For diagnostics as well, there are first examples for potential applications, e. g. a biosensor intended for detecting the Ebola virus for which a cell-free system with a genetic circuit has been developed. While most of these approaches are still in early, pre-clinical phases of research, some procedures have already reached the stage of clinical trials, large-scale field experiments or even commercial production. This includes modified viruses for combating cancer, genetically modified mosquitoes for controlling dengue fever, as well as the production of the phytochemical artemisinin, as an important ingredient of anti-malarial drugs, based on micro-organisms with newly designed metabolic pathways.

Biosensing and bioremediation 2.3

As cell-based biosensors, genetically modified micro-organisms (GMMO) can allow an easy and cost-effective measurement of toxic substances in soil or water samples. A first commercially available product (not requiring any release of GMMO) is the ARSOlux biosensor for determining the arsenic content in drinking water. For the remediation of contaminated soils by means of GMMO, however, no approaches are known that are ready for application. Environmental release is likely to be a prerequisite for many applications and the effective control of the GMMO can hardly be envisioned. Moreover, well-adapted natural micro-organisms or consortia of micro-organisms exist for the removal of major contamination by organic substances (as e. g. oil).

Overall assessment 2.4

Altogether, it can be summarized that the state of development and application of synbio is still at an early stage and that a future superiority and economic viability of synbio approaches cannot be seriously assessed yet. The latter particularly applies to potential applications of synbio in the narrow sense which today still have a mere visionary character. Currently, it is not possible to predict whether (more or less completely) artificial organisms or »bio-like« systems will ever be of major significance with regard to an efficient, reliable and safe »bio-based« production.

Likewise, methods and procedures of synbio in the broad sense have to prevail against other options already existing or also being at the development stage. Some projects and products are already competitive today, but those are rather low-volume, but high-value products (specialty chemicals, flavouring substances, pharmaceuticals and vaccines). For these, neither cost nor biosafety issues are playing a major role, because existing or alternative procedures are complex as well; and because either production processes are restricted to contained systems (bioreactors) or unintended side effects and risks are accepted more readily (pharmaceuticals/therapeutics). It should not be ignored that particularly those product examples of synbio which are most discussed – artemisinin as an anti-malarial drug, vanillin as flavouring substance produced by means of modified yeast cells as well as a palm oil substitute made of micro-algae – are not that »far away« from »conventional« applications of genetic engineering.

Earlier forecasts have seen the greatest potential of synbio in the production of bulk chemicals and in energy production. This was supported by the fact that several entrepreneurial activities as well as massive investments have been observed worldwide and mainly in the bioenergy sector – but have been significantly reduced recently as a consequence of the fluctuating and overall decreasing oil price development. Both in the field of bulk chemicals and in the energy and fuel sector, it has to be considered that these are mass markets in which new procedures have to prevail against cost-optimized technologies often established for decades. How slow this process can be (at least so far) is shown by the example of industrial or »white« biotechnology, i. e. the technology preceding synbio. Its share of the production of (bulk) chemicals has developed only slowly during the past 25 years. The assessment of ecological and biosafety issues as a criterion for the superiority and competitiveness of new production systems is gaining more and more importance. Thus, in particular with regard to biofuel production by means of genetically optimized micro-algae, the question is whether these micro-algae would have to be cultivated on a large scale in (semi-)open water basins (for economic reasons) or whether – and to what extent – contained systems (combined with continuous production processes) could be used.

The future development of synbio will strongly depend on the commitment of public and private investors. Their motivations, however, are quite heterogeneous. While public research funding focuses (or should focus) on sustainability issues, industry primarily wants to secure the future basis of their business. Despite of the recent decline of the oil price, it has to be assumed that these objectives – in the years to come – will converge more and more towards an economic approach based on renewable and environmentally friendly raw materials (in terms of a bio-economy). Although, there will not necessarily be a

consensus regarding the preferable approaches with regard to this bio-economy, this common objective, however, generally is an argument in favour of the great potential of all bio-based production strategies. Most likely, at least from a global point of view, the question in the long term is not whether or not synbio shall be used in general. It is about reaching a »competitive coexistence« with alternative procedures aiming at an intelligent use of the existing biological diversity and its inherent properties (e. g. in terms of a knowledge-intensive agroecology) – similar to the way both organic and conventional agriculture are practiced today.

It is even less possible to assess the prospects of success of therapeutics, vaccines and gene therapy approaches in a generalizing way. Particularly with regard to medicine, the effectiveness and relative superiority often become evident at rather late stages of development or during application only. For this reason, the principal debate on the risks and benefits of synbio applications in the health sector currently focuses on other aspects: on the ecological risks of using populations of genetically modified mosquitoes and on issues concerning social justice with regard to new procedures for the production of pharmaceuticals and vaccines.

The significance of synbio in the different areas of application is likely to be rather different depending on its economic success and societal acceptance – as can be observed for the situation of »conventional« genetic engineering in green, red or white biotechnology. In this context, special attention will be paid to the consumer-sensitive field of flavouring substances and fragrances or other ingredients for the food, cosmetics and detergents industry. Though procedures of genetic engineering have been applied here partly for a long time already, the use of enhanced synbio procedures in this field is likely to experience considerably more public awareness and criticism in the future, as it was the case last year.

Safety and security issues of synthetic biology 3.

Right from the beginning, the scientific and non-scientific debate on synbio has always been accompanied by issues of biosecurity and biosafety. As most products and procedures of synbio are still at the beginning of their development, their potential safety-relevant properties such as toxicity, allergenicity, proliferation properties, and ability to survive in the environment remain widely unknown. In connection with the debate on the nature and novelty of synbio, the debate with regard to »biosafety« focuses, for a long time already, on the politically relevant question whether today's and future developments will (still) be covered by the current regulations (for

pharmaceuticals, novel therapies, medical products, chemicals and, above all, for genetically modified organisms [GMO]). In addition, the biosafety debate concentrates on whether these developments are covered by the current regulations in an adequate way – or whether they go far beyond the scope of the categories involved, and current procedures of risk assessment and risk management are no longer effective. A second topic area refers to issues of biosecurity, i. e. illegal (»biocrime«) or even malicious (»bioterrorism«) use of biological agents or of the underlying knowledge. Even if much-debated and controversial experiments (particularly with avian influenza viruses) associated with the risk of such a misuse did not primarily have their origin in research projects on synbio so far, wide-ranging concerns are linked to scenarios of a future synthetic biology and have already led to first regulatory efforts.

Biosafety issues – challenges with regard to risk assessment and risk regulation 3.1

In spring 2015, no immediate need for revising the risk regulation of GMO in Germany or Europe with a specific view to »synthetically« modified organisms (SMO) could be identified. However, given the dynamic scientific-technological development and the differences regarding regulation in the different regions of the world, it seems to be quite necessary to deal with the risk regulation of a possible future release of SMO in a proactive and more intensive way.

The central issue for the risk assessment and risk-benefit analysis of future SMO is the question on how safety assessment without any substantial equivalence to a known donor organism can be performed in such a way that the results would be accepted by actors from research, industry and politics as well as by civil society organizations and the public/citizens – as a basis for the approval of field applications. For plants, this questions arises rather in case of a larger »genetic reconstruction« process, whereas for micro-organisms it is raised for any type of field application (e. g. open cultivation of micro-algae for biofuel production), since they have been used almost exclusively in contained systems so far. Interventions in the human intestinal flora or other types of microflora (in recent times increasingly researched as a future therapeutic approach) might become a highly controversial issue, because regulatory competencies are unclear in this field. For instance, the German Genetic Engineering Act (»GenTG«) does not refer to the application of genetic engineering in humans and thus neither to any constituents of the human microbiome, as long as these are inside the human body.

Dealing again with safety requirements regarding production organisms, even in contained systems (»contained use«), might become another major

issue. Particularly in view of potential »fully synthetic« organisms that have been designed »de novo« to a large extent or that have been subject to massive xenobiological modification. Even if these organisms are still far away from being ready for application, they have been increasingly put up for discussion in early 2015 by some scientists as a supposedly particularly safe option for the future. This is due to their fundamental biochemical differences, which are assumed to render impossible i. a. the functional gene exchange with natural organisms.

In particular due to the increasing possibilities of genome editing procedures, the risk debate on genetically modified insects, or animals in general, most likely will gain more and more importance in the years to come. In view of the experience made with the approval of transgenic plants, a consensual positive risk assessment of genetic interventions in animals – particularly those with a high potential to spread such as insects – is very unlikely in the EU.

Biosecurity – protection against misuse 3.2

Besides the targeted development, production and proliferation of biological weapons/warfare agents by official military institutions or, however, by terrorist organizations, the deliberate misuse of life science expertise also includes criminal activities (e. g. aiming at the illicit manufacture of drugs, doping substances and counterfeit medicines). Naturally, only little is known about these activities which either are kept secret or are illegal. For this reason, a detailed factual debate for assessing the risks of »bioterrorism« and »biocrime« (as a consequence of synbio activities, but also in general) actually cannot be conducted in public. As a matter of principle, however, questions can be asked with regard to a potential misuse of technologies which can be used for social benefit, but also deliberately for harmful purposes – so-called »dual-use« technologies. In this context, two fundamentally different aspects have to be considered: First, the generation of sensitive knowledge – e. g. for synthesizing and producing toxic substances, highly pathogenic viruses or resistant bacterial pathogens – and, secondly, access to this knowledge as well as to the technologies and instruments (laboratory equipment) required for implementation.

The control of an undesired proliferation of knowledge and technologies in life sciences is facing major technical, but also conceptual, legal and ethical challenges. The latter are due to questions concerning a restriction of the constitutionally protected freedom of research as well as of tangible, potentially important opportunities for health research and preventive health care.

Furthermore, these challenges are linked to questions on whether and how knowledge can be passed on selectively to specific groups, and on who could and/or should decide on this knowledge and on the selection of the people authorized to receive the knowledge. There is consensus that additional governance measures are required besides international agreements on arms control, legal export restrictions for dual-use goods and technologies, and possible other legal provisions – in order to reduce the risk of a potential misuse of life science research in general and of synthetic biology in particular. All people working with biologically active substances should develop strong safety/security awareness. Furthermore, they should know whom they can involve in assessing the risk of their projects, without having the feeling of being supervised in an inadequate manner (such as it might occur in the United States where the Federal Bureau of Investigation [FBI] wants to ensure the preventive control of risks regarding biosecurity and i. a. systematically designated liaison officers for the do-it-yourself [DIY] biology community).

In Germany, the dual use issue has been picked up proactively and discussed intensively by scientific organizations, non-governmental organizations (NGOs) and politics in recent years with a view to so-called »Dual Use Research of Concern« (DURC). As a consequence, the German Federal Government commissioned the German Ethics Council to work on an opinion paper concerning the topic »Biosecurity – Freedom and Responsibility of Research«. This paper was presented in May 2014 and is likely to be the reference point for the further political debate on the issue in Germany for the years to come. The German Ethics Council is calling for adequate legislation with regard to DURC. As key topics, the Council further recommends the creation of a biosecurity code of conduct for responsible research that should be adopted by all public and private research facilities throughout Germany, as well as the appointment of a central and interdisciplinary DURC commission which has to be informed by all researchers prior to the implementation of DURC projects.

With regard to tangibly reducing the potentials for misuse of gen(om)e synthesis – which shall become significantly more efficient, less costly and possibly decentralized in the future – a compulsory registration for institutions using gene synthesis as well as the registration of DNA synthesizers seems to be an option which at least could be tested. Even though risks relating to biocrime and bioterrorism are most likely to come from organizations and countries that cannot or do not want to be controlled by (supra)national regulations.

Synbio and the public – from non-knowledge to active involvement 4.

For years already, the demand for a broad societal dialog on the risks and opportunities of synbio as an element of »good governance« is one of the major recommendations in almost all statements or opinions by scientific or political bodies. A common diagnosis from research and politics shows that – in the past – a systematic debate on the social consequences of scientific-technological developments was initiated at a very late stage only. Thus, ethical concerns or social requirements of these developments could not be taken into consideration in an adequate way. As a consequence, very often products already developed or systems already implemented were broadly rejected (examples most often mentioned are green biotechnology and nuclear energy). In response, technology assessment (TA) called for a targeted »upstream engagement«, i. e. dealing as systematically as possible with the societal opportunities and challenges already at early stages of development. Currently, synthetic biology is *the* prime example for such targeted »upstream engagement«. Both at the EU level (within the EU Framework Programme for Research and Innovation called »Horizon 2020«) and in the member states, sometimes very complex processes of public discourse have been initiated as novel types of accompanying research and governance with regard to research and development (R&D).

Media coverage, awareness and strategies of public communication 4.1

The report's overview on the press coverage of synbio as well as on the awareness and attitudes of the population shows in an exemplary way the challenges emerging from public communication on synbio due to the early stage. To a very large extent, it is not yet known where development is heading and which products will result from it. Media coverage is only sporadic and mostly at the occasion of a particularly hyped research success (such as the creation of the »synthetic« bacterial cell nicknamed »Synthia« by Craig Venter and his team), though the true future significance must remain widely unknown. Finally, the general public is hardly aware of the scientific development at this early stage and thus would have to be motivated actively to deal with the issue. Another aspect to be considered for synbio is that its definition is fairly unclear, so that different actors have a quite different understanding of the topic they shall discuss. As a consequence, it is rather

difficult to develop strategies and frameworks for public communication of synbio.

Promoting discourse and new governance models of synbio 4.2

Current discourse activities in the Netherlands, the UK, in Germany and within the framework of EU projects that are presented in the report represent efforts made in order to reach at least some groups of the public. Furthermore, they aim to enable an involvement of society in terms of a joint and responsible development as well as use of science and technology. These activities represent an element of research policy and in part are closely linked to tangible research policy agendas (so-called roadmaps). For several years now, particularly the European Commission has been promoting systematic reflection and participation processes as a new type of governance of R&D processes (for synbio specifically by the current SYNENERGENE project) under the title »Responsible Research and Innovation« (RRI).

It is not clear yet whether this might actually result in a new type of discourse – one that can involve society as a whole – on the development of new technologies in general and synbio in particular. RRI activities themselves have to be considered as a kind of experiment or learning process. The corresponding projects are deeply rooted in (participatory) TA activities as an almost »classical« type of accompanying research. It is particularly unclear whether and to what extent public discourse activities actually affect R&D processes of synbio in public and private research institutions – rather than only having an effect on accompanying research itself.

With regard to the further design of discourse activities, realistic objectives should be defined at an early stage and communicated in a transparent way. In this context, particularly the understanding and quality of participation must be well-founded in order to prevent disappointment of the parties involved. The great efforts required for ambitious participatory projects and the ambivalent experience with previous activities, however, are opposed to an extension of the offers regarding direct participation. Instead, it may be appropriate to indirectly increase the public's interest for synbio in general and for the influence of society on its development. For this purpose, science journalism could be promoted and supported in its efforts to achieve a high-quality and professional media coverage regarding developments of synthetic biology (and other relevant new technologies). Moreover, societal actors, such as civil society organizations in particular, but also DIY biologists, might be supported in their role as discourse participants through appropriate funding measures.

DIY bio(techno)logy – actors and perspectives 5.

While funding of public discourse activities by research policy bodies, at least originally, is guided by a top-down engagement, the do-it-yourself (DIY) biology community is a bottom-up movement. By definition, it represents an active involvement of actors outside the conventional research and innovation system. Besides interested non-experts and do-it-yourselfers, this heterogeneous community particularly includes visual artists as well as scientifically educated protagonists (focusing on life sciences and information sciences). So far, however, the significance of the DIY biology or biohacking community for synbio hardly results from the development of innovative project ideas or even from tangible research projects, as mostly the technical capacities and possibilities are still rather limited. However, there are at least three major reasons to examine the phenomenon in a more detailed way in the context of the issue of synbio and thus of this report:

- First, the technological gap might decrease or, in some respects, even disappear. At the latest when the major objective – or the vision – of synbio in the narrow sense will become reality, namely the digital modeling and automated production of synthetic organisms.
- Second, already now, DIY biology provides fresh input for the debate on perspectives of synbio (in the broad sense), its usefulness for and desirability in society, as well as on the public's demand for real participation in the research and innovation process.
- Third, voices have repeatedly been raised classifying DIY biology to be an undesired form of citizen science due to safety concerns, though most experts consider those concerns – particularly with regard to biocrime or even bioterrorism potentials – to be rather exaggerated.

Developments so far 5.1

»Hacking« means releasing objects or even ideas from their original context and giving them a completely new function. In industrialized countries, this often is a rather artistic and playful way of dealing with technology, whereas the approach can provide tangible solutions (called »Jugaad«) for everyday life in developing countries. One of the core issues of biohackers is to provide access for basically everyone to knowledge, materials and methods of life sciences.

The first phase of DIY biology dates back to the early 1990s and was characterized by activities of a small group of bioartists. From the year 2000 on, a phase of »global networking« followed during which mainly scientists and

students started to exchange their ideas via the Internet. By the year 2008, non-commercially operated biohacker spaces were set up as semi-publicly usable bio-laboratories in large metropolitan areas of industrialized and newly industrialized countries worldwide. The work performed there is dealing with art, education, social criticism, technological innovation and scenarios of the future. These biohacker spaces offer their members and visitors the option to learn and to use molecular-biological techniques on their own without depending on schools and universities. The increasing technological emancipation of the DIY biology community as well as its media coverage stimulated a critical debate on societal issues. So far, efforts to introduce own ethical rules in form of so-called »Codes of Ethics« are limited in their scope due to the heterogeneity of the international biohacker community.
In recent years, an increasing commercialization can be observed resulting in several start-up companies. Some of the development projects announced in this context, e. g. for the production of auto-luminescent plants, provoked sharp criticism both among NGOs critical of genetic engineering and within the DIY biology community itself. The activities in the DIY biology community also raised fears among some biosecurity experts (mainly in the US): biohackers might harm the environment or humans by making errors (»bioerror«), by knowingly or unknowingly committing criminal acts (»biocrime«) or even by conducting bioterrorist activities. In recent years, however, these fears have been strongly put into perspective after a detailed analysis of the situation.

Future prospects and scenarios 5.2

DIY biology likely will become significantly more powerful in the future as a consequence of further technological developments – primarily concerning the automation, decentralization, miniaturization and price reduction of DNA synthesis and lab-on-a-chip technologies. As a result, more and more questions are asked already today within the DIY biology community itself regarding biosafety, freedom of research and common welfare-oriented economic use. In this context, the TAB report presents considerations regarding a so-called »Bio-Commons concept« devised within the European biohacker community. It comprises considerations on the necessity and possibilities of monitoring and controlling genetic data, both in order to prevent risky applications and to promote a distribution as open as possible of the molecular-biological and (bio)technological knowledge. The latter shall ensure a globally fair and sustainable use of the potentials of synbio. The approach proposes a fundamental reform regarding the protection of intellectual property in life sciences, so that claims for protection can be acquired non-bureaucratically and

at a reasonable price for a rather short period of time (a few years). Furthermore, they can be combined with share-alike conditions similar to the Creative Commons licenses based on copyright. Finally, a limited deregulation of gene sequences or organisms considered to be safe or free of risk is put up for discussion, building on the already existing legal scope (i. a. for self-cloning) and practices (in schools and universities).

The DIY biology community could play an important role for the communication and the critical debate of the life sciences as well as in research on their possible consequences. Committed citizens, hackerspaces and more open academic structures provide an opportunity to open up application-oriented research increasingly for an effective societal dialogue.

Future issues and fields of action 6.

A resumptive consideration regarding the question for the novelty value and social relevance of synbio as well as for political responsibilities is the starting point for describing the fields and options for action involved. While synbio in the narrow sense is unlikely to gain major practical significance in the foreseeable future, the debate on synbio in the broad sense (as a synonym for the next level of biotechnology and genetic engineering) is likely to be conducted much more intensively in the years to come. Main reasons are genome editing techniques which have not been dealt with under the label of synbio so far. The enlarged groups of actors (such as the DIY community, but also the participants of the iGEM student competition) and the increased demands on societal participation that have emerged in recent years are likely to provide fresh impetus. Altogether, the results of the present report provide six different fields of action or thematic areas primarily for research policy, but in part also for environmental and economic policy.

Funding of basic and applied research and development projects 6.1

The most important principle of public R&D funding should be to broaden available options and to keep them open. This prohibits a premature commitment to specific technologies or processes – particularly in view of the complex challenges inherent to a global sustainable bio-economy. While the potential short- and medium-term applications should result from synbio in the broad sense, the future potential of synbio in the narrow sense is difficult to predict. For this reason, specific funding for the development of »fully

synthetic« – or at least xenobiological – organisms beyond basic research is currently hardly justifiable. It thus seems appropriate that, so far, the German Federal Ministry of Education and Research (»BMBF«) largely avoids the strategic use of the term »synbio«, but, at the same time, promotes manifold new methods of biotechnology and genetic engineering in different funding lines. This is in keeping with the more open concept of synbio in the broad sense and seems to be worth pursuing in the future as well.

Though still neglected too often, a further point of reference for the development of potentially controversial technologies, such as synbio as the next level of biotechnology and genetic engineering, meanwhile should be a matter of course: moving away from an isolated consideration of technology potentials towards a comprehensive and solution-oriented assessment of options. In this context, the involvement of societal stakeholders from outside the science system or the classical innovation system is of particular importance. These stakeholders could bring in their expertise and everyday knowledge, e. g. on agriculture or health care issues, which cannot be provided by scientific approaches and analyses alone.

Prospective biosafety research as a basis for future risk assessment and regulation 6.2

On the one hand, most international experts agree on the fact that the existing procedures of risk assessment will be sufficient for dealing with products of synbio (in the broad sense) in the years to come. On the other hand, however, it is pointed out for some years already that the procedure used so far – based on a case-by-case examination and on the comparison with largely similar (substantially equivalent) organisms which have been used for a long time already (i.e. which are »familiar«) – is put into question by several scientific and technological developments of synbio. This results in the central question on to what extent and by which methods substantially modified or largely »redesigned« organisms that may proliferate and spread can be and must be characterized – with a view to a societally acceptable decision-making process regarding the use of these organisms.

It seems to be almost urgent that the German Federal Ministry of Education and Research (»BMBF«) – together with the other Federal ministries concerned, i. e. the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (»BMUB«) and the German Federal Ministry of Food and Agriculture (»BMEL«) – will deal with the topic of biosafety research again, after this topic has been funded only within the framework of European projects since 2012. This assessment of the situation takes into account first

examinations during the past years concerning risk assessment of genetically modified plants (GMP) with substantially modified properties (e. g. regarding their biochemical composition or their drought or salt tolerance) and the advancing possibilities of synbio in the broad sense, primarily of the genome editing techniques.

The controversial nature of questions dealing with the approval of GMP and of biosafety research as a basis for future risk assessment and regulation is even increased since (when this report went to press) some genetic engineering applications is not (or no longer) covered by risk regulation, and thus by safety evaluation, in the EU and in Germany. This is because only few letters of the genetic code in the DNA are altered. At the same time, however, multiple such small changes might result in substantially modified GMP.

In order to be able to develop a research policy agenda for a prospective biosafety research with regard to synbio in the broad sense, it seems to be indispensable to reinvestigate the existing unresolved controversies concerning the risk assessment of »conventional« GMO. Furthermore, an attempt to a comprehensive and discursive evaluation regarding the weak points and controversial issues of risk research should be made. In this context, it may not be expected that the controversial issues will be resolved; rather the objective should be to improve communication between the different actors with regard to the (still) open questions in biosafety research on GMO. In order to increase the chances of success of such a process, the objectives set should be as realistic and precise as possible. Moreover, negative experience and insights from earlier attempts at achieving consensus should be evaluated and taken into consideration.

The relevant issues in the risk assessment of GMO are only partly linked to scientific aspects. Therefore, a future biosafety research programme would also have to be oriented towards social and economic sciences, law and the humanities, conceived on the long term and across policy areas. In addition, it would need to offer opportunities for true participation, allowing to bring in the competencies and interests of all relevant societal stakeholders. The coordination of such a process for developing a research programme would have to be carried out by an institution or a (steering) body which should be recognized as being neutral and fair by as many actors involved as possible.

In this context, financing will be a major issue. It needs to be evaluated whether the private sector in terms of industry associations, insurance companies or investor networks would or should pay into a corresponding fund. A first tangible step would be the organization of an exploratory conference by the responsible ministries with a broader participation of relevant groups from society.

Involving stakeholders and the broad public in the design of research agendas for synbio 6.3

When it comes to defining the orientation of research areas and agendas, the involvement of stakeholders from society outside the (traditional) science system is becoming a key element of increasing significance in European and German research policy. In the field of research funding oriented towards benefits and options, but also with a view to future funding programmes for research into the risks or safety of synbio, the involvement of representatives from (critical) civil society organizations is of particular importance.

Large scientific organizations and institutions including academies, but also large societal actors like trade unions and churches as well as the private sector are usually able to rather easily participate in the development of research agendas, by organizing support in terms of personnel and know-how. Yet this is significantly more difficult for organizations from civil society dealing with environmental, developmental or social issues, as they often have only few paid employees the work of whom is financed to a large extent by means of membership fees. For this reason, demands made for quite some time now saying that research policy should make available funds not only sporadically, but with a long-term commitment regarding an organized participation of representatives from NGOs, seem to be reasonable.

As regards the promotion and organization of discourse activities in society, a direct involvement of as many segments of the public as possible seems to be less appropriate than indirect measures, since synbio is still at a rather early stage of development. Besides the involvement of stakeholders in research and innovation processes, and the analysis and discussion of future scenarios (»vision assessment«), the concept of »Responsible Research and Innovation« (RRI) provides corresponding methods. These include the support of international actors such as science journalists, artists and other science communicators.

Perspectives of an active participation of citizens in biotechnological progress in terms of citizen science/DIY biology 6.4

While the participation of individual persons in the discussion or even design of research agendas finally can only comprise a small group of people, the different forms of citizen science basically offer many people the opportunity to participate even in tangible research projects. In recent years, projects of citizen

science have been promoted by the German Federal Ministry of Education and Research (»BMBF«) in a targeted way.

In this context, projects in which citizens primarily participate in data acquisition (e. g. by counting animal species or making astronomical observations) are dominating so far – thus being a kind of »science *with* citizens«. DIY biology represents a more active way of participating and thus can be referred to as »science or research *by* citizens«. So far, the members of the very heterogeneous DIY community have different objectives ranging from a mere leisure activity, a claim for participation (in the scientific progress and the debate on life sciences) based on democratic theory to the development of potential business concepts. At least some representatives – due to their combination of a certain affinity for biotechnology/genetic engineering and social criticism – stand for a new voice in the (still divisive) debate on genetic engineering and synthetic biology.

For research policy, the question is whether a comprehensive involvement of society in scientific progress with regard to biotechnology or synbio in the broad sense should also include the targeted support of bio-hackerspaces, as it is the case to some extent e. g. in France or in the United States. It would also be possible to explore the development of »citizens' laboratories« which are more closely attached to university or research institutes. In this context, however, it would have to be ensured that these laboratories go beyond educational or communication measures like the existing »open laboratories« and that they are explicitly open for individual ideas of non-professional actors. As is often the case, a decisive aspect of this approach would be the financing of those citizens' laboratories. Similarly, the time resources of employed scientists from the »hosting« institutes would be important to be able to commit themselves to an open exchange and experimentation together with the »citizen scientists«, without being under the pressure to succeed or to publish. Of course, the communication of and compliance with biosafety regulations have to be guaranteed. In this context, a moderate further development by slightly reducing the requirements on the expert knowledge or professional experience of the operator, by defining a biosafety level 0.5 or a whitelist of self-cloning could be examined.

How to deal with biological risks and issues of dual use 6.5

Dual-use issues are far from being limited to life sciences. They have to be dealt with in many areas of research. In this respect, activities for creating interdisciplinary awareness and establishing commissions for ethics in research as interdisciplinary points of contact in all German research institutions appear

completely reasonable and worth supporting. Corresponding efforts have been made i. a. by the German Research Foundation (DFG), the Max Planck Society, the Leibniz Association and science academies (e. g. Leopoldina).

In view of dual-use research projects of concern (DURC), however, the question of the necessary competencies of the corresponding bodies for assessing specific possibilities of misuse and the degree of obligation for participation arises. Since only very few cases appear to exist, the recommendation of the German Ethics Council on setting up a central national DURC commission seems obvious. This also applies to the proposal for enshrining this body in law, because a possible, but exceptional restriction of the freedom of research as a fundamental right would require strong legitimization.

The systematic integration of biosecurity and dual use issues into university curricula and other education schemes of the life sciences seems to be at least as important. A fundamental problem for researchers dealing with issues concerning a potential misuse is the ever decreasing duration of fixed-term contracts in universities and other research institutions. On the one hand, the researchers' loyalty to the respective institution (and thus their corresponding codes of conduct) may not be that strong; on the other hand, the pressure to succeed and to publish will increase. The motivation, but also the possibilities of individual scientists of more intensively dealing with ethical issues of their own research thus will be limited.

Gen(om)e synthesis may become increasingly decentralized, and possibly significantly more efficient and less costly, in the future. In view of such scenarios it might be necessary – as a major prerequisite, but also as an expectable further development of synbio – to deal with the very difficult question as to whether registration and control of devices, their users and specific applications (i. e. of the gene sequences produced) should be and can be performed. Theoretically, corresponding measures and processes would have to be introduced by consensus on a global and nationwide scale. They would have to be affordable and must not unnecessarily impede R&D competition in science and industry or even make it impossible.

Sustainable models for the protection and use of intellectual property 6.6

For economic and ethical reasons, the question on how intellectual property emerging from modern life sciences can and shall be protected is one of the most controversial questions in the debate on genetic engineering. The very confusing data situation and debate concerning this issue could not be dealt with in depth in the present report. It could only be addressed briefly with

regard to some specific aspects of synbio and DIY biology. Thus, with regard to future »designed« molecular structures, genes or even organisms, a commercial protection may be more plausible for these than for primarily analytical results linked to naturally occurring DNA sequences. Moreover, it is a novelty that besides the established (bio-)patent law (with all its controversies and pitfalls) copyright is being discussed increasingly as a future concept for protection and use. These discussions are based on the assumption that the future of synbio will head towards designing biological information (mainly DNA, but also other molecules or properties of synthetic systems) just like programming software codes.

For research policy, the question is whether (and which types of) funding can or should be linked with specified conditions for access and use of the results. This question is being discussed intensively in science and politics for years, and far beyond the field of life sciences. It is obvious that dealing with intellectual property within the framework of an increasingly digital economy will remain one of the major challenges for science as well as for economic and research policy in the years to come. The development of regulatory models which are innovative and realistic in terms of science, economy, society, politics and law would be a very challenging and complex task for in-depth technology assessment.

Challenges of the upcoming new debate on genetic engineering 6.7

In spring 2015, the perspectives and potentials of synbio in the narrow sense – i. e. the production of cells or organisms developed from scratch and designed »de novo« – have still been considered to be a vision of the future. At the same time, the situation of synbio in the broad sense (as the next phase of biotechnology and genetic engineering) has changed tremendously. In recent weeks, the debate on the new opportunities and consequences of genome editing techniques has been extended and intensified in such a way that a fundamental change of the debate on the further development and use of genetic manipulation techniques can be assumed.

It can be anticipated that the issue of risk assessment without having a substantially similar, familiar reference organism will be of greater urgency in the foreseeable future if genome editing techniques will be used worldwide for an extensive modification of genomes. In this respect, an intensification of biosafety research is likely to be indispensable, both at the national level and by means of international collaborations. The global dimensions and the consequences of this development are difficult to predict in detail. However, it

seems to be obvious that, in the years to come, many new questions with regard to funding, to socio-economic and ethical evaluation and to the regulation of applications of genetic engineering will arise not only for research policy, but also for the German Bundestag as legislative authority. Finally, for these questions, it does not matter whether the technologies and methods are referred to as synthetic biology. The new aspect here is the increased significance of the international dimensions of the issues (or corresponding answers/solutions), resulting – last but not least – from the grown and ever increasing scientific and technological capacities of the newly industrialized countries. For this reason, continuous monitoring of the global developments using scientifically valid indicators and regular reporting seem to be obvious.

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