acatech IMPULSE
Executive Summary

Innovation Potential of Biotechnology

acatech (Ed.)

Biotechnology – a key industry for the 21st century

Ever since the discovery of the genetic code in the 1960s, rapid progress has been made in the understanding of biological processes. In particular, methods of genetic engineering are being applied in increasingly diverse fields and new tools continuously open up more approaches to analyse and modify life. Most recently, with the development of the CRISPR/Cas method in 2012, a decisive breakthrough was achieved. In combination with modern types of analysis and data evaluation this method has opened up **brand new possibilities in the engineering of biological processes**. Many experts believe that this convergence of technologies for analysis, data processing and modification in the life sciences, and in biotechnology in particular, unlocks a **potential for transformation** comparable to digitization. Biotechnology is a **key technology for the 21st century**. In this acatech IMPULSE this **substantial innovation potential** in a variety of different areas and sectors are illustrated.

Biotechnology is defined as the application of science and technology to living organisms with the goal of creating or modifying living or non-living materials and using them for different purposes, for example, in healthcare, or for the production of goods and services. This study is focused on healthcare and medicine (red biotechnology), although industrial applications (white biotechnology) and agriculture (green biotechnology) are also addressed.

Trends and challenges in the engineering of biological processes

Life sciences and biotechnology are characterised by particularly **long development and innovation cycles** compared to other disciplines. Frequently it takes several decades until fundamental research findings result in specific applications such as new medicines or industrial processes. For this reason, stable framework conditions in research and the provision of continuous research funding are particularly important. According to the experts who were surveyed, **Germany** currently is in a **leading** international **position** in the **area of biotechnology research**.

Advances in **genome sequencing** on the basis of the Human Genome Project and the development of new generations of high-throughput processes have led to significant cost and performance improvements in the area of **analysis**. With them, rates of improvement have been achieved that far exceed Moore's law in microelectronics. Due to cheaper and continuously improving technologies it is now feasible to capture the entirety of the genes and even the proteins of an organism ('**Omics technologies**'). This allows for a better understanding of the relationship between genotype and phenotype. The use of these technologies results in the creation of **very large volumes of data** that subsequently need to be processed. For this reason digital infrastructures are playing an ever bigger role in the area of biotechnology, and crucial importance is being attributed to bioinformatics.

Diagnostics will benefit from novel and even **individualized procedures**. Utilizing them will make it possible to diagnose many diseases earlier and more effectively. Companion diagnostics, a new class of diagnostic test, are being developed which allow physicians to forecast the effectiveness of a medicine on a specific patient. Through this the effectiveness of treatments can be increased, side effects can be reduced, and unsuitable treatments can be avoided.

In the area of the engineering of biological processes, new technologies allow for **easier and more accurate modifications of genetic material**. Genes can now be precisely added and existing genes can be targeted for deactivation, removal or the replacement by new genetic material. Terms such as '**genome editing**' or '**genome surgery**' highlight the precision and simplicity of these processes, particularly the CRISPR/Cas method, which in ease of use have been compared to word processing programs. Major progress is currently being made in the reduction of so-called off-target cuts in the genome. These unintended cuts in the genome

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continue to remain a challenge which has to be addressed before genome editing can be used to safely treat patients.

Genome editing has the potential to be used as a form of **gene therapy** so as to **rectify congenital defects**. The goal is to perform targeted **'repairs' of somatic cells** so that they lose their pathogenicity. While cell modifications outside the body such as bone marrow modifications are relatively straightforward, an effective and safe application of genome editing on tissues within the body still remain an unresolved challenge in need of fundamental research.

Currently there is great hope for advances in **cancer treatment**. Medicines on the basis of biotechnology already have led to significant improvements in oncology. Experts consider upcoming **immunotherapies to be the next major step to combat cancer**. Some experts hope that this avenue of research might ultimately lead to a cure for cancer. To achieve this goal, mechanisms of the immune system are used to directly attack cancer cells or to enable the immune system to effectively detect and destroy cancer cells. Compared to classic chemotherapy or radiotherapy, healthy tissues are less affected. Novel cancer treatments therefore have the potential not only to be **more effective**, but **gentler** in their effects on patients as well.

Experts already consider the combination of genome editing and **induced pluripotent stem cells (iPS)** to offer **considerable potential for research into complex diseases** and for finding possible cures for them in the future. In addition, it is hoped that further progress will be made in the area of bio-implants and **xenotransplantation**. For example, pigs could be genetically modified to reduce rejection reactions in human recipients of their organs.

A further area of research and application is the targeted modification of **micro-organisms** to cause them to either **produce certain substances** (for example, insulin, enzymes, biofuels) or extract them (for example, metals from ores or waste water). To achieve this goal of customizing organisms, approaches from engineering and IT are currently starting to be applied to biology ('**synthetic biology**'). Ultimately this could lead to the creation of micro-organisms which function as **platform organisms**, meaning they would only be equipped with genes indispensable to survival. As part of a **modular system** they then could be rapidly and flexibly equipped with specific genetic **modules** so as to produce the desired special chemicals, active agents or fuels.

One particular challenge in the cultivation of micro-organisms and other cells is the development of customized **bioreactors**. Depending on the area of use they can process a single drop of liquid or up to tens of thousands of litres. The **automation and industrial scaling up of biotechnology processes** are of decisive importance for a scientific breakthrough to become an innovation in the field of medicine, manufacturing or farming. According to many experts, **Germany** still has traditional, though endangered, strengths in **process engineering** which could be put to good use in this area.

The experts surveyed for this study generally attested to the scientific expertise in Germany, as well as its potential as an international leader in the **engineering of biological processes**. Their assessment of how well these opportunities can actually be put to commercial use in the light of the current framework conditions is more varied.

Economic importance and market potential

The aforementioned trends in science and research are associated with considerable potential for the **creation of economic value and highly skilled jobs**. The experts agree that **almost all sectors** are making increased use of bio-based processes and products, and that their **value-added chains** are being supplemented with **biotechnological components**. This is taken into account by the concept of the **bio-economy**, which covers all economic sectors that produce, process, use and trade in renewable resources and their products. These often indirect effects on different industries must be taken into account when forecasting the **market potential** of biotechnology. These potentials can be differentiated according to the following three dominant fields:

- **Agricultural** ('green') **biotechnology** is a global growth market. The cultivation of genetically modified plants – mainly soya, maize, cotton and rapeseed – is particularly widespread in North America and emerging nations. They now account for 13 % of the arable land available worldwide. The market value of genetically modified **seeds** is predicted to increase to **USD 28 billion** by 2019 (2014: USD 16 billion). This technology finds practically no use in Germany. Nonetheless, the fundamental research in this field performed in Germany continues to be highly regarded.
- A significantly greater value-added potential for Germany is seen in **industrial** ('white') **biotechnology**, where existing strengths in the chemical and pharmaceutical industries can be leveraged. Approximately 20 to 30 percent of chemical products and processes can be replaced with the use of biotechnology. This could allow for a total revenue of more than USD 500 billion worldwide by 2020. Key segments of industrial biotechnology are the enzyme

Core findings

1. Digitization is set to be followed by the next **revolution** in the world of business and society: the widespread use of biotechnology in medicine, agriculture and industry. As a **key technology of the 21st century, biotechnology** offers considerable innovation potential to a variety of different sectors.

2. Germany is **superbly positioned** in life sciences and biotechnology research, but also has **untapped potential** in the area of transfer.

3. Due to long research and development cycles and huge capital requirements, biotechnology involves a high level of investment risk (**high risk, high return**). This requires **a considerable degree of perseverance** of all involved participants.

4. In the area of medicine, the German biotechnology sector is currently limited largely to the roles of **supplier or service provider**. A focus on the development of medical drugs themselves has so far been prevented by unfavourable regulatory framework conditions.

5. Germany now stands at a **crossroads**: to prevent the loss of relevant biotechnology expertise in the area of design, development and production, continuous support not only to research but also to the **development of a competitive biotechnology industry** must be given. The latter can be achieved by creating appropriate framework conditions.

6. A public **political commitment** to Germany as an innovation-friendly business location which uses the opportunities of biotechnology and supports its further development with a **clear mission** is essential.

7. To enable a biotechnology-based industry to develop in Germany, the **framework conditions** for the publicly financed **validation** of research results and the **availability of private venture capital and growth capital** need to be significantly improved. The government has the necessary financial means and tax-related instruments to be able to achieve this and it should use them.

8. To tap the potential of biotechnology in the area of healthcare, the **benefits and costs of new treatments** need to be assessed across the entire duration of the disease and/or the lifetime of the patients. This requires a **reliable pool of medical data**, which does not exist so far.

9. **Vocational training courses and study programs** need to be adapted to the new areas of research and business opened up by biotechnology. In particular **engineering and technical sciences** are of increasing importance for biotechnology. To leverage Germany's traditional strengths in these disciplines, they **need to be closely linked to life sciences and IT**.

10. The **acceptance** of innovations in biotechnology requires their **benefit to be evident to society**. In this respect, it is necessary for the political and public debates to keep pace with the technological development in order to be able to assess risks and opportunities on a well-informed basis.

market and biofuels. The latter could achieve a significant growth spurt through processes that make use of waste and residual materials ('second generation biofuels'). These could generate up to USD 185 billion in revenue on a global basis by 2021.

- The experts assign a particularly high degree of **social value** as well as high value-added potential to the area of **medical** ('red') **biotechnology**. In 2015, 23 percent of the revenue in the global pharmaceutical industry was achieved with **bio-pharmaceuticals**. By 2020, an increase to 27 percent is expected, which is equivalent to a worldwide sales volume of almost **USD 280 billion**. Among the various therapeutic areas, **oncology** is seen to possess the largest growth potential. **Biosimilars** represent another very promising area. Along the same lines as generics in conventional drugs, they can represent a cost-effective alternative to the prescription of expensive original products when the patent protection of the latter expires.

The biotechnology sector in Germany

Comprising around 600 companies, the sector of the so-called **dedicated biotech companies** in Germany is still quite small (mainly SMEs, total revenue in 2015: EUR 3.4 billion, but investments of more than EUR 1 billion in R&D). These values rise sharply if companies in the pharmaceutical and chemical sectors are also included. In most cases it is not possible to put numbers to the share of biotechnology in the overall R&D-spending of these companies.

While the development of active medical substances is regarded as the pinnacle of achievement in red biotechnology, **German biotech companies** are more likely to operate as contract manufacturers, suppliers or other **service providers** than their international competitors. Their business models involve fewer risks, but they also offer far fewer opportunities at the same time. Service business of this kind is often pursued because of the **particularly low accessibility of venture capital** and other sources of finance for 'high risk, high return' research in Germany. The **lack of a continuous financing chain** from the seed phase to an IPO or to other exit options is seen as the **key obstacle** to the development of a bio-based industry in Germany. The main reason for those inadequate financing conditions is seen in **tax-specific peculiarities in Germany** (discrimination against equity capital when compared with external borrowing).

Further **hurdles** to the development and growth of biotechnology companies are identified as an insufficient **entrepreneurial spirit** and a low international visibility of German companies and centres of biotech activity. In addition, Germany suffers from a **validation gap**. This lack of funding often prevents drug candidates from academic research from being further developed up to the 'proof of concept' stage, which is attractive to private investors. Finally the experts fear that the low acceptance of genetic engineering in the agricultural sector among the German public might negatively affect other fields of biotechnology as well. They perceive the dangers of a loss and/or departure of expertise and a decline in biotechnology investments.

Due to these weaknesses, biotech companies in Germany either fail to secure access to capital in order to fuel their growth now and/or in the future, or are likely to be bought out by foreign players. For both reasons **Germany** has already **lost significant value added potential**. In summary, many experts believe Germany is now at a **crossroads**: if the capabilities to design, develop and produce biotechnology in Germany are to be maintained or developed further, **a considerable mobilisation of additional (venture) capital is necessary**.

Ethical, legal and social implications

Applications in the areas of medical and agricultural biotechnology do not only depend on the **creation of favourable regulatory framework conditions**. Their use is highly dependent on their **societal acceptance** as well. An increase in acceptance is dependent on satisfactory answers to **controversial ethical, legal and social issues** which arise with new methods and applications.

The availability of **skilled workers**, both now and in the future, is another important factor. The experts attest to the **high quality** of current vocational and academic training in fields relevant to biotechnology in Germany. It will be necessary however to further **integrate IT and data processing competences into the training of biologists and chemists** to maintain this level. In the same vein biotechnology topics and skills need to be further embedded into **study programs and vocational training in technological fields** and their visibility increased. In the area of engineering sciences, it is also necessary to prevent a **looming loss of expertise** in the field of **process engineering**.

The handling of **personal data** has proven to be particularly sensitive in the healthcare sector. At the same time, research into and the application of **individualized medicine** is highly dependent on the collection and combination of health-related data. Therefore data has to be protected in the best possible way so that patients are able to maintain control of their data and can agree to its transfer and use on a well-informed basis. At the present time forging such links between the scattered sets is impossible in the German healthcare system due technical reasons and conflicts of interest. Data aggregation of this kind, however, would allow for the evaluation of the **cost-benefit ratio of a particular therapy** over the entire **life cycle** of a patient. On this basis, it could be assessed as to whether the use of a costly one-time but nonetheless effective new medicine would not only be of considerable personal benefit for the patient, but also be more cost-effective than the long-term treatment with conventional drugs. On this basis **new models of payment or reimbursement**, such as 'Pay by Performance' could be developed and utilized.

Scientific and technological breakthroughs often lead to previous **political decisions and legal categories being 'superseded'** and becoming unable to fulfil their original purpose. A development of this kind is also evident in the field of genome editing. While there is a broad consensus in Germany that **human germline intervention** should **not take place** for ethical reasons, the experts perceive **a need for conceptual clarifications** by

Strenghts

- Excellent research capabilities in all areas relevant to biotechnology (biology, medicine, bioengineering)
- Good balance of fundamental research and applied research
- Mix of dynamic SMEs ('Drivers of Innovation') and global players in the chemical and pharmaceutical industries (Bayer, BASF, Boehringer Ingelheim, Merck, Henkel et al.)
- Highly skilled academic and non-academic workforce
- Competences in knowledge-based industries
- German engineering

Weaknesses

- Underdeveloped culture of knowledge transfer (focus on the production of knowledge, deficits in the subsequent validation and commercialization of ideas)
- Lack of venture capital
- No integrated 'funding chain' (public grants, seed-funding, venture rounds, exits, IPOs)
- German companies focus on service and supplier roles, no emphasis on the development of active pharmaceutical ingredients (with high potential ROI).
- High public funding of academic research, but lack of adequate leverage of investments in the commercial sector (fiscal policy, regulation)

Opportunities

- Biotechnology as a cross-sectional technology with wide application potentials in many industrial sectors
- Participation in the global transformation of the chemical and pharmaceutical sectors (steady increase in biopharmaceuticals and biosimilars; soft chemistry etc.)
- Biotechnology as a knowledge-based industry with high expertise requirements (comparative advantage), creation of high quality jobs
- Emerging biotechnology enables sustainable economies; establishment of new industries with high value creation potential
- Development of smart production technologies to introduce principles of 'Industrie 4.0' to biotechnological production and manufacturing
- Mission-oriented public funding (biotechnology as 'next moonshot')

Threats

- Corporate loss of competences and connectivity necessary for cooperation with academic research due to cuts in in-house R&D
- Problematic relations of exchange and cooperation between big corporations and a biotechnological sector consisting mostly of SMEs
- Lacking commercialization due to low public acceptance of biotechnology (e.g. green genetic engineering, genome-editing)
- Loss of competences in bioengineering
- Decline or departure of medical biotechnology expertise due to lack of funding and growth potential, resulting in loss of competences in the design, development and production in the medium term

SWOT-Analysis of biotechnology in Germany (source: authors' own diagram) ethical experts and legal scholars in several areas. Chief among those are the meaning of the term 'embryo' in terms of the German legislation on embryo protection and stem cell research as well as the **definition of genetically modified organisms**. There now are cases where genome-edited plants cannot be distinguished from conventionally bred plants. Currently, in legal terms, the intentional increase in mutation rates through the use of radioactive irradiation or mutagenic chemicals is considered to be conventional plant breeding. If the more precise method of genome editing would be classified as 'genetic engineering', it would be subject to considerably stricter approval and control mechanisms, although it is associated with fewer risks than the application of previous methods. For this reason, most experts argue that the definition of GMOs should focus more on the product and less on the process of modification.

Despite this most experts express their belief that genetically modified animals and plants should **not to be introduced by exploiting legal loopholes**. This would only serve to increase public resistance against genome editing. They stress **the necessity of a public debate** instead. Likewise treating the currently arising ethical and legal issues as 'taboo' is seen to only lead to even greater problems in the long run.

According to the experts, however, there is **no formula for success** on how to conduct this urgent debate at the public level. They agree that a **concerted effort** by stakeholders from **science, industry and politics** is necessary. **Risks** are not to be ignored, but above all else, the **specific benefits** of the new technologies are to be made evident to both users and the wider general public.

Methodology

The acatech IMPULSE *Innovation Potential of Biotechnology* is based on the evaluation of the latest specialist literature as well as expert interviews with 76 representatives from science and business. The interviews were conducted between May and October 2016. The goal was to gain an overview of current developments in life sciences and biotechnology. On the one hand, the experts were questioned about the leading trends in life sciences and biotechnology, while on the other hand, the attractiveness of the business location of Germany, as well as the political and public framework conditions were subject to evaluation. Building on this, the participants were consulted about possible measures to make the best use of the innovative potential of biotechnology in Germany.

Editor: acatech – National Academy of Science and Engineering

Munich Office
Karolinenplatz 4
80333 Munich | Germany
T +49 (0)89/52 03 09-0
F +49 (0)89/52 03 09-900

Berlin Office
Pariser Platz 4a
10117 Berlin | Germany
T +49 (0)30/2 06 30 96-0
F +49 (0)30/2 06 30 96-11

Brussels Office
Rue d'Egmont / Egmontstraat 13
1000 Brussels | Belgium
T +32 (0)2/2 13 81-80
F +32 (0)2/2 13 81-89

www.acatech.de
info@acatech.de

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