BIOTECHNOLOGY TREND ANALYSIS 2023

A CALL FOR VISION, DECISION AND DIRECTION

MARCH 2023

SUMMARY

The scientific and technological advances being made in biotechnology are proceeding at a rapid rate and the possibilities for modifying organisms have grown enormously. New products and applications are appearing in increasingly rapid succession, including Covid vaccines, biochemicals and proteins produced by micro-organisms, and plant breeding techniques. As a result, biotechnology is becoming increasingly important. For this reason, the Minister of Infrastructure and Water Management – also on behalf of four other ministries: Agriculture, Nature and Food Quality; Health Welfare and Sport; Economic Affairs and Climate Policy; and Education, Culture and Science – asked COGEM and the Health Council of the Netherlands to prepare a new trend analysis of developments in biotechnology. This *Biotechnology Trend Analysis 2023* describes the main developments, focusing on three areas: the circular economy, food production and healthcare.

Biotechnology is accelerating and integrating into other fields

The advance of biotechnology is being driven by a combination of technological developments. The use of information technology, automation and robotisation is making techniques such as reading the base sequence of genetic material (sequencing), making targeted modifications (gene editing) and inserting genes from other species (genetic modification) *simpler, quicker, cheaper* and *more accurate*. This applies to the complete spectrum of living organisms, from microorganisms, plants and animals to humans. These developments have led to a situation in which modifying living organisms to give them desirable functional capabilities or traits is taking place on an *increasingly large scale*. As a consequence, biotechnology is gaining momentum and influence, and its applications have found their way into numerous economic sectors and research fields. While these applications present new opportunities for innovation and for achieving the UN's Sustainable Development Goals, they also raise new questions and dilemmas about their desirability and safety, and concerns about property rights.

Potential benefits for the circular economy, food production and healthcare

The trend analysis focuses on the opportunities that biotechnology provides in three areas:

1) Industrial biotechnology can contribute to creating a fully circular economy. Micro-organisms are used to make products and chemicals that are now manufactured by the petrochemical industry, such as fuels and plastics. Whereas the petrochemical industry uses fossil fuels and is responsible for high CO_2 emissions, industrial biotechnology aims to use renewable raw materials from agriculture and waste streams. Considerable research is also being conducted into biotechnological processes in which CO_2 is used as a raw material, along with electricity or green hydrogen.

2) In the agro sector, biotechnology has a part to play in the progress towards sustainability and security of food production, as described in the EU's *Farm to Fork Strategy* and the Dutch National Protein Strategy (*Nationale Eiwitstrategie*). Gene editing can speed up the plant breeding process and produce plants that are tolerant of drought, extreme temperatures and salinisation or resistant to pests and diseases. There is a global research effort on creating microorganisms that can produce 'animal' proteins and on the production of cultured meat. The first products have already appeared on the market. In countries outside the EU, gene editing is also being used to increase the productivity of farm animals.

3) In healthcare, biotechnology is involved in the control of infectious diseases, the treatment of cancer, the prevention and treatment of genetic disorders and, in future, possibly the transplantation of animal organs into humans (xenotransplantation). The power of large-scale sequencing was demonstrated during the COVID-19 pandemic, when this new technology was instrumental in the rapid development of diagnostic tools and vaccines.

New developments also raise new issues

Biotechnology not only holds the promise of benefits to society, but also raises complex ethical and social questions involving different, possibly conflicting values. Moreover, applications are not always without risks to human health and the environment. The legislation must ensure safety, but it must also allow room for innovation. It is therefore time to modernise the regulations surrounding biotechnology. Not only do EU regulations date from the previous century and are based on outdated scientific insights, but opinions differ on which applications are desirable and which are not, and on how to weigh up the potential benefits against the risks. Decisions on which applications should be encouraged and which should be prevented are therefore inherently ethical and political.

There is public resistance to genetic modification, particularly in food production. Moreover, the new technologies raise ethical questions, such as whether modifying human or animal embryos is acceptable or desirable. Cellular agriculture, which is mainly geared to producing alternatives to animal proteins (such as cell-cultured meat), may become a disruptive technology, especially for conventional forms of livestock farming. Finally, the competitive position of the Netherlands and the EU may be at risk because significant technological innovations, such as CRISPR-Cas, are taking place outside the EU and Dutch companies are becoming dependent on patent holders elsewhere, especially in China and the US.

Government must provide an integrated vision and direction

To exploit the opportunities, the 'biotechnological innovation ecosystem' must be in good order. COGEM and the Health Council of the Netherlands are of the opinion that the system needs to be improved as the Netherlands is ill prepared for new developments and is missing out on opportunities to make full use of the economic and social potentials of biotechnology. Although the government does develop initiatives, these are piecemeal and lack clearly formulated goals. What is needed is an *integrated long-term vision* on the direction of advances in biotechnology that would benefit Dutch society, as well as steering by government to implement this vision. A government-wide approach is needed.

Elements that should be considered in such an approach include: improving the research infrastructure; ensuring fundamental research, partly with a view to developing new technologies and the associated intellectual property rights; parallel research into socially accountable biotechnological innovation; clear ethical principles, including a good balance between the protection of privacy and property rights and the exchange of information; a just distribution of costs and benefits; and future-proof biotechnology legislation. To this end, each chapter of this trend analysis, particularly the final chapter, contains a number of recommendations and possible courses of action.

Putting such a vision into practice requires the concerted engagement of the various parties active in biotechnology, such as government agencies, scientific institutions, the business community, professional groups, NGOs and consumer and patient organisations, with government taking the lead. Essential for this is active communication about developments in biotechnology between government, stakeholders and the public, involving both participation and education.

CONTENTS

1 INTRODUCTION

Biotechnology is advancing at a rapidly increasing rate. That was one of the conclusions of the *Biotechnology Trend Analysis 2016*. Since then, numerous new developments have taken place. Not only is biotechnology advancing at a rapid rate, but sometimes also in intermittent bursts. Now it costs just 600 dollars to sequence a human genome and the price is still falling. CRISPR-Cas9 (a technique used to make precise, targeted changes to DNA sequences) has developed rapidly from a scientific discovery to become a standard tool for altering genetic material that is used by laboratories and companies around the world. In China, children have been born with an edited genome (although this was illegal). A modified pig heart has been transplanted into a living patient for the first time, although with limited success. And in the United States, there are plant-based burgers on the market that look more like meat hamburgers than ever through the addition of an iron-rich protein (heme) produced by genetically modified organisms (GMOs). Cultured meat is on sale in Singapore, and soon will be in the US. The importance of biotechnology to society became clear to everyone during the COVID-19 pandemic, when the new vaccines and rapid tests that proved crucial for controlling the virus were made available very quickly. The pandemic and heightened geopolitical tensions have led to growing calls for greater strategic autonomy for the Netherlands and the European Union, and this applies to biotechnology and its applications as well. This Trend Analysis attempts to make sense of the developments in biotechnology by giving as joined up a picture as possible of their importance for the Netherlands and the questions they raise.

1.1 BIOTECHNOLOGY TREND ANALYSIS 2023

The Biotechnology Trend Analysis 2023 was prepared at the request of the Minister of Infrastructure and Water Management (dated 24 June 2021, Appendix A), which was also made on behalf of four other ministries: Agriculture, Nature and Food Quality; Health, Welfare and Sport; Economic Affairs and Climate Policy; and Education, Culture and Science. The minister asked COGEM and the Health Council of the Netherlands to describe the trends and developments in biotechnology and related key technologies with the aim of providing Parliament and policymakers with an overview of the latest developments and applications in biotechnology, both within and outside the Netherlands and the EU, including any identifiable trends, as well as the social and economic opportunities and possibilities these present and associated ethical questions. The minister also felt it would be both useful and valuable to look into the bottlenecks and dilemmas arising from review and assessment procedures and the possible changing role of various stakeholders and other parties involved. The Trend Analysis was not to be limited to analysis, but also provide pointers for developing future-proof policies and regulatory frameworks. And it had to take the international perspective into account. This Trend Analysis is the fifth in an occasional series. Previous reports were published in 2004, 2007, 2009 and 2016.

In response to this request for advice, COGEM and the Health Council of the Netherlands set up a joint project committee on 26 January 2022. The members of the project committee are listed in Appendix B.

1.2 WHAT IS BIOTECHNOLOGY?

This Trend Analysis explores the trends and developments in modern biotechnology. Biotechnology encompasses a broad swathe of activities, applications and products, which makes it difficult to provide a comprehensive definition of what modern biotech-

nology is. The most commonly used definition is that of the *Organisation for Economic Cooperation and Development* (OECD), which consists of two parts: a description and a list-based definition of techniques (see Appendix D). The description also covers traditional activities, such as brewing and cheesemaking, and so it should always be accompanied by the list of categories of techniques. In this Trend Analysis the committee used the OECD definition, with a minor alteration:

> *Biotechnology is the application of science and technology to living organisms, as well as parts, products and models thereof, to characterise or alter living or non-living materials for the production of knowledge, goods and services.*

The committee considers that this broadening of the definition is important, because characterisation (or mapping) of genetic information and biotechnological processes is an indispensable part of the development of modern biotechnology.

1.3 CHALLENGES

Society faces enormous challenges in its bid to eradicate poverty and hunger and promote good sanitation, as well as in healthcare, education and ensuring employment for everyone, combating climate change and protecting ecosystems and biodiversity. The 17 United Nations Sustainable Development Goals (SDGs) for 2030 provide a normative framework for government action in these areas.[1] The Netherlands is committed to working towards realising these goals, either as part of an EU-wide effort or on its own, and this commitment has been detailed in many recent policy documents. These documents express a clear obligation to seize all opportunities for bringing us closer to fulfilling these goals. Also, the Universal Declaration of Human Rights states that everyone has the right to share in scientific advancement and its benefits (Article 27).[2] Although the means to achieve these goals can never be purely technological in nature and far-reaching changes in society will be needed, biotechnology – like other technologies – could make a substantial contribution. Nevertheless, this does not mean that advances in biotechnology should be pursued unreservedly. Despite the possible benefits biotechnology can bring to society, it clearly raises complex social concerns, including issues that impinge on certain values, while some applications are not without risks to human health and the environment. Opinions differ on which applications are desirable and which are not and on how to weigh up the potential benefits against the risks. The question is how the Dutch public perceives the possibilities of modern biotechnology and what conditions they want to place upon it. Such decisions are therefore inherently ethical and political. Crucial to the making of these decisions – and to the political and social values that underlie them – is knowledge of current developments and the potential social impacts of biotechnology.

1.4 THE APPROACH TAKEN IN THIS TREND ANALYSIS

Biotechnology has developed into a highly diverse field, with branches in numerous other sectors. New developments and scientific breakthroughs that deserve the attention of politicians and policymakers are constantly taking place. Discussing all these developments would not only be impractical, but neither would it serve the purpose of this Trend Analysis. The committee therefore selected a number of developments that are indicative of the trends in biotechnology and that raise opportunities and questions for the policymaking process.

The selection of trends and developments discussed in this report was informed by input from stakeholders in the field and interviews with experts. The committee approached

NGOs, companies and academic organisations and asked them to suggest trends that in their opinion deserve to be examined in this Trend Analysis. Nine organisations responded (Appendix C). The committee also carried out a literature study. Based on the resulting information, it compiled a 'landscape of biotechnology', which involved studying how the full range of living organisms (from microorganisms and plants to animals and humans) are being characterised and modified and what applications are being developed.

The decision was made to concentrate on three areas – food production, the circular economy and healthcare – and a selection of the most relevant trends and developments was made on the basis of the possible opportunities and on the ethical, legal and societal questions raised by the identified applications. Interviews were then held to explore and investigate them in more depth (Appendix C). Some of the trends and developments described in this Trend Analysis had already been identified in the 2016 Trend Analysis.

Technological innovations arise within an 'innovation ecosystem', an environment in which various groups of stakeholders work together. To operate successfully this system depends on well functioning knowledge infrastructure, good legislation and sufficient funding and investment (see Figure 1).[3] Accordingly, this Trend Analysis also looks at the ability of the Dutch biotechnological infrastructure to support the identified developments. To capitalise on the opportunities that arise, politicians and policymakers must quickly address the questions and dilemmas they throw up and devise an appropriate response. The project committee hopes that this document will make a valuable contribution to this process.

The Scientific Council for Government Policy (WRR) commented on a draft version of this Trend Analysis and the various COGEM subcommittees and the Standing Committee on Ethics and Law of the Health Council of the Netherlands were also consulted. The project committee made grateful use of the comments it received when finalising its analysis.

1.5 STRUCTURE OF THIS REPORT

Chapter 2 describes the technological trends and developments that are driving the rampant growth of biotechnology. The subsequent chapters go into the applications that have emerged from this growth. Chapter 3 is concerned with developments in industrial biotechnology, Chapter 4 with agriculture, cellular agriculture and food production, and Chapter 5 with healthcare. In each case, the technological developments are discussed first, followed by their social impacts and policy relevance. As many of the social and political concerns are common to all fields and are closely connected, they are treated in several chapters. The final chapter is a synthesis of the previous chapters and describes a number of possible courses of action for politicians and policymakers to pursue. Prior to that, Chapter 6 offers a glimpse of possible future applications.

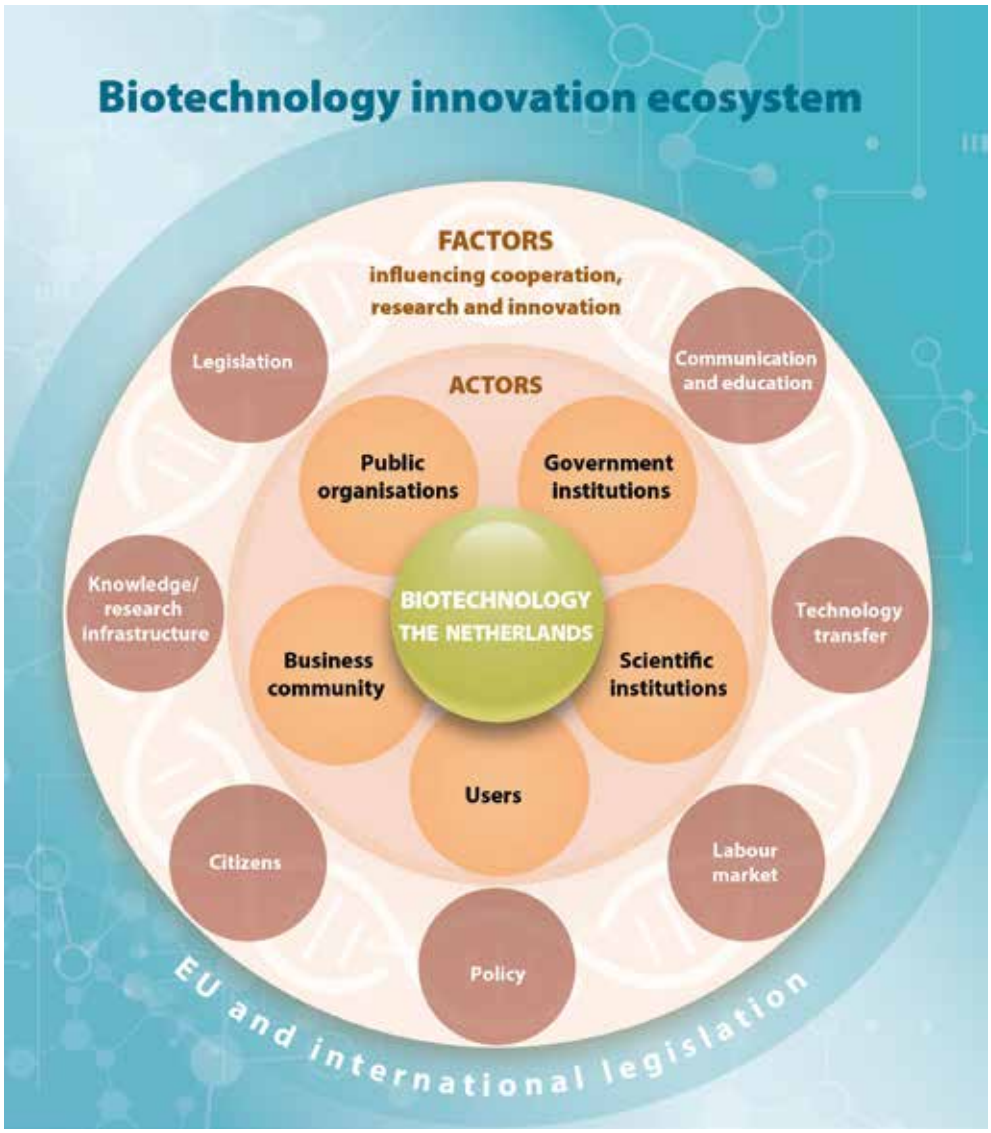


Figure 1: The biotechnological innovation ecosystem

2 THE DRIVERS BEHIND DEVELOPMENTS IN BIOTECHNOLOGY

The advances in biotechnology are being driven by a combination of technological trends. To start with, the techniques for reading and interpreting the base sequence of genetic material (sequencing) are continuing to improve. The same is true for making site-specific modifications to the genome (gene editing). A key development is the ongoing integration with information technologies, including artificial intelligence, and the growth of automation and robotisation, which has transformed the field. As the sequencing and modification of genetic material becomes faster, cheaper, more accurate and simpler to perform, modifications to living organisms are being made on a greater scale and are becoming increasingly complex in nature. This reflects the deepening of our knowledge of and control over biological functions across the complete spectrum of living organisms, from microorganisms and plants to animals and humans. As a result, biotechnology has increasingly significant implications.

This chapter describes the technological developments that are behind the advances being made in biotechnology. Applications in the agro and industrial sectors and in healthcare, and their associated issues, are dealt with in the following chapter.

2.1 SEQUENCING AND X-OMICS: READING AND UNDERSTANDING THE GENOME

2.1.1 Sequencing has become quicker and cheaper

The speed and scale at which genomes can be sequenced has skyrocketed since the last Trend Analysis.[4] Existing methods have been further developed and new techniques have emerged, allowing sequencing to be performed even faster, cheaper and with less material. The newest sequencing machines can generate 6 terabytes of data in 24 hours, equivalent to the complete genome sequences of 48 people.[5,6] This means the cost of determining the entire genome of a single person can be reduced from 600 to about 200 dollars.[7] It is also now possible to make more accurate determinations of difficult genome sequences, such as highly repetitive sequences. When it was announced in 2000 that the sequence of the human genome had been determined in its entirety, many pieces were actually still missing because they were hard to determine with the techniques available at the time. It was not until 2021 that the last pieces of the puzzle were completed.[8,9]

The reduction in the amount of genetic material needed to perform sequence analyses is particularly important for reproductive medicine, because it means a single cell from a starting embryo can be isolated and tested for genetic abnormalities. The importance and power of large-scale sequencing became apparent during the COVID-19 pandemic. The almost immediate availability of the sequence of the SARS-CoV-2 genome aided the rapid development of vaccines and diagnostics and the monitoring of the spread of the virus (see Chapter 5).

New portable sequencing equipment makes it possible to collect and analyse samples in the field, even in countries lacking proper research infrastructure. This equipment is also

used for ecological research in the field or during laboratory classes.[10,11] These small and relatively cheap devices bring sequencing within the reach of people who have no access to large-scale sequencing facilities.

2.1.2 Major strides in X-omics

Determining the sequence of genetic material is just one part of the story. Many processes that take place in the cell start with reading the genes on the DNA, leading to the formation of mRNA (messenger RNA), which is then translated into proteins. The proteins, in turn, determine the cell's metabolism and, to an important extent, the regulatory processes in the cell. Since the previous Trend Analysis major strides have been made not only in genomics, the field that deals with genetic information, but also in technologies that seek to better understand the metabolic pathways in the cell (metabolomics) or the function and operation of proteins (proteomics). All these technologies are referred to collectively as X-omics.

A relatively new field currently in the spotlight is epigenetics, the science of making reversible heritable changes in gene expression without altering the DNA sequence. Whether genes are active or not depends on the degree to which the DNA can be accessed and read by certain enzymes in the cell.[a] This 'epigenetic status' of genes is influenced by environmental factors, it can be heritable (over several generations) and is a factor in various developments, such as the emergence of cancer in humans and drought resistance in plants. The active genes in a cell can be investigated on a large scale by sequencing all the mRNA in the cell to identify what is called the 'transcriptome'. It is also possible to determine the epigenetic status of the genes themselves, down to the level of the individual cell.[12,13] Epigenetics is attributed an important role in the development of medical applications and in plant breeding. The ability to influence the epigenetic status of genes makes it possible to determine the function of genes, explain the mechanisms behind drought and heat tolerance in plants, investigate the adverse side-effects of medications and cure diseases.[14,15,16,17] However, specific applications are still in the research stage and not yet available.

Text box 2.1: GMO legislation

In the EU and the Netherlands genetically modified organisms are subject to rules to ensure human and environmental safety. A permit is required for all activities involving genetically modified organisms, including research in laboratories, animal houses and greenhouses, and experiments conducted outside laboratories, such as field trials with GM crops and veterinary and clinical trials. Issuing permits for these activities is a national responsibility. Authorisation for marketing GM crops and medicines takes place at EU level, with a key role for the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA). To give consumers the choice of whether or not to buy genetically modified products, manufacturers must label food products that contain more than 0.9% genetically modified ingredients.

The legal status of organisms with induced epigenetic changes, however, is not entirely clear. A European Commission report states that they should fall under the GMO legislation, despite the fact that the base sequence of their DNA has not been changed.[18] This would have major implications for both medical applications and plant breeding. There are several cancer medications whose mechanism of action involves the modulation of the epigenetic status of genes.[15]

a This is determined by the proteins (histones) which bind to and condense the DNA and the chemical status (methylation) of the DNA.

2.2 TARGETED MODIFICATION OF THE GENOME: GENE EDITING BY CRISPR-CAS

2.2.1 Breakthrough in targeted modification of the genome

The discovery and application of the CRISPR-Cas9 system[b] is one of the most important developments in biotechnology over the past twenty years. CRISPR-Cas is now an essential tool in biotechnological research. CRISPR-Cas systems occur naturally in bacteria, where they form a defence mechanism against viruses and other non-endogenous genetic elements. In 2012 a paper was published describing how CRISPR-Cas9 can be used to make breaks at specific positions in DNA in a relatively straightforward way, allowing specific changes (mutations) to be made in the genome at the site of the break (see Figure 2).[19] This publication led to a breakthrough in the potential for gene editing. Since then the use of CRISPR-Cas has risen sharply, both in fundamental research and in various agricultural and medical applications, and clinical trials with CRISPR-Cas are underway.[20] CRISPR-Cas has been a breakthrough, because it is much cheaper and easier to use than previous systems that cleave DNA at specific locations, such as Zinc fingers and TALENs.[21] Nevertheless, zinc fingers and especially TALENs are still widely used, both for modifying plants and in gene therapies.

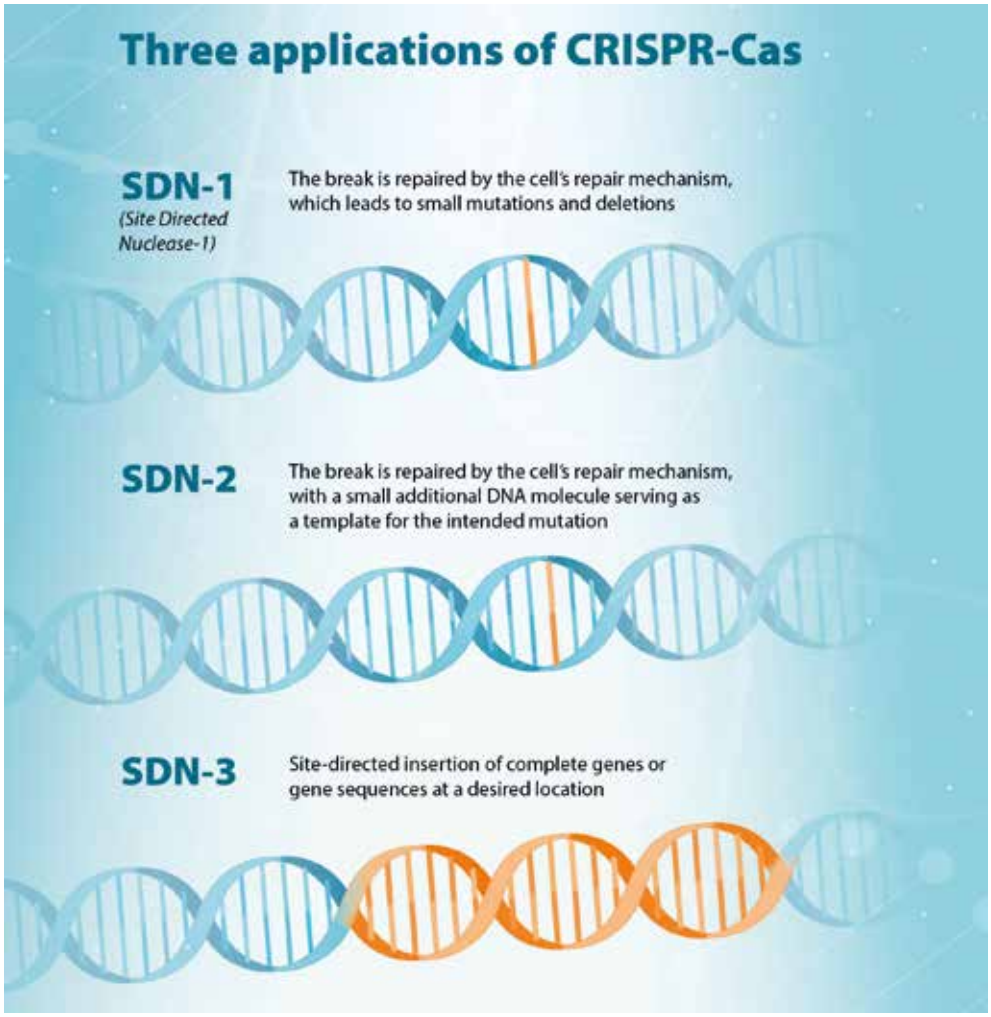


Figure 2: Three different applications of CRISPR-Cas: SDN1, SDN2 and SDN3

b Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) associated proteins (Cas). The original CRISPR-Cas system contained the Cas9 protein from the bacterium *Streptococcus pyogenes*. Numerous other Cas proteins are now also used. The term CRISPR-Cas covers all these different CRISPR-based systems.

The breaks in DNA made by CRISPR-Cas9 or other gene-editing systems are repaired by the cell's repair mechanisms.[22] Both DNA strands are reconnected, during which small changes (mutations, deletions or insertions) may arise at the site of the break which can lead to genes being inactivated, altered or even repaired.[23,24] To prevent random mutations occurring at the site of the break, a donor sequence in the form of a short piece of DNA (oligonucleotide) containing the desired base sequence can be added, which acts as a template for the repair. In addition to gene editing, CRISPR-Cas can also be used to insert larger pieces of DNA or genes at a specific site in the genome.[25] These three different applications are known internationally as site-directed nuclease 1, 2 and 3 (SDN1, SDN2, SDN3) (see Figure 2).

Mutations and other changes in the genomes of organisms can also occur naturally, for example under the influence of radiation, including sunlight, or spontaneously during cell division. Evolution would not be possible without these natural mutations. CRISPR-Cas9 and other gene-editing techniques speed up this natural process by making desired changes at precise locations in the genome, but otherwise there is no difference between these induced mutations and natural mutations. Technologies do not stand still and it is now possible to introduce numerous targeted changes in different genes in a single experiment.[26,27] The question is whether gene editing will go beyond the boundaries of natural variation by introducing or constructing new genes or modifying organisms in such a way that they become a different organism. For example, researchers think that extinct species could be brought back to life by using gene-editing techniques to modifying the genome of related species.[28]

2.2.2 CRISPR-Cas techniques greatly expanded

Although CRISPR-Cas systems are very effective at inducing site-directed mutations in the genome, unwanted effects can also occur, both at the targeted site on the genome (on-target) and at other positions in the genome (*off-target*). These unwanted effects may result in the introduction of small insertions, deletions or point mutations, and even large deletions or rearrangement of chromosomes are possible.[29,30,31] The risk of unintended side-effects is therefore one of the most frequently mentioned objections to any relaxation of the GMO legislation on gene editing. Much of the research conducted in recent years has been devoted to reducing the risks of unwanted side-effects. This is particularly important for medical applications (see Chapter 5).[32,33] Unwanted changes in the genome of plants or microorganisms can be discovered by fully sequencing the genome, after which any unwanted variants can be removed.

This research has helped to drive the enormous expansion of the arsenal of possibilities and applications of CRISPR-Cas techniques.[34,35] These include modifications of the Cas9 protein itself, the guide RNAs that identify the target sequences, and the way the system is regulated, and the outcomes of the CRISPR-Cas system have become more efficient and reliable, for example through the creation of Cas proteins with increased specificity.[36,37,38] In addition to the original Cas9 protein from the *Streptococcus pyogenes bacterium*, various similar proteins have been discovered in other bacteria.[39,40,41] Cas proteins have been found that can cleave RNA instead of DNA.[42] Other Cas proteins cleave just one strand of the DNA, which minimises the number of unwanted changes, such as rearrangements in the genome, because the DNA is not cut completely in half.[43,44]

The use of proteins that do not cleave DNA (or RNA), but convert the bases in the DNA into other bases (base editing) is considered to be a significant breakthrough for making safer applications of CRISPR-Cas.[45] DNA consists of four bases: cytosine (C), thymine (T), adenine (A) and guanine (G). Together they form, in alternating order, the genetic code. There are proteins, and CRISPR-Cas systems, which can convert a C into a T or an A into

a G (see Figure 3).[46,47] The first clinical trials on the application of base editing systems began in 2022.[48]

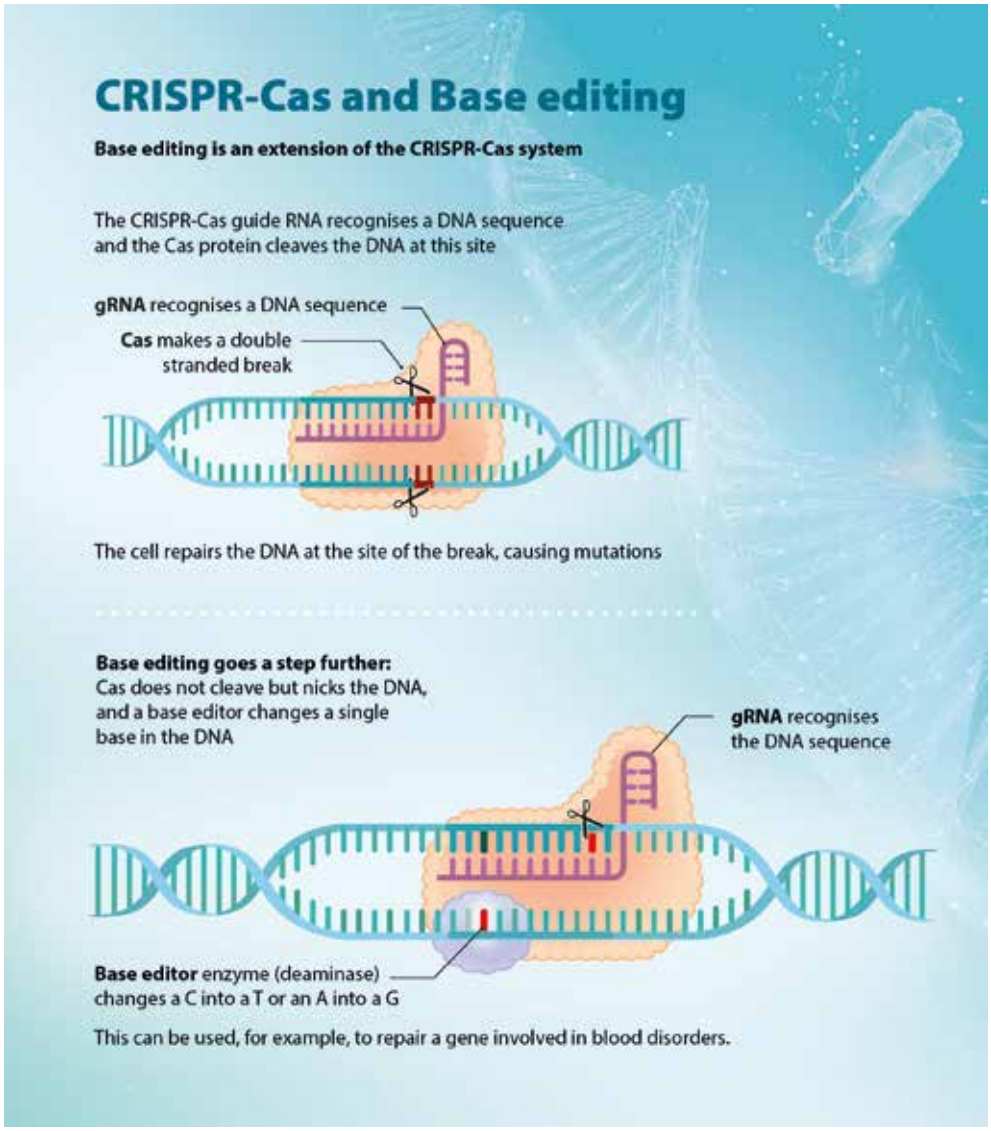


Figure 3: CRISPR-Cas and base editing

CRISPR-Cas can also be used to induce epigenetic changes that modify gene expression without changing the base sequence of the DNA itself. This can be done using a modified CRISPR-Cas complex that does not cleave the DNA, but instead binds to the regulatory signal of a gene, therefore blocking the transcription of the gene.[49] Expectations for this application are high.

The science of CRISPR-Cas and related systems is developing further and in the years to come numerous new systems and applications will emerge.

Text box 2.2: Detection and diagnostics with CRISPR-Cas

CRISPR-Cas applications are not limited to gene editing. In particular, its use as a method for detecting pathogenic bacteria and viruses in humans and plants and mutations in DNA that cause cancer is growing rapidly.[50] Several CRISPR-Cas de-

tection systems have already been developed, including those for the COVID-19 virus, Zika virus, human papillomavirus in humans and for plant pathogens.[51,52] CRISPR-based detection systems for SARS-CoV-2 have been approved for use in the US.[53]

One advantage of CRISPR-Cas detection systems is that they are highly sensitive and specific and can be carried out at a single temperature, in contrast to PCR tests – the current gold standard for detection – which require complex and expensive laboratory equipment.[54] These tests can therefore be used in the field or in countries with limited financial resources. Most systems involve amplification of the RNA or DNA to be detected, followed by detection of the amplified sequences by a CRISPR complex with fluorescent marker molecules or gold nanoparticles. Because CRISPR-Cas recognises and cleaves specific sequences, certain sequences or mutations in DNA or RNA, such as carcinogenic (oncogenic) mutations, can also be recognised, or a distinction can be made between virus variants, for example.

2.3 BIOINFORMATICS: ANALYSIS, INTERPRETATION AND MAKING CONNECTIONS

2.3.1 A changing research landscape

Modern sequencing techniques and related technologies generate large amounts of data. Those data can be linked to biological information or characteristics to reveal the functions of genes and gene variants. For example, analysis of hundreds of thousands of sequence databases and linking them to clinical and biological characteristics has successfully revealed the role of genetic variations in complex diseases as a first step towards treatments.[55]

The explosive growth in the volume of data has changed the research landscape. Analysing these data and making connections between them relies on bioinformatics and the computational power of supercomputers.[56,57,58] Using artificial intelligence in the form of algorithms and machine learning,[59] predictions can be made about the structure of proteins and how modifications affect how they function.[60] This can considerably expedite the development of medicines, for example. Machine learning is used to optimise conditions in bioreactors by predicting in advance or in real time what changes will affect the culture conditions and production.[61] Machine learning can also be used in plant breeding to make better predictions of the influence certain genes will have on the whole plant.[62]

The power of supercomputing became apparent in June 2022 when researchers analysed 20 million gigabytes of sequence data in databases and revealed the existence of 100,000 unknown RNA viruses – ten times the number of RNA viruses that were known up to that point.[63,64]

Text box 2.3 Forensic DNA analysis: new opportunities and dilemmas

Forensic DNA analysis is becoming increasingly important in detecting offenders. Traces of DNA can be used to identify the geographical origin as well as the eye, skin and hair colour of an unknown offender.[65] Improvements in the technology mean that DNA profiles can be drawn up from smaller amounts of available material. This has led to convictions in several cold cases. DNA kinship analysis has proven to be helpful in this regard, although it is still a relatively little used investigative technique.[66]
In the US the police have successfully used (private) genealogical DNA databases to identify suspects.[67] In the Netherlands a study is underway to identify how genea-

logical databases could be used to help identify unknown deceased persons, and the conditions that should apply.[68] The use of databases where permission was not given for these purposes when the material was deposited poses ethical dilemmas. While the data can be helpful in the identification of offenders and victims, there is a risk that other people and relatives of offenders and victims may also be caught up in the justice system.

2.3.2 A tsunami of data: data storage and processing

The developments describe above have led to an exponential growth in the amount of data to be stored and processed. Sequence data are deposited in international databases. In May 2020 the International Nucleotide Sequence Database Collaboration (INSDC[69]) already contained 9 petabytes of data (that is 9,000 terabytes, 9 x 10^{15} bytes) and in June 2021 The Sequence Read Archive,[70] a database where raw sequence data are stored, contained almost 17 petabytes.[71,72] The volume of data will continue to grow. It is estimated that between 2 and 40 exabytes (2 to 40 x 1018 bytes) of sequence data will be generated in the next ten years.[73] For comparison, 1 exabyte is roughly equivalent to 100,000 times the complete digitised content of the American Library of Congress (the largest library in the world, with millions of books, newspapers and audiovisual materials).[74]

The growing stream of biotechnological data means that storage capacity will have to be expanded, including capacity in the Netherlands. This increase in demand for storage capacity and supercomputing to process large amounts of data is not limited to biotechnology, but affects other fields as well. Universities are already building new data centres, either individually or jointly. Such infrastructure is essential for the whole sector. Data processing will eventually have to be done entirely via cloud computing. At the moment the market for cloud services in the EU is dominated by large American companies, which is problematic for reasons of privacy, data protection and regulatory control.[75,76]

Text box 2.4: The Nagoya Protocol and digital sequence information

The Nagoya Protocol[77,c] regulates access to genetic resources and the fair and equitable sharing of the benefits arising from their utilisation.[78] Genetic resources refer to plants, animals and other organisms as well as traditional knowledge about them. The Protocol requires companies and institutions to obtain permission from or have an agreement with countries to use material originating from those countries. For many years the question of whether digital sequence information (DSI) falls under the Nagoya Protocol or not has been a bone of contention.

The 2022 Conference of Parties to the Convention on Biological Diversity (COP15) came to a historic framework agreement in which DSI was brought within the scope of the Nagoya Protocol.[79] It was further agreed that a compensation system will apply to all commercial products, but not to accessing sequence databases.[80] This addresses some of the concerns among researchers regarding access to and the use and exchange of data[81,82] and the associated costs.[83,84,85] The practical implementation of the agreement is expected to be completed within two years. For companies and institutions that develop products, the questions of the details of the compensation system, what the costs will be, how they will be distributed and whether or not it will be a multilateral system avoiding multiple individual national systems remain to be answered.

c In the EU the Nagoya Protocol is implemented by Regulation (EU) 511/2014, which in the Netherlands is in turn implemented in the Nagoya Protocol Implementation Act.

2.4 AUTOMATION AND ROBOTISATION

Automation and robotisation are becoming increasingly important in biotechnology. Just like other industrial processes, automation and robotisation can make production more efficient and reduce costs.[86] Sequencing and diagnostics are already almost fully automated in large facilities. The industrial production of biochemicals, medicines and cell cultures is also highly automated.

After a late start, universities and research institutes are now increasingly adopting automation and robotisation.[87,88] A number of manufacturers make equipment and software for automating various operations and experiments.[86] Automation offers several advantages, such as the ability to analyse or screen a large number of samples (high-throughput analysis), the standardisation of processes and increased reproducibility of results by avoiding human error and inconsistency in execution, faster transition from the laboratory to commercial production and increased safety for employees.[87]

Despite the constraints imposed by the higher costs of the equipment, which affect research laboratories in particular, it is expected that the level of automation will continue to increase over the coming years. A factor driving this automation is that high-throughput systems can be used to process the torrents of digital data that are becoming available. The scale and speed of laboratory research will increase, but it will become more capital intensive. It will also be necessary to broaden the expertise of laboratory teams to include the skills required for the automation and robotisation of experiments. This means that researchers will have to receive training in automation in addition to experimental skills.[89]

3 BIOTECHNOLOGY FOR THE CIRCULAR ECONOMY

The transition to a sustainable economy is considered to be an urgent major global challenge. The Dutch government aims to achieve a fully circular economy by 2050.[90] Transitioning to a circular economy should contribute to four major societal challenges: reducing carbon emissions, conserving biodiversity, improving the quality of air, water and soil, and securing the availability of raw materials.[90] Industrial biotechnology can play a major part in this transition. It uses microorganisms such as bacteria, fungi and yeasts to manufacture products and chemicals that are currently produced mainly by the petrochemical industry, such as fuels and plastics. Industrial biotechnology uses renewable raw materials (sugars) from agriculture and waste streams. Considerable research is also being conducted into biotechnological processes in which CO_2 or (green) hydrogen can be used as a raw material. These types of innovations are also relevant in the context of the Sustainable Development Goals on sustainable consumption and production and for combating climate change.[91]

From both a scientific and industrial perspective, the Netherlands is in a strong position to profit from the opportunities offered by industrial biotechnology. This will require vision and direction from government on the development of industrial biotechnology and the efforts that will be needed, including an appraisal of the costs and benefits.

3.1 TECHNOLOGICAL DEVELOPMENTS AND COMMERCIALISATION

3.1.1 Ongoing rapid development

The rapid development of industrial biotechnology described in the 2016 Trend Analysis is continuing and is linked to the developments described above in genetic analysis and modification techniques, robotisation, bioinformatics, big data and artificial intelligence. As with biotechnology in general, these developments in industrial biotechnology are converging and reinforcing each other.

Genetic analysis and modification techniques are becoming more precise and faster and cheaper to perform. Importantly, the possibilities for synthesising DNA fragments – and even complete genes – on an industrial scale are expanding and becoming cheaper. There are now many companies around the world that are specialised in the chemical synthesis of DNA fragments, and these can be ordered online by companies and researchers.[92] DNA sequencing makes it possible to perform the quality control of genetically modified microorganisms rapidly and inexpensively, which in turn facilitates the design and optimisation of the genomes of production organisms such as bacteria, fungi and yeasts, resulting in the production of better enzymes or proteins. These developments underpin the emergence of 'biofoundries', facilities which construct and test thousands of genetically modified microorganisms per week, supported by robotics.[93] These facilities can be cost-effectively used by researchers, companies and start-ups that do not have access to complex and expensive equipment, which means they can be a significant catalyst for industrial biotechnology.[93] An example of this is the

Edinburgh Genome Foundry established under the Synthetic Biology for Growth programme of the British Research Councils and the Biotechnology and Biological Sciences Research Council (BBSRC).[93,94] The Edinburgh Genome Foundry is currently being used to produce antibodies more effectively for the treatment of cancer and autoimmune diseases.[95]

Big data and artificial intelligence are very important for interpreting the rapidly increasing stream of complex bioinformatics data. Implementing these data in predictive computer models makes it possible to model and design microorganisms (and processes in bioreactors) more precisely and quickly *in silico* (virtually). This is important for businesses because it saves valuable time, money and materials, allowing new products and processes to be brought to market more quickly. It is expected that artificial intelligence will be increasingly important in the design and construction of useful microorganisms and production processes in future.

3.1.2 Sustainable industrial biotechnology based on CO_2 and hydrogen

The industrial production of bioethanol and other chemicals currently uses sugars from agricultural crops such as maize and sugar cane as feedstocks.[96] Although plant-based sugars are renewable raw materials, their production competes with food production and takes up agricultural land. Alternative production methods are therefore being investigated, an important innovation being the development of processes that use CO_2 as a raw material for industrial biotechnology.[97]

A major challenge in the fight against climate change is limiting carbon emissions. The petrochemical industry is a major emitter of CO_2, but the gas can be a useful raw material for industrial biotechnology production processes. Photosynthesis in cyanobacteria and algae captures CO_2 and converts it into sugars, which can then be used to produce different types of bioplastics and ingredients for beauty products, detergents and biofuels.[98,99] Microorganisms like these use sunlight as a source of energy.

In addition to the use of CO_2 and sunlight in manufacturing, hydrogen is being investigated as a basis for production organisms. Hydrogen can be produced by electrolysis, which splits water into hydrogen and oxygen. This process requires electricity, which ideally should be generated sustainably using solar or wind energy (in which case it is called *green* hydrogen).[100] Hydrogen is considered to be an important carrier for renewable energy, and it also enables sustainable and clean industrial biotechnological production. It can be converted by microorganisms – with CO_2 – into useful chemical building blocks and proteins.[101] Figure 4 shows this approach schematically. In the Netherlands this method is used to produce sustainable feed for cultivated fish as an alternative to fishmeal or soy imported from South America.[102] An alternative approach is first to make small organic molecules (such as methanol or formic acid) via chemical catalysis using hydrogen (or electricity), which can then be used for culturing microorganisms.

Several companies (including Dutch companies) are trying to market these developments, although not yet on a large scale.[103,104,105] This illustrates how industrial biotechnology can be used in practice to pursue the goal of a circular economy. It is expected that industrial biotechnology based on CO_2 and sunlight or green hydrogen has the potential to become a major player in a future circular economy and in combating climate change.

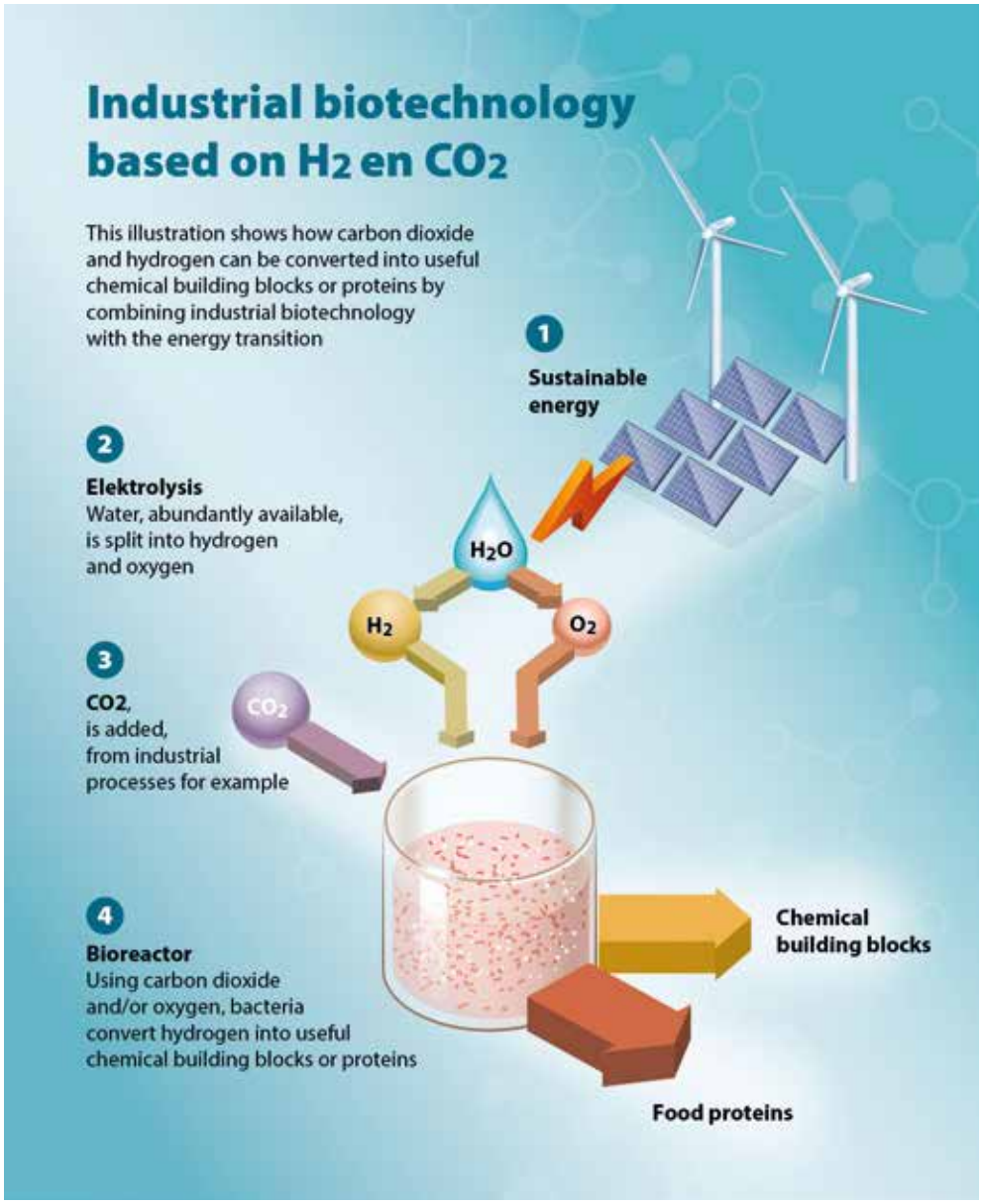


Figure 4: Industrial biotechnology based on H_2 and CO_2

3.1.3 Application of modern industrial biotechnology in the Netherlands

The Netherlands has a significant industrial biotechnology sector with a strong knowledge base and infrastructure.[106] Various universities are carrying out research in this field, such as Delft University of Technology, the University of Groningen, the University of Amsterdam and Wageningen University & Research. In addition, the Netherlands has a strong industrial biotechnological sector that commercialises these innovations in partnership with leading international companies (see box 3.1 for an example). An international report by McKinsey mentions several Dutch companies as pioneers in modern industrial biotechnology.[106] In addition to established companies, there are several start-ups active in the Netherlands that make use of recent developments for the sustainable manufacture of a broad range of products and chemicals, from aromatics and flavourings and bioplastics to spider silk (which can be used in shoes and clothing, for example) and sustainable animal feed.[107,108]

Text box 3.1: From wastewater to polymer
An example of successful cooperation between Dutch universities, companies and other partners is the product Kaumera, a biobased polymer material extracted from the granulated sludge produced by bacterial treatment of wastewater. Kaumera is an adhesive agent with fire-retardant properties. It can serve as a replacement for chemicals produced from fossil fuels used in agriculture and the paper, textile and concrete industries, and as an environmentally friendly flame retardant. The production process was developed by a partnership between Delft University of Technology, Royal Haskoning-DHV and several regional water authorities.[109]

3.2 THE SOCIAL ASPECTS OF INDUSTRIAL BIOTECHNOLOGY

A growing industrial biotechnology sector can provide sustainable, circular alternatives for a broad range of products that are currently produced mainly from petrochemicals. Many products manufactured using industrial biotechnology are already in everyday use, such as the enzymes that make modern detergents effective at low temperatures, giving considerable energy savings. Other examples are vitamins, aromatics and flavourings and bioplastics used in food packaging and furniture, for example.[106,110,111] It is essential that production capacity can be scaled up within the foreseeable future and compete with the petrochemical industry; cost-effectiveness and production at scale are essential for their competitiveness.[106] However, scaling up production can sometimes be frustrated by unpredictable market dynamics (see box 3.2).

Text box 3.2: Industrial biotechnology and market dynamics
For many years there has been interest in the potential of industrial biotechnology to replace traditional fuels with biofuels. Although the technology has been available for some time and is becoming increasingly efficient, large-scale production of biofuels is still not profitable. One example is the biotechnology company Amyris, which around 2006 became known for using synthetic biology to produce artemisinin (an antimalarial drug). This component can normally only be obtained from the sweet wormwood plant, which used to be scarce. The team at Amyris developed a type of yeast into a broad production platform that can be used to produce this component, and other substances too.[112] However, commercialisation did not get off the ground because production proved not to be profitable due to the growing supply of traditionally obtained artemisinin.[113] In the meantime, Amyris planned to use its production platform to produce sustainable fuels.[114] However, this too turned out not to be profitable, because the market for biotechnologically produced fuel depends heavily on the price of oil, which fluctuates under the influence of geopolitical developments. More recently, therefore, Amyris has turned its attention to producing components for cosmetic products, such as squalene (previously obtained from shark livers), which is used in serum and creams.[114] As the cosmetics industry also has to become more sustainable, this is a positive development. The unpredictable market dynamics that Amyris faced is also felt by other biotechnology companies, some of which have also been forced to switch to other products that do yield a profit.[115]

A continuing concern is ensuring a fair distribution of resources and land use. Some of the innovations currently being made in industrial biotechnology make use of raw materials that compete less or not at all with food production on agricultural land, such as wastes and residual streams (e.g. the use of non-edible parts of plants).[116,117] The potential for using CO_2 and (green) hydrogen as raw materials in industrial biotechnology, as mentioned above, is also relevant in this context. However, these innovations are not yet widely available and so industrial biotechnology is still largely dependent on sugars from plant biomass. The efficiency of

converting raw materials into products is therefore not only of direct economic importance, but as industrial biotechnology scales up it will become increasingly significant in terms of land use and sustainability.[118] This lies at the heart of the whole food versus fuel debate, which concerns the competition for the resources needed to manufacture end products, the land needed for the relevant crops and the potential displacement of food crops.[119]

Another issue is appropriate risk management. The microorganisms used in industrial biotechnology could accidentally be released, which may pose a risk to human health and the environment. Dealing with possible risks to human health and the environment has received considerable attention ever since the first experiments with genetic modification in the 1970s. As industrial biotechnology is now growing rapidly and the number of production facilities is increasing, including in the Netherlands, safety rules are increasingly relevant (see box 5.1 Biosafety). At the same time it is important that the rules do not stand in the way of scaling up. Many stakeholders find the authorisation procedures for GM too complex and the legislation too detailed and restrictive.[120] They also say that the risks to human health and the environment from industrial production are minimal.[119] This raises the question of what form of risk management for industrial biotechnology is appropriate and proportional and how should responsibilities best be shared. Consideration should be given to revising the existing legal procedures to release the power of the industrial biotechnology sector while at the same time managing the risks.

3.3 POLICY RELEVANCE

Industrial biotechnology is developing rapidly and the Netherlands is in a strong position to benefit both scientifically and technologically from the opportunities for creating a circular and sustainable economy and strengthening the earning power of the Dutch economy. A clear vision and coordination by government will be needed to steer the development of industrial biotechnology in the desired direction. Consideration should be given to the tensions between the benefits and the risks to society, including the possible environmental risks of industrial biotechnology. Current GMO policy leaves little or no room for political judgements on the balance between costs and benefits, because GMOs are only permitted if the risks are negligible. As a result, some potential gains for society may be missed and innovation frustrated.[121]

The Dutch government could take inspiration from the recent American Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe and Secure American Bioeconomy[122] presented by President Joe Biden in September 2022. It sets out how the US government thinks industrial biotechnology should develop, what efforts are being made to make that happen and how at the same time attention should be given to risk management and ethical aspects. See the following quote:

> *"It is the policy of my Administration to coordinate a whole-of-government approach to advance biotechnology and biomanufacturing towards innovative solutions in health, climate change, energy, food security, agriculture, supply chain resilience, and national and economic security. Central to this policy and its outcomes are principles of equity, ethics, safety, and security that enable access to technologies, processes, and products in a manner that benefits all Americans and the global community and that maintains United States technological leadership and economic competitiveness."*

Based on an integrated vision, thought should be given to what is needed, in the Dutch context, to achieve the stated goals and what type of steering will be necessary. Without steering there is no guarantee that these goals will be achieved.

A lack of clear direction is evident, for example in the implementation programmes for the circular economy, where there is no mention of the contribution that could be made by biotechnology. This applies both to the government-wide programme 'Circular Netherlands in 2050'[123] and to the recent 'Circular Economy Implementation Programme 2021–2023'.[90] This is a missed opportunity.

Furthermore, targeted government investments in research and infrastructure will be very important to ensure the desired development of industrial biotechnology. The growth fund initiative 'Biotech Booster', financed in 2022, aims to stimulate the translation of academic research into new business opportunities, including in industrial biotechnology.[124] Government investments in fundamental scientific research into industrial biotechnology at the beginning of this century (in public-private consortia such as the Kluyver Centre for Genomics of Industrial Fermentation and BE-Basic) underpin the current strong position the Netherlands enjoys in this field. However, in contrast to comparable initiatives elsewhere, such as the Flemish Institute for Biotechnology (VIB), there is no structural support and there is a danger of fragmentation. In various countries biofoundries are considered to be an important catalyst for industrial biotechnology, but the Netherlands does not have a biofoundry. A national biofoundry facility for academic researchers and SMEs is needed to maintain the Netherlands' competitiveness in this field and therefore deserves to be given serious consideration by the government.

4 BIOTECHNOLOGY AND FOOD PRODUCTION

Agriculture stands on the threshold of several major challenges. The global population, and with it the demand for food, is rising. Global warming is leading to more extreme weather conditions,[125] resulting in lower yields and crop failures.[126,127] Reduced availability of water and salinisation of agricultural land will increase significantly. Higher temperatures are leading to lower crop yields and some crops will no longer be profitable where they are currently grown.[128] The Netherlands has signed up to the UN Sustainable Development Goal to ban hunger from the world, focusing its efforts on sustainable production.[129] In its Farm to Fork Strategy the EU sets several goals for more sustainable food production,[130] including reducing dependence on chemical inputs and halving the use of fertilisers. There is worldwide growth in the demand for animal proteins, while current animal protein production and consumption have adverse environmental impacts on ecosystems around the world. Transitioning to plant proteins and proteins produced by microorganisms is seen as one of the solutions to this dilemma. The Dutch National Protein Strategy aims to reduce imports of plant proteins by ensuring a large supply of alternatives and plant proteins and increasing the level of self-sufficiency of the Netherlands and Europe within five to ten years.[131] Modern biotechnology can play an important role in meeting these ambitions. Gene editing can speed up the breeding of crops plants that are tolerant of drought, extreme temperatures and salinisation or are resistant to pests and diseases.[126,132,133] Outside the Netherlands and the EU, gene editing is also being used to increase the productivity of farm animals and to genetically modify plants. There is a global research effort to create microorganisms that can produce 'animal' proteins and on the production of cultured meat. The first products have already appeared on the market.

Certain technical obstacles have to be overcome before it will be possible to capitalise on the opportunities. A related concern is ability of the current legislation to adequately regulate the new developments and ensure public safety while at the same time permitting innovation. The new technologies also raise questions and dilemmas on issues such as the effects on the agro sector, consumer choice and coexistence with the organic farming sector.

4.1. GENETIC MODIFICATION AND GENE EDITING OF CROPS

4.1.1 Genetically modified crops

The first commercial cultivation of GM crops was in the early 1990s. The total area under GM crops now amounts to about 190 million hectares worldwide.[134] Most of these are insect-resistant and herbicide-tolerant maize, soy, oilseed rape and cotton. Resistance and tolerance are obtained by inserting bacterial genes into the crop genome. Other GM crops are grown on a smaller scale, including virus-resistant papayas, herbicide-tolerant sugar beet, soy and oilseed rape with an altered fatty acid composition, drought-tolerant maize, maize that is easier to process for ethanol production, and blue carnations, roses and chrysanthemums.

After an initial rapid increase in the global land area under GM crops, growth flattened off after 2010 as hardly any new cultivation areas (countries) or crops were added. There have, however, been shifts in the characteristics of GM crops. Many GM crops are tolerant to the weedkiller glyphosate (Roundup), but now that glyphosate-resistant weeds are appearing

with increasing frequency, tolerances to other herbicides, such as dicamba and 2,4-D are being introduced.

Genetic modification has not yet led to an increase in yields other than through protection against loss of yield due to insect damage, disease and competition from weeds. In 2022 researchers reported that making changes to photosynthesis increased yields of GM soy by up to 30% in field trials.[135,136] In theory, the same result could be achieved by gene editing because this involves increasing the expression of plant genes. The increase in yield appears to be highly dependent on conditions during the growing season and it remains to be seen whether and to what degree the modification could be commercially interesting.

The cultivation of GM crops has remained limited largely to maize, soy, oilseed rape and cotton, mainly because of the high costs of developing a GM crop and obtaining the necessary permits. These costs are estimated to be about 115 million dollars, of which 43 million dollars for the costs of global authorisation for cultivation and import (research into food safety and the environmental risk assessment).[137] Although it is not clear which costs are included and if the amounts mentioned are correct, there is no doubt that obtaining authorisation for GM crops is a very costly business. These costs can only be recovered if the resulting crops are grown on a large scale throughout the world.

GM crops are cultivated mainly in the US, South America, Canada and India, while in the EU a single crop has been authorised for cultivation, the insect-resistant maize line MON810.[d] Cultivation of this crop is limited mainly to Spain. There is now little or no development of GM crops in the EU. Companies have either withdrawn altogether or moved their operations to countries outside the EU. Dutch industry is not involved in the development of GM crops at all, but more than 80 permits have been issued for importing GM crops and their products in the EU.[138] This means that the EU is mainly a market for GM crops.

4.1.2 Gene-edited crops

Gene editing (site-directed mutagenesis or precision breeding), in which no foreign DNA is inserted but specific changes are made in the genome, can considerably speed up the breeding process. Breeders no longer have to rely on finding spontaneous mutations, lengthy back-crossing (to weed out unfavourable traits in the identified mutant) is unnecessary, and it is possible to go for the mutation that will deliver the most favourable traits. As described in Chapter 2, CRISPR-Cas is the most significant breakthrough for gene editing. Field trials with gene-edited crops are being held around the world to investigate a wide range of traits, from resistances to pests and diseases, drought tolerance, altered composition, increased yields and plant architecture to herbicide tolerance.[139,140,141] In the US, Japan, Canada, Brazil and Argentina various gene-edited crops (and a gene-edited mushroom) have been authorised or exempted from the GMO legislation.

Text box 4.1: High expectations for stress tolerance through gene editing

Increased tolerance of adverse environmental factors such as heat, drought and saline conditions is an important plant breeding objective for which conventional breeding, genetic modification and gene editing are used. However, breeding for stress tolerance is difficult and complex.[142] Not only must changes be made in the plant's metabolism and photosynthesis, but also in its morphology and anatomy.

d The procedure for granting authorisation for placing on the market of GMOs is a centralised EU procedure and the permission applies to all EU member states. A qualified majority of EU member states is required to grant or refuse permission. If the member states fail to reach an opinion by a qualified majority, the European Commission has to take the final decision.. No applications for cultivation have been made for many years.

Numerous genes are involved and how the plant reacts depends on environmental conditions.[143,144,145] Increased stress tolerances often lead to lower yields under more favourable growing conditions. The value of the drought and stress tolerant crops is therefore sometimes hard to assess and depends to a certain extent on specific regional growth and cultivation conditions.

Crops with increased drought tolerance have been produced by both conventional plant breeding and genetic modification.[146,147,148] In all cases, though, the acquired drought tolerances appear to be relatively limited.[142] Gene editing is expected to be a major factor in the acquisition of drought tolerance in plants.[133,149] It works by disabling genes or changing the expression levels of genes to achieve the desired stress response in plants or in the plant architecture, such as deeper rooting.[142] It has been demonstrated that drought tolerance can be increased by changing just a few nucleotides in the plant genome.[150] Although numerous genes have been identified that may play a role in drought and stress tolerances, and field trials with drought-tolerant crops are taking place, no commercial crops have yet appeared.[142,151]

Gene editing is a recent technology and developing products takes time. It will be some years before it becomes clear whether or not gene editing can live up to the high expectations. It must be remembered that gene editing is a tool for speeding up the breeding process and obtaining quicker results. Many years can be saved, but the range of what can ultimately be achieved with conventional breeding will probably not be exceeded. Overly optimistic scenarios for the benefits of gene editing should therefore be viewed with caution.

4.1.3 Social aspects

Genetic modification is a controversial innovation. In many EU member states and elsewhere there is strong political and public opposition to the genetic modification of crops. The EU and the Netherlands are mainly markets for GM agricultural products for animal feed. The emergence of gene editing changes the social and economic impact of biotechnology for the EU, and particularly for the Netherlands with its large breeding industry and leading transit port for agricultural products. The EU legislation, the differences with countries outside the EU (see text box 4.5) and the patent situation surrounding gene editing are important issues.

Gene editing is being widely adopted in countries outside the EU, where gene-edited crops are often no longer considered to be genetically modified.[152,153,154] China in particular has invested heavily in gene editing.[155] At the beginning of 2022 the Chinese regulations for authorising gene-edited crops were relaxed with the aim of improving food security and reducing the country's dependence on imported vegetable seeds.[156,157] CRISPR-Cas was developed in the US and Europe, but after the US, China now produces the highest number of publications on CRISPR-Cas and its applications in general.[158] Chinese researchers publish twice as many scientific articles on agricultural applications than American researchers,[159] and this is reflected in the numbers of global patent applications. In 2020 there were already about 2,000 patent applications for gene editing of plants,[160] and this is probably an underestimate. Patent applications come mainly from countries outside the EU, such as the US and China; Dutch institutions make a very modest contribution. Wageningen UR has a patent on the CAS12 protein with the Broad Institute. Recently Wageningen UR made licences for five of its other patents freely available to NGOs that want to improve global food security. [161]

The American multinational Corteva has established a patent pool for CRISPR applications in the agro sector with the Broad Institute.[162] Licences are freely available to

universities, non-profit organisations and for non-commercial applications. Companies looking for commercial applications can obtain a 'one-stop licence'. The desirability and legal tenability of the possible monopoly position this could create are questionable.[160] The French company Vilmorin has become the first European company to obtain a licence.[163]

The uncertain legal status surrounding patents and high licensing costs may result in this technology only being used by large multinational plant breeding companies to introduce new crops. It is questionable whether Dutch breeding companies can afford these costs.

Text box 4.2: CRISPR-Cas and patents

Doudna and Charpentier received the Nobel Prize in 2020 for the discovery of CRISPR-Cas9 as a gene-editing system, but this does not mean that they hold the intellectual property rights. Since 2006 there has been a patent war between two research consortia, the University of California at Berkeley and the Broad Institute at MIT. In 2022 the American Patent Office (USPTO) ruled largely in favour of the Broad Institute and awarded them several patents.[164] In the EU the Berkeley group seems to have the upper hand as the patent applications by the Broad Institute were rejected because of procedural errors. This difference between the situations in the US and Europe may become problematic when licences need to be obtained. The legal battle is expected to continue for some years. The high licensing costs and legal uncertainties may prevent Dutch companies and institutions from developing commercial applications.

Whether gene editing of plants for commercial purposes will take place in the Netherlands partly depends on the outcome of the proposed revision of EU GMO legislation. The revision will have considerable economic ramifications for the Netherlands. The Netherlands has a large seed and plant breeding industry, mainly for vegetable crops, ornamental plants and potatoes. The sector is responsible for about 46% of the global export value of source material for vegetables, ornamentals, potatoes and grasses.[165] These are sectors where genetic modification has so far not been used, mainly because they are mostly smaller crops and the costs of safety studies and authorisation procedures cannot be recovered. Now that gene editing is being exempted from the GMO legislation outside the EU, Dutch companies could be put at a disadvantage. If the EU legislation is not revised, companies may move some of their R&D activities outside the EU, with negative consequences for innovation and the Dutch economy.[166] One potato breeder has already moved part of their breeding research activities to Canada.[167]

There may also be import problems if the EU decides that gene-edited crops should be labelled as GMOs. The Netherlands imports about 70 million euros worth of agricultural goods each year.[168] Detection of gene-edited crops or products is technically possible in some cases, as long as the mutations concerned are known. But if, as expected, the number of crops and products rapidly increases, import controls will become impossible to carry out. Moreover, where cross-contamination has occurred, distinguishing between random natural mutations and 'contamination' with a gene-edited product will present legal difficulties. It is likely that unintended or undetected imports will occur, and consumers will be faced with products on the shelves that are wrongly labelled as GMO free.

4.2 ANIMAL PRODUCTION: BIOTECHNOLOGY AND FARM ANIMALS

The Netherlands has a 'no, unless' policy on the genetic modification of animals. Permits are issued subject to an ethical review. Genetic modification of animals for sporting performance or entertainment is prohibited.[169] Permits are issued only for medical research (see also text box 4.3). Incidentally, these rules do not apply to imported GM animals because they fall under EU environmental and other legislation geared to safeguarding human and environmental safety, and these offer little room for ethical and social considerations.[170]

In most other parts of the world the rules are not as strict, but there is opposition to the genetic modification of animals elsewhere as well and few GM animals and products have appeared on the market. However, the gene editing of animals seems to be quickly gaining ground in the US, China and Japan and the first gene-edited animals have already appeared on the market in these countries.

4.2.1 Genetic modification of farm animals

The genetic modification of farm animals has made few inroads into farming anywhere in the world. The bull Herman was the first GM farm animal in 1990. Herman was modified with the aim of producing (human) lactoferrin in cow's milk. It was only in 2019 that the first GM animal for human consumption was authorised in the US: a GM Atlantic salmon that grows faster due to the insertion of the growth hormone gene from the chinook salmon. This GM salmon was developed in 1989 and it took twenty years before the company had all the licences and permits it needed to sell the fish in the US.[171] The second animal was a genetically modified pig. These GalSafe pigs have been authorised in the US for food and medical purposes.[172] No GM animals have been approved for food purposes in the EU.

There have been small herds of GM sheep, goats and other animals in South America, Australia and China for some years. The introduced traits include better wool and 'self-shearing' sheep, but these GM animals have never been authorised for commercial use. Research is underway into disease resistance in farm animals, such as resistance to viruses that cause diseases in chickens and pigs, but no actual applications have emerged yet. [173,174]

Text box 4.3: Genetic modification as answer to unwanted male chicks?
An experimental application of genetic modification in the poultry sector which is interesting from both a scientific and an ethical point of view is to produce only female birds, which could be used to eliminate surplus male chicks in poultry farming.[175] In birds, the gender of the offspring is determined by the hen. The relevant chromosomes for gender are the Z and W chromosomes. Hens are ZW and cockerels are ZZ. A lethal gene, under the control of a promoter induced by blue light, can be inserted into the Z chromosome of the hen (the breeding hen). After fertilisation by non-genetically modified cockerels, the male offspring will have the Z chromosome containing the lethal gene, resulting in the premature cessation of the development of male embryos, while the laying hens will have the non-modified Z chromosome from the cockerel. The English animal rights organisation Compassion in World Farming (CIWF) is positive about this application. In response to a question from the German government, the EC has announced that laying hens and their eggs do not fall under the GMO legislation, because they do not possess the inserted construct.[176]

4.2.2 Gene editing in animals

The authorisation procedures for GM animals are lengthy and difficult to navigate due to lack of political and public acceptance, and hardly any GM animals have been authorised for production and consumption However, the situation is different for gene-edited animals. In Japan two fishes were authorised within a short time, a red sea bream and a pufferfish which produce more meat because a gene that regulates muscle growth has been inactivated using CRISPR-Cas.[177] The Japanese government has stated that gene editing is not essentially any different from traditional breeding.[178] In Brazil, a gene-edited tilapia and cow have been exempted from the GMO legislation[179] and in the US meat from gene-edited cattle has been authorised.[180] These cattle have a smoother and short coat which makes them more heat-tolerant. The FDA has ruled that they do not fall under the legislation because the genetic make-up of the animals has not been altered and the relevant traits already exist in other breeds of cattle. It will be some years before the meat is available for sale, because the animals must first be bred in numbers.

Research is being conducted around the world into numerous traits that could be altered by gene editing, such as resistance to diseases, higher productivity and wool colour. China in particular is wholeheartedly pursuing the gene-editing (and genetic modification[e]) of animals.[181] In the US a gene-edited calf was born that is less susceptible to the viral infection bovine viral diarrhoea (BVD).[182] In Europe research into gene editing in animals is limited. In the EU Rumigen research project, CRISPR-Cas has been used to introduce a gene variant from a Norwegian goat breed into an Alpine goat breed.[183]

A development that has received much attention in the media is the use of sterile surrogate sires in pig, cattle and goat breeding.[184,185] These animals do not produce their own sperm because an essential gene has been inactivated using CRISPR-Cas gene editing.[186] Instead, they make sperm produced by stem cells transplanted from a donor animal. As this means a large number of animals can produce sperm from the best breeding animals, it is possible to breed by means of natural fertilisation instead of artificial insemination. Insemination is not possible for all farm animals, such as goats, or, in some parts of the world, free range cattle. Moreover, the offspring do not have any modified genes.[187] This still experimental technology is expected to have a major impact on the livestock industry.[188]

Text box 4.4: Genetic modification in non-farm animals is successful

Genetic modification in animals has made major inroads in biomedical research. Genetically modified mice are now an indispensable disease model. In the EU, at least two medicines isolated from milk from GM animals have been authorised: Ruconest (a treatment for angioedema, produced by GM rabbits, production facilities in the Netherlands and elsewhere) and Atryn (a treatment for thrombosis, produced by GM goats, produced in the US). Large-scale field trials with sterile GM mosquitoes to control mosquito populations and prevent the spread of diseases are being carried out in various places, including the Caiman Islands, Brazil and recently the US (Florida Keys).[189] Research on synthetic gene drives to control pest insects, however, has not yet been successful. Gene drives spread rapidly through a population because 'normal' transmission of heritable traits is disrupted and the construct is passed on to more than half of the offspring.[190] Gene drives are controversial because of the potential risks to ecosystems. The rapid development of resistance to gene drives in insect populations has so far held up application of the technology. [191,192]

Outside the EU large numbers of GM animals are sold for ornamental purposes, the GloFish,[193] aquarium fish that possess fluorescent GFP proteins. In Brazil, GM zebra fish have escaped from the production facilities and appear to be surviving in shallow creeks.[194]

e This sometimes leads to international consternation, for example concerning experiments in which human genes involved in human intelligence were inserted into monkeys. https://www.technologyreview.com/2019/04/10/136131/chinese-scientists-have-put-human-brain-genes-in-monkeysand-yes-they-may-be-smarter

The Netherlands takes a cautious approach

The Dutch animal breeding industry appears for the moment to be reluctant to adopt gene editing.[195] Scientific research in the Netherlands also avoids gene editing in animals, except as a research instrument to investigate gene function and develop animal models for human diseases (see text box 4.3). Research into genome variation in relation to heritable traits (phenotypic character) is necessary to speed up conventional breeding and to predict the effects of genetic variation. It is also useful for identifying adverse gene variants that should be avoided as far as possible in breeding programmes. The data obtained are essential sources of information for future applications of gene editing.[196] This Dutch research effort is generating the knowledge that is needed for the practical application of gene editing, but the actual use of this knowledge is taking place outside the Netherlands.

This restraint by Dutch industry and research institutions is not only based on expected public objections to gene editing in animals, but also on doubts about whether the high expectations can be met. There are several technical hurdles that still have to be overcome. Gene editing can be used to make changes in genes that should lead to changes in traits in the animals concerned, but the number of traits that are known to be determined by a single gene (monogenic) is still very limited. In animals, most traits are complex and determined by multiple genes. Changes made to just one of these genes will at most lead to a gradual improvement in the trait concerned, and that can also be achieved through conventional breeding.

Another aspect is that the modified trait then has to be bred into the population, which means that a large number of animals will have to be modified to avoid inbreeding (which leads to adverse characters). This reduces efficiency and increases costs, which throws any competitive advantage over conventional breeding into doubt.[197]

However, if a monogenic trait is found in future which has great advantages for productivity or animal welfare, gene editing will be a game changer and deliver considerable competitive advantages.

Text box 4.5: Gene editing and nature conservation

It has been proposed that gene editing can be used to save endangered species or breeds. Inbreeding in critically small populations of animal species will lead to unfavourable genes becoming dominant, preventing the survival of the species. The genetic health of such animal species could be restored by repairing adverse gene variants using CRISPR-Cas. Disease resistance could also be introduced to endangered species as a form of protection.[198]

4.2.3 Social aspects

Animal biotechnology is controversial in the Netherlands and there is little or no support for the genetic modification of animals for food production.[199] Genetic modification in animals for production, entertainment and sport is prohibited in the Netherlands, even if there are potential benefits for the modified animals themselves. For ethical reasons the former Committee on Animal Biotechnology (CBD) took a positive view of an application for the genetic modification of chickens (insertion of the GFP gene on the Z chromosome) to avoid the killing of day old chicks. The House of Representatives was opposed (see also text box 4.3).[200] It is doubtful that gene editing in animals will gain broader public support, and any support will depend on the application in question. One of the prime considerations is that gene editing must not lead to or increase suffering among animals.[201]

The first gene-edited animals or their products are already on sale in countries outside the EU. Given the speed at which gene editing has been accepted in these countries as a 'normal' form of animal breeding, the likelihood of unintentional imports is increasing, not only as products for further processing but also in the form of breeding material, such as semen.

Several Dutch organisations, including COGEM and the Council on Animal Affairs (RDA), have informed the government about the scientific and ethical aspects of gene editing in animals.[202,203] The SAGE project was initiated to gain an understanding of the conditions under which gene editing could be used in the breeding of farm animals.[204] A public debate on this, such as that conducted in England by the Nuffield Council on Bioethics,[205] has not been held in the Netherlands and has been recommended by the RDA.[199]

Text box 4.6: Process-based or product-based regulation?

The EC has come to the conclusion that the development of gene editing and other technologies has outstripped the current legislation on GMO crops, which must be revised. Some stakeholders argue for a radical alteration of the principle underlying the legislation.

The regulation of GMOs varies considerably across the world. The EU has what is known as a process-based regulatory system in which the production method (the process) determines whether or not an organism falls under the GMO legislation. If certain techniques are used (i.e. if the genome has been altered in a non-natural manner), the organism falls under the GMO legislation and requires authorisation. An exception is made for organisms that have been created by mutagenesis caused by radiation or chemical agents. Although they are GMOs (because the DNA has been altered in a non-natural way), they do not require a permit and do not have to be labelled as genetically modified. This is because mutagenesis has been widely used in plant breeding since the 1930s and the resulting crops have a history of safe use.

Some countries, including Canada, have a product-based regulatory system in which the decision revolves around whether or not the product has new traits (not previously present in a crop), irrespective of the way it has been made. There is therefore no specific GMO legislation. Crops obtained by conventional breeding can in principle also fall under the regulatory framework.

In the past the global differences in regulation have not been insurmountable for trade because almost all GM crops in the world were regulated. But this has changed since the emergence of gene editing.[206] Outside the EU, Argentina, Brazil, Canada, Chile, the US and Japan have decided to exempt gene-edited crops from regulation, to a greater or lesser extent, as long as they do not contain any 'foreign' DNA.[152,153,154] However, the European Court of Justice has ruled that in the EU products resulting from gene editing are subject to all the requirements of the GMO legislation.

Several stakeholders have urged the EU to switch to a product-based regulatory system in the hope that this would break the current impasse in the authorisation of GM crops in the EU and bring the EU in line with other major trading blocs. Certain aspects of the EU legislation are also illogical. For example, herbicide-tolerant crops produced by genetic modification fall under the GMO legislation, but herbicide-tolerant crops obtained by conventional breeding methods do not.[207,208,209,210]

In its policy report 'No Rose Without Thorns' COGEM pointed out that while both types of legislation have their advantages and disadvantages, in practice the differ-

ences are smaller than was thought and that the stalled decision-making on the authorisation of crops in the EU is caused by internal divisions between the member states.[211]

4.3 CELLULAR AGRICULTURE: BIOTECHNOLOGY AND THE PROTEIN TRANSITION

Biotechnology can make a major contribution to the protein transition. Industrial biotechnology is already responsible for producing food ingredients that used to be obtainable only from animal sources, such as vitamin B12 as an additive in non-animal meat substitutes. Some innovations are designed to make the taste and texture of meat alternatives more appealing, such as the *Impossible Burger*, a plant-based burger that contains a soy-derived haemoglobin produced using GM yeasts. This iron-containing protein imparts a meaty flavour. The hamburger is not yet for sale in the EU, but is a success in the US and Canada.[212]

Much research is being done on a broad range of new biotechnological 'animal' products that are made without animals, or with minimal use of animals.[213] Research institutes in the Netherlands have formed a consortium called the CAN Foundation (Cellulaire Agricultuur Nederland Stichting) to promote and create a fully-fledged ecosystem for cellular agriculture.[214] The economic potential is great. The worldwide market for substitutes for products of animal origin was 20.7 billion dollars in 2020 and will grow to 23.2 billion dollars in 2024.[215] Investors think that biotechnology companies can capture a share of this growth market.[216] In addition to the economic potential of these innovations, they can help tackle various challenges facing society, such as climate change, the nitrogen problem and animal welfare.[217]

4.3.1 Microbial protein production as an alternative to animal production

There is an intensive worldwide research effort on the microbial production of food proteins as a sustainable and animal-friendly alternative to animal production. These proteins and other substances are produced in bioreactors by microorganisms, either genetically modified or not, using sugars as raw materials. Investments in companies that produce proteins from microorganisms are growing rapidly, as is the demand for and sale of the products.[218]

A number of the products have been on the market for some time, such as Quorn®, which is based on a cultured fungus as a meat substitute. Recently a large number of new companies and products have sprung up around the world, most of them involved in the production of substitutes for meat, milk and eggs. A company in Breda produces a protein it developed called Fermotein®, which is an alternative to both animal and plant proteins.[219] A pilot plant is currently being built which will be able to produce the amount of protein equivalent to the meat from ten cows every hour. The company expects to launch a number of full-scale plants at locations around the world from 2023.

Many companies and start-ups are using GM microorganisms to produce animal proteins, milk proteins being particularly popular. The global market for vegan cheese is growing rapidly.[220,221] A Dutch company employs GM yeasts to produce the milk protein casein using peas as a raw material.[222] The casein can be used as a raw material for vegan yoghurt or cheese. Another Dutch company is also working on the production of cheese from fungi and yeasts[223] and presented their first experimental product at the end of 2022.[224] Finnish scientists have been successful in producing the protein ovalbumin (which is found naturally in eggs) from a GM fungus and a pilot plant is under

construction.[225] Compared with the poultry industry, this microbial production would reduce land take by 90% and greenhouse gas emissions by 55%.[226]

4.3.2 Meat from a bioreactor

In 2013 the Dutch scientist Mark Post presented the first cultured hamburger. Since then interest in cultured meat has grown, both in the Netherlands and internationally, as a way of meeting the growing global demand for meat while minimising the impact of the intensive livestock industry on land use, climate change and animal welfare.

To culture meat, a biopsy is taken from a live animal, from which stem cells are isolated for development into muscle tissue. The cells start to divide when they are cultivated in a suitable medium consisting of nutrients and growth hormones (see Figure 5). This usually consists of foetal calf serum,[227,228] which presents a problem for scaling up production and meets with objections from consumers who are vegetarian or vegan.[229] A Dutch company is one of the first to have succeeded in eliminating the use of calf serum.[230]

Figure 5: Production of cultured meat

International interest in cultured meat is strongest in the United States, Israel and Singapore. In Singapore consumers can take part in small tasting events and in the US cultured chicken meat was recently approved for human consumption.[231,232] In 2022 a motion was passed in the Dutch House of Representatives to facilitate tastings of cultured meat in the Netherlands.[233]

Besides cultured beef and chicken, there are start-ups in various parts of the world that produce cultured bluefin tuna, shrimp, zebra, yak and kangaroo meat.[234]

Several technological hurdles must first be overcome before cultured meat can become a significant source of protein.[235,236] So far, cultured meat lacks any real structure and can only be used as mince or filling for chicken nuggets. An Israeli start-up has produced a ribeye steak using 3D printing, but this is currently unaffordable.[237,238] Cultured mince is also still significantly more expensive that beefsteak of animal origin. It is still unclear if and when cultured meat will be able to compete with the conventional meat industry.[239,240] There is also competition from plant-based meat substitutes. The National Growth Fund is investing 60 to 85 million euros in cultured meat and dairy products to speed up their development.[241,242]

From a sustainability or health perspective, there are still uncertainties about whether cultured meat can become a real alternative to traditionally produced meat.[243] A life cycle analysis (LCA) of cultured meat shows that it offers sustainability benefits over conventional beef (in reduced CO_2 emissions) and is comparable to the production of pork and chicken.[244] In the future, cultured meat could be more sustainable than conventional meats if renewable energy is used in its production.

If it becomes possible to produce cultured meat on a large scale and at competitive prices, there still remains the question of whether sufficient production capacity can be created to claim a part of the market for meat.[245,246] Even if the efficiency of producing cultured meat is greatly increased, numerous new facilities will have to be built. On the other hand, land take will be much reduced compared to current livestock production.

Text box 4.7: Ethical questions surrounding innovations in animal production

In addition to question of naturalness, ethicists have drawn attention to various arguments both for and against the large-scale implementation of the innovations discussed here. Gene editing in farm animals may deliver benefits for the economy (animal breeding, innovation) and for the animals themselves (disease resistance) – but it violates the integrity of the animal, can have adverse effects on animal welfare and health, and marks a further step towards the instrumentalisation of animals. Some philosophers argue that replacing products of animal origin with cultured meat may mentally divorce us from nature and farm animals, or even animals in general. Others point out that farm animals probably lead lives that are 'not worth living' and some argue that, from the perspective of animal welfare, the development of cultured meat is a moral imperative. It is also argued that it does not mean the end of farm animals at all, but that they could fulfil a different role in society, such as petting zoos for example, which could actually bring people into closer contact with animals and nature.[247]

4.3.3 Social aspects

Cellular agriculture can make a significant contribution to reducing land take and emissions of CO_2 and nitrogen, but several technological hurdles must be overcome and this

will require considerable investments. It also represents a radical change to a different way of producing food.

Unlike the use of genetic modification in agriculture, genetic modification in industrial biotechnology has generated hardly any public debate at all. The innovations in cellular agriculture discussed here concern industrial biotechnology applications, but they nevertheless lead to products we eat. Food is closer to people and so it can be a source of controversy.

Some consumers are critical of the biotechnological production of proteins and cultured meat as unnatural. The *Impossible Burger* has met with resistance from some groups because of its perceived unnatural character and concerns about food safety.[248,249] Focus group research has shown that food manufacturers also take a critical view of the artificial nature of cultured meat.[250] It is ironic that rennet from the stomach of calves is used in cheesemaking in the Netherlands, while the relevant enzyme, chymosin, produced by GM microorganisms in an animal-friendly process, is exported to foreign cheesemakers because of concerns that consumers in the Dutch export markets, such as Germany, would otherwise avoid the cheese.[251] Moreover, GM chymosin may not be used in the production of Gouda or Edam cheese.[252,253]

Dependence on big business is a concern in the still nascent public debate. As with GM food crops, the fear is that the production of cultured meat and microbial proteins will be concentrated in the hands of just a few big multinationals.[250] This concern is also fed by the enthusiasm with which investors embrace cellular agriculture as a 'disruptive technology'.[234]

The production of cultured meat and alternative products of animal origin could have a major impact on traditional animal husbandry and agriculture, affecting not only the livelihoods of livestock farmers, but also the cultural role farmers have in Dutch society. There may be reasons why the government and society in general want to invest in the opportunities that biotechnology can offer to the country, but the division of benefits and burdens remains an area of concern. With this in mind, the possibility of the current producers of meat being involved in the production of cultured meat is being looked into.[254,255]

In addition to the technological hurdles, the complicated EU regulations and assessment frameworks may also be a hindrance to the introduction of cellular agriculture products. Cultured meat and other 'animal' food products that can be manufactured using industrial biotechnology are 'novel foods', which have to be assessed for food safety and authorised at the EU level. Authorisation under the Novel Foods Directive is perceived as complicated and there still seem to be no food safety assessment frameworks for cellular products. Companies may well lack the resources and capacity to initiate these assessments. Several companies have already indicated that they want to market their products outside the EU first because it is easier to obtain the necessary authorisation than in the EU.

4.4 POLICY RELEVANCE

Technological developments and differences in GMO legislation around the world necessitate the making of political and policy choices. The difficulties of incorporating 'new biotechnological techniques' into the GMO legislation are not new and were mentioned as a priority trend in the previous Trend Analysis. Since then the European Commission has also come to the conclusion that the current GMO legislation is no longer adequate and has launched a policy action to revise the legislation.[256,257] A proposal is not expected before the second quarter of 2023 at the earliest, which means that the Netherlands must now formulate and communicate its position.

- The European Commission appears to be moving towards a revision of the GMO legislation, putting the sustainability of applications at its heart. What this will look like remains to be seen, but it could result in an additional authorisation requirement (on top of safety) and higher costs in connection with sustainability requirements.
- In the interests of the economy, innovation and the sustainability of agriculture, the revision of the legislation should also take account of the objections of part of the European population to what they perceive is genetic modification. Several motions on this have already been adopted in the Dutch House of Representatives.[258,259,260,261]
- The organic farming sector sees gene editing as a threat.[262] A notification requirement or register of gene-edited crops and products could help to ensure consumer choice and coexistence, although it is not clear to what extent domestic and foreign producers will be willing to register their products. To guarantee consumer choice the current GM labelling requirement could be extended to include a non-GM label for products that the producer is certain have not undergone any genetic modification or gene editing. However, this would involve higher costs for producers and production chains.
- The EU policy action to revise the GMO legislation is limited to the new techniques in plant biotechnology; animal biotechnology is not included. However, developments surrounding gene-edited animals are progressing rapidly outside the EU, which could lead to import and trade problems. Given that gene-edited animals seem to be increasingly exempted from regulation and registration outside the EU, similar problems of unintentional imports could arise as with gene-edited plants. A proactive approach and discussion on how to respond to gene editing in animals is advisable in the Netherlands and across the EU.

The situation concerning who holds the patent for CRISPR-Cas and the advantages gene editing can bring by speeding up crop breeding has put patents in plant breeding[263] back on the agenda. The costs of CRISPR licences could become an obstacle that the Dutch plant breeding industry finds hard to surmount, particularly for smaller crops that are grown on a large scale worldwide. It is also a hurdle for the transition to sustainability, because it will not be profitable to use CRISPR-Cas to introduce disease and pest resistances into these crops.

Cellular agriculture, and cultured meat in particular, are expected to make a significant contribution to the protein transition. These biotechnological applications raise a number of questions about regulation and the effects on other economic sectors and on society.

- Several companies have indicated that they will market their products outside the EU first, because obtaining the necessary permissions and authorisation is easier outside the EU. While ensuring food safety through the application of the Novel Foods Directive[264] is of great value, it raises the question of whether the EU authorisation procedures can cope adequately with the new technologies or are too complicated and lengthy.[265] However, there are fierce opponents of cultured meat in the EU, including the new Italian government, which may make the simplification of EU authorisation procedures more difficult.[266,267]
- Cellular agriculture is a potentially disruptive technology. It can lead to changes in the agro sector, such as consolidation, job losses and marginalisation of livestock farming. This calls for an integrated vision from government on how such innovations can find a place in the Dutch food system.

5 BIOTECHNOLOGY AND HEALTHCARE

Nowhere does the impact of modern biotechnology affect us so directly and profoundly as in the area of our health. Scientific research, diagnostics, prevention and medical practice are changing radically under the influence of biotechnology. The power of large-scale sequencing was demonstrated during the COVID-19 pandemic, when this new technology was instrumental in the rapid development of diagnostic tools and vaccines. The development of new drugs for cancer and autoimmune diseases is focused on monoclonal antibodies,[268] while genome editing and gene therapy open up new opportunities in reproductive medicine and the treatment of heritable diseases and cancer. Gene editing has also brought the clinical application of xenotransplantation a step closer.

There are major opportunities, but also risk and safety issues, and particularly difficult legal and ethical issues. Government direction and regulation are necessary to exploit the opportunities and fend off any unwanted developments.

This chapter addresses developments in surveillance and diagnostics, germline modification, vaccines, cell and gene therapy, xenotransplantation and antimicrobial resistance.

5.1 SURVEILLANCE AND DIAGNOSTICS

5.1.1 Faster detection of pathogens and cancer

The ongoing technological advances in reading and modifying genetic material were discussed extensively in Chapter 2. The base sequence of DNA can not only be determined faster, but at lower cost and with less material. In some cases the genetic material from just a single cell is sufficient. It is also now possible to make more accurate determinations of difficult sequences, such as highly repetitive sequences.[9] In addition to the large and expensive machines, portable sequencing equipment is now also available. Major steps have also be made in the analysis of the epigenome, transcriptome, proteome and metabolome.

Significant progress has also been made with the application of CRISPR-Cas. It is no longer limited to modifying genetic material, but is now also used as a detection method, for example for mutations that could cause cancer or (variants of) pathogenic bacteria and viruses (see also box 2.1). The advantage of CRISPR-Cas systems is that they are highly specific and do not require expensive laboratory equipment.

5.1.2 Social aspects

The importance and power of large-scale sequencing became apparent during the COVID-19 pandemic. The sequence of SARS-CoV-2 became available almost immediately, allowing the rapid development of diagnostics and vaccines based on previously obtained knowledge of corona viruses. In some countries the sequencing of virus isolates from patients and sewage allowed the emergence and spread of new variants to be followed in real time. Moreover, the availability of much cheaper and smaller sequencing equipment has made it is easier in developing countries to quickly identify pathogens such as Zika virus and the Ebola virus in the field and track their spread.[269,270]

The genetic testing and selection of embryos for implantation can greatly benefit from the ability to carry out DNA research with little material. In the Netherlands, more than 1,000 children have been born from genetically tested embryos.[271] Indications for these tests are serious monogenic genetic disorders and chromosome translocations in parents. In the United Kingdom, plans to sequence the complete genome of all newborn babies to detect children with a heightened risk of certain conditions appear to have the support of the majority of Britons.[272] In the US, genetic pre-implantation testing of embryos is also done to choose the gender of the baby for non-medical reasons.[273] There are also commercial providers that use genetic pre-implantation tests to make predictions or calculate the likelihood of certain diseases, such as cancer and heart conditions. This goes far beyond the standard pre-implantation tests performed in the Netherlands. The scientific basis, reliability and usefulness of such analyses and advice can be questioned,[274] as can claims made by providers of services via the internet that they can analyse DNA to identify genetic diseases and provide health advice. There are other ethical issues as well, such as safeguarding privacy. The new EU legislation on in vitro diagnostic medical devices places certain conditions on DNA tests offered directly to customers.[275] Implementation of this EU legislation and of relevant national legislation, such as the Dutch Population Screening Act, faces delays for several reasons, including the availability of government designated notified bodies (for inspection) and experts for regulatory oversight.

There is a danger that authoritarian governments will misuse genetic information to identify ethnic groups within their populations in order to track them and discriminate against them.[276,277] In this connection some scientific publications were recently withdrawn because the genetic information on Uyghurs and Tibetans they contained was not obtained according to the required informed consent procedures or reviewed by an authorised medical ethics committee.

The pharmacogenetic profile or passport could offer health benefits. An individual's genes greatly influence the absorption, transport, breakdown and excretion of drugs by the body. Genes also partially determine the sensitivity of drug targets – the receptors on or in cells – and thus the efficacy of medicines. The variants of the relevant genes have already been identified for more than 90 drugs and so doctors and pharmacists could use pharmacogenetic profiles to select the best medication and dosage for patients and so reduce the risk of side-effects or treatment failure. Currently, several university medical centres are working on the implementation of pharmacogenetics. Some, including the Erasmus MC and the Leiden UMC offer patients a broad genetic analysis of pharmacogenes. Better integration of pharmacogenetics into healthcare could prevent a significant disease burden and mortality in a cost-effective manner. [278,279,280] However, because responsibility for the various matters required for the national introduction of the genetic passport is not clearly defined, the opportunities for obtaining these health benefits are not being taken up and implementation seems to be many years down the road.[281,282]

The 1+ Million Genomes Initiative is currently underway in the EU and aims to enable secure access to genomics and the corresponding clinical data in all member states for better research, personalised healthcare and health policymaking across the whole European Union.[283] The relevant organisation in the Netherlands is the Health Research Infrastructure (Health-RI) initiative.[284] In 2022 the European Union published the European Health Data Space (EHDS),[285] a proposal for a regulation for the quick and easy exchange of medical data. Such a regulation would regulate access to medical data for citizens, its use for other purposes, such as research and policymaking, and the development of digital healthcare products such as electronic medical record systems. In the same year the American president, Joe Biden, issued an order to set up a similar but broader Data Initiative for secure and broad access to biological datasets for academic and industrial research in the US.[286]

5.2 GERMLINE MODIFICATION

5.2.1 Prevention of genetic diseases

Medical applications of CRISPR-Cas technology can lead to changes made in the gametes or in pre-implantation embryos being passed on to offspring. This form of the technology is called germline modification, or human genome editing. The previous Trend Analysis indicated that repairing and preventing genetic disorders in future generations, particularly those involving just a single gene, would appear to be within reach.[96]

As was discussed in Chapter 2, when repairing defective genes with CRISPR-Cas9 unintended insertions or deletions of bases may occur at the repair site. Unintended changes may also be made elsewhere in the genome and sometimes (parts of) chromosomes are lost. This can have serious health consequences. Moreover, using the technique on multicellular embryos may lead to mosaicism, which results in the correction of the DNA in just some rather than all of the cells in the embryo. That may not be a problem when the disorder is an enzyme deficiency, but it is for a cancer predisposition. The technology is therefore not yet fully effective and safe.

Meanwhile, new forms of the CRISPR technology are under development.[9,287] Two promising approaches are base editing (see Figure 2) and prime editing. The first method is the most developed and clinical trials are currently being held on somatic cells for the treatment of sickle cell anaemia and leukaemia. However, only specific errors in the DNA can be repaired. The other approach is still in the research stage with laboratory animals, but a lack of suitable embryos for scientific studies is holding up research into the effectiveness and safety of the method. It is therefore not expected that CRISPR-Cas-like techniques to correct DNA in the germline will be available in clinical practice within the next five years. Genetics experts are not particularly concerned about possible applications for human enhancement as most traits, such as high intelligence, depend on the cooperative action of many genes. Scientific understanding of how this interplay between many different genes works and how to modify all those genes at the same time is far beyond the reach of current technical possibilities.[288]

5.2.2 Social aspects

In 2018 it was made known that the Chinese researcher He Jiankui used germline gene editing on Chinese twins to make them resistant to HIV. The next year a third baby was born who had undergone the same treatment.[289] Since then various organisations and scientists have published position papers on CRISPR-Cas germline gene editing.[290,291,292] They feel that germline gene editing should be permitted under certain conditions for fundamental and preclinical research, but consider the technology to be as yet insufficiently developed for application in clinical practice. An inventory of policies in several countries has shown that 75 countries expressly prohibit the use of genetically modified in vitro embryos to initiate pregnancy.[293] Modification of the genome in human germline cells to initiate a pregnancy is prohibited in the EU.

Before CRISPR-Cas can be used for human genome editing, further research is needed to determine when the risks will be small enough. Research on animal models is inadequate for this purpose, which is why scientists are calling for research on human embryos to be permitted under certain conditions. As the availability and suitability of human embryos are limited, it is necessary to create embryos specifically for research purposes. This is permitted in several countries, including the United Kingdom, Belgium and Sweden, but in the Netherlands it is prohibited under the Embryo Act. In 2017 the Health Council of the Netherlands advised the Minister of Health, Welfare and Sport to rescind the prohibition on carrying out scientific research on specially created embryos.[294] The

same recommendation was made by an expert committee that evaluated the Embryo Act in 2021.[295]

The problems with the effectiveness and safety of CRISPR-Cas for germline modification are not expected to be resolved within the next five years. If the techniques become sufficiently effective and safe in the future, they may only be of added value in a limited number of cases, in particular where the condition is 100% certain to be inherited, in other words when both parents are affected by the same recessive monogenic disease (such as cystic fibrosis) or when one parent is homozygous for an autosomal dominant inherited condition (such as Huntington's disease). However, the greatest practical value of germline modification may well be in its use in combination with preimplantation genetic testing where the risks of passing on the condition are 25–50%, so that affected embryos can be used for implantation following repair.[288]

There is much debate both nationally and internationally about the desirability of germline modification. The results of public consultations in the Netherlands published in 2021 show that the majority of the participants think that altering the DNA of future individuals is only acceptable when it is done to prevent sufficiently serious genetic disorders.[296,297] Drawing a distinction between preventing conditions and making improvements is proving difficult, as is what should be considered to be sufficiently serious. A small group feels that altering the DNA of an embryo is unacceptable under any conditions. Among the population there are different views about the use of embryos for research purposes. In March 2022, as part of the Dutch Science Agenda (Nederlandse Wetenschapsagenda), the Dutch Research Council (NWO) awarded a subsidy of 2 million euros to an interdisciplinary consortium for research into germline modification (Public Realm Entrance and Societal Alignment of Germline Editing – PRESAGE project).

Text box 5.1: Biosafety

Many laboratories work with microorganisms that can cause diseases in plants, animals or humans. There may be risks to human health and the environment if these microorganisms, genetically modified or otherwise, escape from laboratories or infect laboratory staff. In the EU, there are rules for preventing the escape or spread of GMOs from laboratories,[298] as well as occupational health and safety rules to protect workers. In the Netherlands, the EU GMO legislation has been implemented in the Genetically Modified Organisms (Environmental Management) Decree (GMO Decree) and the Genetically Modified Organisms Order. The Dutch GMO legislation is characterised by detailed rules and regulations. In addition to a permit from the Ministry of Infrastructure and Water Management to conduct experiments with GMOs, an environmental permit is required for the laboratories. Incidents involving GMOs or pathogens from laboratories, such as the presence of the polio virus in the sewers in Bilthoven,[299] are exceptionally rare in the Netherlands. In 2022 the Rathenau Institute observed that the development of further understanding of the risks of new biotechnology is under pressure and argues for mandatory inclusion of biosafety in study programmes and making it an integral part of innovation research.[120]

5.3 VACCINES

5.3.1 New vaccine technologies

In the previous Trend Analysis, discussion of RNA was limited to agricultural applications and the development of mRNA vaccines was only mentioned in passing.[96] In the meantime, the development of these and other new vaccines has skyrocketed.

Conventional vaccines are generally classified either as attenuated live vaccines or as inactivated vaccines. The development of both types of vaccine is a complex, laborious, lengthy and costly business. On average it takes more than 10 years and the likelihood of a vaccine making it onto the market is 6%.[300] In the case of live vaccines, moreover, there is a risk of a reversal of the weakening, as with the polio vaccine.[301,302] It is clear that the established methods cannot protect the world's population against the sudden emergence of new and (as yet) poorly defined pathogens. There was therefore an urgent need for technologies that enable rapid reaction to impending pandemics. New vaccine technologies, such as mRNA vaccines and vector vaccines, offer a way forward.

mRNA Vaccines

The underlying principle of mRNA vaccines is the delivery of an mRNA containing the genetic code for an immunogenic protein from the pathogen into the cytoplasm of the host cell.[300,303,304,305,306] The DNA of the vaccinated individual is not changed. The host cell then produces the protein, which accumulates in or around the cell and triggers an immune response. The manufacturer can produce the necessary mRNA once the genetic code for the immunogen has been determined. Various modifications to the mRNA promote stability and ensure optimal production of the immunogenic protein by the host cell. An mRNA vaccine can be designed and produced on a clinical scale within a few weeks. In terms of effectiveness and safety, mRNA vaccines appear so far to be at least as good as traditional vaccines. They trigger multiple immune responses (humoral and cellular) and have few side-effects. However, it remains important to monitor for any long-term adverse effects. Because no cells are needed to produce them in the laboratory, they can be produced relatively quickly and cheaply in easily standardised and scalable processes and produced on a large scale in relatively small facilities.[307,308] Moreover, the vaccines can be easily adapted to increase their efficacy, reduce side-effects or respond to mutations in the pathogen. This makes mRNA vaccines eminently suitable for rapid response to a sudden outbreak of a new pathogen.

There are two types of mRNA vaccines: in addition to the 'regular' (non-amplifying) mRNA vaccines there are types that can self-replicate. As well as the code for the immunogenic protein of the pathogen, the mRNA then contains a code for a protein complex from a virus that causes the mRNA to replicate in the host cell. Such vaccines trigger a more powerful and longer immune response with less mRNA, but their production and stability present a major challenge. They are also more difficult to adapt.

For a long time, the development of mRNA vaccines was impossible because of a lack of suitable delivery systems. However, various delivery systems have recently been developed. The most commonly used are lipid nanoparticles, which consist of a complex of lipids and lipid-like substances. They protect the pieces of mRNA and promote their uptake into the cell and release into the cytoplasm. Moreover, the nanoparticles have the effect of an adjuvant, strengthening the immune response to the coded protein. After the particles have done their work, they are broken down or excreted.

Initially, the development of mRNA vaccines was directed towards fighting cancer, because conventional vaccines aimed at infectious diseases were unsuitable for this purpose. Vaccines against cancer have a therapeutic rather than a prophylactic character. They code for one or more proteins specific to cancer cells and against which an immune response must be elicited. In the US, more than 100 clinical trials with mRNA vaccines against a wide range of cancer types have been registered.[300] In the simplest approach, patients are immunised with a vaccine that codes for tumour-specific proteins, such as those for metastatic prostate cancer, for example. In another approach, personalised pieces of mRNA are used. A patient's tumours often have a unique set of

mutations that can be identified by sequencing, which makes it possible to produce an mRNA vaccine tailored to the individual patient. The utility, safety and clinical feasibility of this approach have already been demonstrated in a clinical trial with 157 patients with metastatic melanomas.[309,310] However, experimental treatments with mRNA vaccines for patients with other, difficult to treat late-stage cancers have so far met with little success.

Other mRNA vaccines are now being developed to combat viral infectious diseases, such as rabies, influenza, Zika, CMV, RSV and COVID-19. Most are still in the early stages of testing, but a few mRNA vaccines against COVID-19 (Pfizer-BioNTech BNT162b2 and Modena mRNA-1273) have already demonstrated their efficacy and safety in practice during the coronavirus pandemic. They are standard (non-amplifying) vaccines directed against the spike protein which facilitates virus entry into the host cell (see Figure 6).

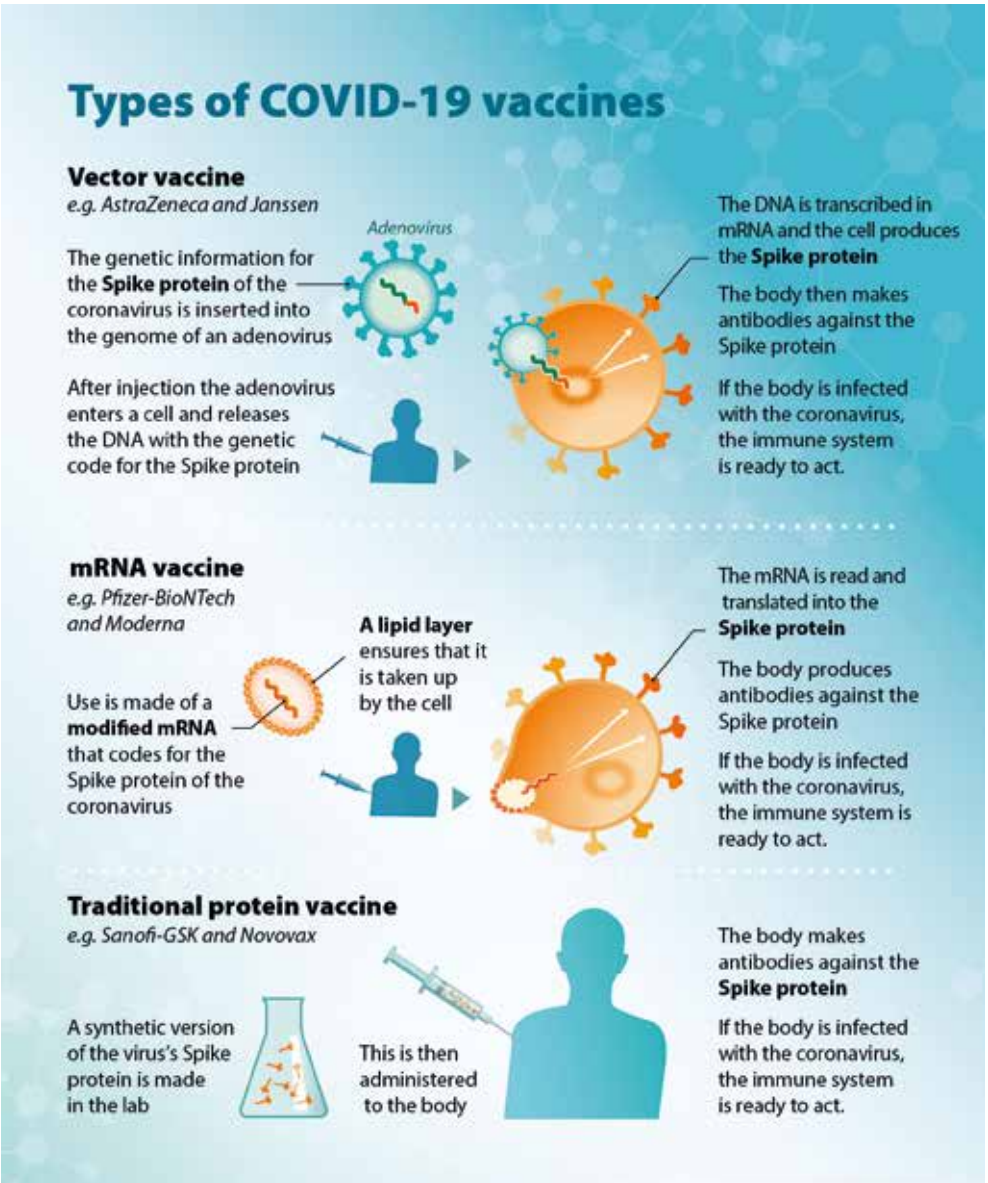


Figure 6: How traditional, viral vector and mRNA vaccines work, illustrated by COVID-19 vaccines

Vector vaccines

In vector vaccines, the genetic code of the immunogenic protein of the pathogen generally consists of a piece of double-stranded DNA and the delivery system (the vector) is usually a virus whose replicative ability has been disabled.[311] An example of a vector is the adenovirus that causes the common cold. For vector vaccines it is also true that the development of therapeutic applications against different forms of cancer is less advanced and less effective than the development of preventive applications to combat infectious diseases.[312] While vaccines against cancer are still in the clinical trial stage, some vaccines against infectious diseases have already received a (conditional) marketing authorisation, including the Ebola vaccine, which was approved by the American FDA at the end of 2019, and various coronavirus vaccines (Janssen/Johnson & Johnson Ad26.COV2-S; Oxford/AstraZeneca ChAdOX1-nCoV). These coronavirus vaccines have also been found to be effective and safe, although they appear to perform slightly less well than the mRNA vaccines in both respects. On the other hand, the vector vaccines do not have to be stored at such low temperatures as the mRNA vaccines, which simplifies storage and distribution.

Self-spreading vaccines

Some experts argue for a proactive approach to the control of infectious diseases.[313,314,315] According to them, vaccines that can spread throughout a population (self-spreading vaccines) show promise. In these vaccines the mRNA or DNA that codes for the antigen of the pathogen to be combated is packaged into an infectious (genetically modified) vector virus. If a limited number of individuals in the target population are infected, the vector virus will spread further, eventually infecting a large proportion of the population and eliciting an immune response in these individuals against the antigen of the pathogen carried by the vector. Experts see potential primarily for applications in animal husbandry and in populations of wild animals where conventional vaccination has not been able to achieve sufficient coverage. Vaccination of populations of wild animals can be used to protect endangered animal species against pathogens. Around the turn of the century, a field trial was conducted on a small Spanish island in the Mediterranean Sea to investigate whether the local rabbit population could be protected against myxomatosis and the rabbit haemorrhagic disease virus (RHDV) with a self-spreading vaccine based on a modified myxoma virus.[316] It has been suggested that the same approach could protect great apes in Africa against the Ebola virus.[317] In addition, it is hoped that self-spreading vaccines may be able to prevent populations of wild animals (such as bats and monkeys) becoming reservoirs of pathogens from which humans can be infected.

Self-spreading vaccines were recently the subject of a controversy in the scientific literature.[318,319] Some experts fear that the intended benefits of applications in populations of wild animals will be hard to achieve in practice and will not outweigh the huge risks that could arise if modified viruses mutate further or recombine with other viruses in nature. Assessing the risks is a highly complicated task, because it has to take account of spread across national borders and possibly even to other regions in the world where the environmental conditions are very different.

Text box 5.2: Biosecurity

Like other technologies, biotechnology and genetic modification can also be used for harmful purposes, such as bioterrorism or warfare (dual use). The risks seem to be increasing as scientific capabilities advance.[320] Not only are organisms being studied to determine which of their genes make them more or less pathogenic, but techniques have been developed to replicate viruses based on genome sequences published in the literature.[321] Biosecurity concerns measures to prevent misuse, although some publications also include measures for combating zoonoses and for biosafety under biosecurity (see box 5.1).

There are a number of international conventions, guidelines and voluntary agreements on preventing the spread and intentional outbreaks of pathogenic organisms.[322,323,324] However, these international conventions do not provide a comprehensive set of instruments. The United States and Israel, for example, have adopted legislation on 'dual-use research of concern'.[325] The approach chosen by the Netherlands is self-regulation and raising awareness of biosecurity and dual use among scientists. This covers both the prevention of exporting risky pathogens and products and preventing the spread of knowledge and information, including espionage. The Biosecurity Office is the central repository of information, organises information meetings and has developed various tools that institutions can use to assess their biosecurity and identify potential dual-use aspects in their research.[326]

Public concern about biosecurity tends to flare up in response to incidents or specific publications. It is expected that the debate on dual use and biosecurity will increase in the coming years in response to expanding scientific capabilities, the aftermath of the COVID-19 pandemic and heightened geopolitical tensions. Ensuring safety requires continual vigilance in the field and by governments. The current biosecurity measures and regulatory systems are based on how to safely handle pathogenic organisms and GMOs. There are now concerns that new research fields are emerging in which newcomers have less experience and awareness of the importance of biosafety and biosecurity.[327] In addition, biosecurity is an issue that requires international consultation and coordination. Countries and organisations worldwide must take and endorse measures, because pathogenic organisms cannot be stopped at the border – as was shown in the COVID-19 pandemic.

5.3.2 Social aspects

Whereas the health benefits of the new vaccines are for the most part still some way off for the treatment of cancer, they are already in use to treat infectious diseases. The social impact of the rapid availability of mRNA and vector vaccines during the COVID-19 pandemic was and is considerable. The vaccines have proved to be highly effective in practice. Serious side-effects have been rare. The economic and social benefits of the earlier ending of lockdowns and other restrictive measures have also been considerable.

At the same time, the rapid availability of the new vaccines raises practical and ethical questions. During the COVID-19 pandemic large quantities of vaccines had to be purchased from foreign manufacturers, while production still had to be ramped up, competition from other countries was fierce and export bans were threatened. As it turned out, most of the available vaccines were acquired by rich Western countries, leaving poorer countries at the back of the queue. Also, an effective vaccination strategy and the necessary infrastructure and public information campaign had to be quickly organised. Issues that had to be addressed included how healthcare professionals could best approach people with doubts about vaccination[328] and to what extent healthcare workers and members of the public could be convinced to get vaccinated.[329,330,331,332] The self-spreading vaccines discussed above raise serious ethical questions precisely because they erode individual autonomy.

There are also legal issues. Vaccines based on recombinant viral vectors fall under the EU legislation on GMOs, including vector vaccines, self-spreading vaccines and possibly also mRNA vaccines with viral codes for proteins for self-amplification. Standard mRNA vaccines do not fall under this GMO legislation because they are not derived from an organism. Under the GMO legislation an assessment of any risks to human health (third parties) and the environment has to be made as part of the approval pro-

cess. During the COVID-19 pandemic, however, the EU suspended the GMO legislation for all clinical trials with GMOs against the coronavirus to allow effective vaccines and medicines to become available as quickly as possible.[333] The reasoning given included the differences in authorisation procedures between the member states and the lack of facilities for emergencies such as pandemics. However, the Netherlands had already introduced a simplified fast-track authorisation procedure before this suspension took effect. In 2022 COGEM commissioned an external study on the suspension of the GMO legislation.[334] Based on this study and with an eye towards possible new crisis situations, it advised the EU to make agreements on accelerated authorisation procedures within the Union to facilitate the earlier availability of vaccines while at the same time ensuring human and environmental safety.[335] In addition, experts argue for the collection of relevant data for assessing the risks to third parties and the environment as early as possible in the preclinical and clinical phases of vaccine development so that they are available if an emergency approval of drugs is needed during a late clinical trial stage.[336]

Text box 5.3: Gain-of-function research

The debate about the safety of gain-of-function (GOF) research has been intensified by the COVID-19 pandemic and speculation that Sars-CoV-2 escaped from a Chinese laboratory. There is no definitive definition of GOF research, but it includes much biological research. The term 'gain-of-function-research-of-concern' is sometimes used for research in which pathogenic viruses are modified in various ways, for example to make them more pathogenic, spread more easily or able to infect other hosts. The aim of such research is to be able to respond more quickly and efficiently if such variants arise naturally. The debate is not new and repeatedly arises following incidents or new developments. Surprisingly, the debate is largely determined by US legislation, which is very different from the legislation and safety provisions in the EU and the Netherlands.

In 2011 there was global concern about the safety of experiments with the bird flu virus in the Netherlands and the US.[337] A moratorium was imposed on US-funded GOF research until the National Science Advisory Board for Biosecurity (NSABB) ruled in 2013 that the scientific advantages of the experiments outweighed the risks. In 2014, experiments with highly pathogenic viruses were again temporarily suspended in the US following incidents in high-risk laboratories.[338,339] In 2017 a publication by Canadian scientists describing how they had reconstructed an extinct poxvirus led to renewed controversy.[340]

The debate about GOF research escalated again in 2022.[341,342] Some scientists and critics believe that stricter safety requirements should be imposed and that some experiments should be prohibited.[343] They point to the growth in the number of high containment laboratories in the world for work with the most dangerous pathogens, the growth in activities outside laboratories, such as the collection of viruses from wild animals, and the risks associated with research into self-spreading vaccines.[318,344] Others, including the Dutch government, point to the importance of research for the development of new treatments, vaccines and diagnostics.[345] At the beginning of 2023, 150 scientists argued in scientific journals for a more nuanced and better substantiated debate about GOF research.[346]

The American government intends to expand and tighten up its criteria for financing GOF research. Some critics hope to initiate a wide-ranging global dialogue on the regulation of research into high-risk pathogens. The Pathogens Project, for example, aims to bring together international experts to work on recommendations for safe working with hazardous pathogens,[347] partly in response to the disparities between regulations governing biosafety and biosecurity between countries.[348] In the

Netherlands the Ministry of Justice and Security is currently assessing the need to revise the current legislation, regulatory oversight, authorisation procedures and self-regulation for GOF research in high-risk laboratories.

5.4 CELL AND GENE THERAPY

5.4.1 Genetically modified immune cells and microorganisms in disease treatment

The advent of cell and gene therapy was one of the developments described in the previous Trend Analysis.[96] In 2016 just one gene therapeutic had been approved as a regular treatment in the EU, but now there are 13, with applications for authorisation for several others pending at the European Medicines Agency (EMA). The approved treatments are for metabolic diseases, haemophilia, cancers and severe combined immunodeficiency (SCID). It is estimated that by 2030, 350,000 patients in the US will undergo treatment with 30 to 60 different gene therapy products.[349] The use of genetically modified immune cells has been shown to be particularly effective for treating certain types of skin and blood cancer. A new development is that CRISPR-Cas has found its way into the clinic and is used for the genetic modification of body cells.

The term gene therapy should be used with caution. In scientific terms, gene therapy involves making changes (mutations, adding or removing pieces of DNA) to the genetic material in somatic or germline cells of a patient or test subject. However, in the legislation and when approving medicines and therapies all clinical treatments with genetically modified organisms, viruses or cells are referred to as 'gene therapy',[350] including cases where no changes are made to the patient's genome, such as when administering GM bacteria or GM vaccines.

To clarify, there are roughly three types of gene therapy applications:

1. Ex vivo genetic modification of somatic cells

In ex vivo gene therapy, human cells are taken from the body, modified and then administered back into the body. This application has grown rapidly in recent years in the form of CAR-T cell therapy,[351] in which T cells (immune cells) a taken from the cancer patient, genetically modified by receiving a modified receptor (Chimeric Antigen Receptor, CAR) that recognises tumour cells, and then returned. More than 500 clinical trials with CAR-T are underway around the world.[352] So far this therapy has been particularly successful in treating skin cancers, such as melanomas, and blood-related cancers, such as acute lymphatic leukaemia and non-Hodgkin's lymphoma. However, the treatment is not successful in all patients. For example, 60% of B cell lymphoma patients do not benefit from the treatment.[353] Also, little success has been obtained with solid tumours (such as breast and lung cancer).[354] Foreign cells are also sometimes used instead of the patient's own cells, for example if the patient has few immune cells. Such ready-made gene therapeutics save money and time and are more convenient for the patient, but do require additional modifications to the cells to avoid immune responses. Similar research with modified T cells is aimed at fighting virus infections, for example with HIV and with modified (blood-forming) stem cells to treat genetic diseases.

2. In vivo genetic modification of somatic cells

In vivo gene therapy involves administering usually viral vectors directly to the patient or test subject. The aim is mostly to cure (treat) a genetic disease by inserting a 'healthy gene' permanently into the genome of the patient or by temporarily expressing it in the cells of the patient. Lentiviruses (sometimes retroviruses) are the preferred vectors for the former and adenoviruses (cold viruses) or adeno-associated virus (AAV, which cause no illness) for the latter.[355] Clinical studies have been carried

out in the Netherlands for a number of years on various treatments, including for a rare genetic liver disorder (Crigler–Najjar syndrome), glycogen storage diseases and retinal degeneration.

3. Administration of genetically modified microorganisms, parasites or viruses as vaccines or clinical treatments

Genetically modified organisms and GM viruses[f] are being tested in clinical research as possible treatments for cancer. The viruses are modified to only infect and burst rapidly dividing cancer cells.[356] Other organisms are also modified to treat cancer. One example is a clinical trial in which a genetically modified bacterial strain of *Mycobacterium bovis* BCG is administered into the bladder of patients to induce an immune response to a bladder tumour. The research effort to develop a malaria vaccine includes a clinical study in the Netherlands with genetically modified malaria parasites (*Plasmodium falciparum*). The modified parasite, which is no longer able to complete its life cycle in the human liver, is administered to the patient to induce an immune response.[357] Vaccines based on genetically modified viruses, such as the AstraZeneca and Janssen COVID-19 vaccines mentioned above, also fall into this type of treatment.

CRISPR-Cas9 is now used in gene therapies. Clinical trials have been conducted with CRISPR-Cas9-based therapies for blood diseases such as beta-thalassemia and sickle cell anaemia,[358] leukaemia,[359] the hereditary form of amyloidosis,[360] Leber congenital amaurosis (a type of hereditary blindness) [361] and hereditary angioedema.[362,363] However, no therapies that use CRISPR-Cas are available on the market yet.

5.4.2 Social aspects

At present, gene therapy primarily offers hope to patients with genetic diseases caused by specific abnormalities in a single gene (monogenic diseases), such as the muscle disease SMA, the eye disease retinitis pigmentosa and certain types of cancer, such as blood and skin cancers.[364,365] These conditions are often difficult or impossible to treat. For genetic diseases in particular, gene therapy can be a game changer because it shifts the nature of the treatment from symptom management to addressing the underlying causes. Instead of long-term care, patients could be cured with a 'one-time' treatment. However, it is still unclear to what extent these expectations can be met. In many cases, gene therapeutics should be administered at as early a stage as possible when little or no irreversible (developmental) damage has occurred in the body. This depends on early diagnosis. The perception by the patient is also an important consideration in the development of gene therapies. Their willingness to undergo the gene therapy appears to be strongly influenced by the severity of the condition and the availability of alternative therapies.[366]

The costs of these promising therapies are very high, often running into several hundred thousand to a few million euros per patient.[367] It is expected that the number of approved treatments will rise sharply over the coming years. If the prices remain at the same level, the Dutch healthcare budget will become a limiting factor. On the other hand, these high prices should be set against the equally high costs of long-term care the patients would otherwise need. On a number of occasions, the Dutch National Health Care Institute has advised against including certain gene therapies in the health insurance package on the basis of a negative cost-effectiveness appraisal. As manufacturers do not reveal any details of cost structures it is unclear to what extent the asking prices reflect a realistic coverage of the costs incurred. Basing prices

f Viruses are not organisms, but in the GMO legislation they are included in the category of microorganisms (Genetically Modified Organisms Decree 2013, Article 1.5).

on the cost of regular treatments and the seriousness of the diseases pushes up costs and restricts access to successful therapies. To be able to undergo treatment, if necessary abroad, desperate patients (and their families) often resort to other means, such as crowd funding, which only increases inequalities.[368] In developing countries, where diseases like sickle cell anaemia are most prevalent, these exorbitantly expensive treatments are entirely beyond the reach of patients. University medical centres should be able to produce some of these therapies at lower cost,[369,370,371] but that will require new innovation models for therapy development and other forms of cooperation with commercial parties. The establishment of the Future Affordable and Sustainable Therapies (FAST) organisation[372] and the financing of project proposals by the National Growth Fund are the first steps towards getting new treatments to the patient faster and at acceptable costs, while reducing dependence on foreign companies.

In addition to these financial and ethical issues, there are also legal questions. In the EU, all clinical treatments with GMOs are subject to the GMO legislation, which aims to prevent any potential risks to third parties and organisms in the environment. Such risks may arise, for example, if modified T cells are passed on in donated organs or blood,[373] or during therapies with replicating oncolytic viruses or replication-deficient viruses and parasites if they recover their disabled replication capacity through recombination with wild types. The risks to patients and test subjects themselves are covered by the EU legislation on drugs and medical research. Any risks to healthcare providers fall under the Working Conditions Act. There is no unnecessary duplication in the safety assessment.

Another legal issue is that the current registration procedure for drugs is designed for the approval of drugs intended for use in the entire population, or at least large groups within it.[374] The procedure is not geared to personalised therapies, such as those for extremely rare diseases,[375] although medical ethics committees can grant approval on an individual basis. The standard procedure for authorisation for placing on the market and reimbursement (inclusion in the healthcare insurance package) is geared to products for which an average effect can be studied in a randomised controlled trial. Personalised therapies require evaluation for small groups using alternative trial designs or patient-specific approaches in which the quality control follows a different procedure, as is currently the case for stem cell transplantation. The existing legislation for orphan medicinal products does not provide a solution and leads to high prices and limited accessibility.

5.5 XENOTRANSPLANTATION, CHIMERAS AND ORGANOIDS

5.5.1 Organs grown in animals or in the lab

Currently there are 1,300 patients in the Netherlands waiting for donor organs.[376] Despite the increase in the number of living organ donors, there is a structural shortage of donor organs. Xenotransplantation – the transplantation of organs from (modified) animals to people – is considered to be a promising solution. Gene editing has brought the clinical application of xenotransplantation a step closer. Technical breakthroughs in 2021 have generated considerable interest in this technique.

Donor organs from animals

The idea of using donor organs from animals for humans is not new, but because of the immune responses by the human body, donor organs from animals, however closely related, will always be rejected. Another major risk is the transmission of animal diseases. In the Netherlands, there is a moratorium on the clinical application of xenotransplantation as long as there is insufficient guarantee of safety. Developments in gene editing can help to overcome both of these hurdles.[202]

The risk of rejection can be reduced in two ways. The first method is by genetically modifying the animal to reduce the immune response by the human body; in essence, the animal is humanised. This is achieved by removing several of the animal's genes and inserting some human genes. Pigs are often used for research in this area, because the size of pig organs is comparable to that of human organs and because pigs can reproduce relatively quickly. Organs from primates are more suitable, but their use raises significant ethical concerns because of their close relation to humans. The other, less conventional route, involves generating human organs in animals. Stem cells from a human donor are introduced into a humanised animal embryo, usually from a pig. The development of a pig organ is prevented by inactivating several of the animal's own genes and the human cells take over the role of the missing pig stem cells to create the human organ. Organisms that contain both human and animal tissue are called human-animal chimeras.

The risk of transmitting animal diseases lies mainly in the presence in the animal donor of viruses dangerous to humans. Pig genomes often contain many inserted copies of a pig virus (*porcine endogenous retrovirus*). Research is being conducted to inactivate viruses in the pig genome using either CRISPR-Cas9 or base editing to create virus-free pigs that are suitable for organ donation.[377,378,379]

Several significant developments in xenotransplantation were reported in 2021 and 2022. At the end of 2021, American scientists reported that they had successfully transplanted pig kidneys into a human.[380] The recipient was a brain-dead patient with kidney failure. The kidneys were attached to the patient's blood vessels, but were kept outside the body for monitoring purposes. The kidneys functioned well, but the experiment was ended after 54 hours by turning off the ventilator, after which the patient died.[381,382] In January 2022 doctors at a hospital in Maryland announced that they had transplanted a heart from a genetically modified pig into a human for the first time.[383] A 57 year old patient with an acute, life-threatening condition was prepared to undergo the experimental treatment because the poor state of his health did not permit a regular transplant. The treatment was successful in the first instance,[384] but in March it was made known that the patient had died.[385] In the following months it became clear that the cause of death of the recipient of the pig heart was a pig virus, the porcine cytomegalovirus; the researchers had mistakenly thought that the donor heart was pathogen free. Although the experiment shows that clinical application of xenotransplantation is getting closer, it also illustrates its complexity and unpredictable safety issues. Finally, in June and July 2022, a team in New York transplanted two pig hearts to brain-dead patients on ventilators.[386] The hearts functioned normally during the test period of three days and no viruses were detected. The researchers see these results as an important step towards safe clinical application of xenotransplantation.[387]

Growing human organs in animals receives less scientific attention than xenotransplantation.[388] However, American and Chinese researchers have inserted human stem cells into monkey embryos to investigate whether it is possible to grow human organs in animals for transplantation.[389]

Organoids

Organoids are another significant and promising development in medical research. They are three-dimensional miniaturised organs grown in laboratories from pluripotent stem cells.[390] Organoids can be used to study the functioning of healthy and diseased organs, the effects of medications and the influence of genetic defects. It is expected that organoids can help reduce the number of animal tests and close the gap between preclinical research with animals and clinical trials with humans.[391] Cancer research is an area where patient-specific tumours can be grown and studied. Organoids are already used to predict the seriousness and progression of the disease and

the therapeutic response to cystic fibrosis.[392,393] Retina organoids offer new possibilities for studying the biology of vision, identifying the causes of eye diseases and developing treatments.[394] Brain organoids are used as a research tool in neurology[395] as they exhibit 'electrical' activity that is somewhat similar to brain activity in premature babies.[396] Human brain cells and brain organoids have been inserted into the brain tissue of mice and monkeys for research purposes.[397-402] Individual nerve cells and cell clusters from the brain appear to function normally in the animal tissue of these chimera and establish connections with the animal brain cells. This research field seems to be advancing rapidly.[403] Its aim is to obtain a better understanding of the development of the human nervous system and open up new avenues of research into the functioning of human nerve cells and the development of neurological disorders.[404,405]

5.5.2 Social aspects

Xenotransplantation may help to alleviate the shortages of donor organs in the future, but the issue of safety first has to be resolved. There are also a number of important ethical questions. Xenotransplantation touches upon the intrinsic value of the animal and can be considered to be a further instrumentalisation of animals. Several animal welfare organisations, including People for the Ethical Treatment of Animals (PETA), are critical of xenotransplantation for this reason.[406] The welfare of the donor animals is also a concern. According to the Council on Animal Affairs, the issue is the ability of animals bred for organ transplants to exhibit their natural behaviour, and for this reason the growth of organs in animals requires ethical justification.[407] A broad public debate organised by the Rathenau Institute and NEMO Kennislink in 2021–2022 revealed that the participants felt that the use of donor animals is justifiable, but that they prefer animal-free alternatives.[408] They also stressed the importance of animal welfare and the need to address safety concerns. Some rejected xenotransplantation on the grounds of it being unnatural.

Brain organoids have also sparked off a significant ethical debate. The question here is whether they have a form of consciousness or not and if it is acceptable to grow them to such an advanced stage of development.[409] Perhaps more important are the ethical issues surrounding human-animal chimera.[410] Some researchers and ethicists consider that the creation of human-animal chimera crosses an ethical line.[411,412] In 2019 the Health Council of the Netherlands published advice on chimera at the request of the Minister of Health, Welfare and Sport.[388] In it they stated that the current legal framework cannot respond adequately to future scientific developments and that a new regulatory framework is needed for the evaluation of research with controversial biotechnological development, such as human-animal combinations. In 2021 an expert committee evaluating the Embryo Act proposed revising the legislation to bring embryos with both human and animal DNA within the scope of the Embryo Act if the animal component is not dominant and within the Experiments on Animals Act if the animal component is dominant.[295] Whether the expectations regarding the value of brain chimera outweigh the ethical objects remains a subject of debate.[413,414] In 2021 the American National Academy of Sciences, Engineering and Medicine stated that the legislation was still adequate and that up to this point experiments have been ethically acceptable, but that the field of brain chimera must be kept under constant scrutiny because the creation of animals with new cognitive abilities in future cannot be ruled out.[415,416]

5.6 ANTIMICROBIAL RESISTANCE

5.6.1 Understanding, monitoring and combating resistance

In addition to the recent COVID-19 pandemic, the world has been plagued for many years by another, more insidious, pandemic, that of microbial resistance.[417] Many pathogens or otherwise harmful bacteria, fungi and other microorganisms are becoming increasingly resistant to the chemical compounds we use to control them. Some pathogenic bacteria are already resistant to almost all the available and usable antibiotics and it has become almost impossible to treat patients infected with such pathogens. The problem is exacerbated by the fact that the development of new classes of antimicrobial substances with a completely different mechanism of action has stalled as the pharmaceutical companies are largely unable recoup the high development costs.[418,419,420]

But there is hope on the horizon, fed by developments in modern biotechnology. New genetic analysis and detection techniques, such as CRISPR-Cas-based[421] and new X-omics techniques, are contributing enormously to the growing scientific understanding of the genetics underlying resistance mechanisms, the evolution and spread of resistance and the environmental factors that contribute to it.[422,423] Understanding is a first condition for effectively tackling the problem of microbial resistance. Moreover, genetic analysis and detection techniques make it possible to monitor the development and spread of resistance and study the effectiveness of control measures, such as using these agents sparingly.

Besides greater understanding, recent developments in biotechnology open up new possibilities that can help to stem the tide of antimicrobial resistance. For example, faster identification with new techniques will make it possible to target pathogenic bacteria more often with narrow-spectrum antibiotics rather than broad-spectrum antibiotics. Furthermore, biotechnology can help in the search for new classes of antibiotics and the development of alternative methods of fighting resistant and other microorganisms.

Most antibiotics now in use are of natural origin or derived from natural substances. Less than 1% of the vast diversity of microbial species have been cultured and investigated for their ability to produce antimicrobial substances. However, technological advances provide increasingly better opportunities to investigate the other 99%.[419] Usable microorganisms can be found in all environmental compartments or in the microbiomes of animals and even humans. It is also possible to extract all the DNA from an environmental sample, sequence it and try to express promising clusters of genes in known bacteria that can be cultured. This search has already yielded its first promising success: teixobactine, a substance that is effective against antibiotic-resistant bacteria such as MRSA and the tuberculosis bacterium. It works in an entirely new way. The substance is still in the testing phase, but may possibly form the basis for a new class of powerful antibiotics.[424,425,426,427]

A very different approach aims to control both resistant and non-resistant microorganisms with monoclonal antibodies.[420] These antibodies can act in two possible ways. The first is by binding to antigens on the surface of bacteria, which are then killed by the host's immune system. The second is by neutralising virulence factors of the bacteria, such as exotoxins and biofilms. This second mechanism appears to be particularly effective. In the past ten years three monoclonal antibodies with this mechanism of action have been approved for use. They target the anthrax bacterium (*Bacillus anthracis*) and *Clostridium difficile*. Four other monoclonal antibodies against *Staphylococcus aureus* are in the clinical trial phase.[420]

A second alternative control mechanism is the use of bacteriophages, or phages,[420] viruses that infect and kill other bacteria. The relation between a bacteriophage

strain and its host, the bacterium, is often extremely specific. The development of antimicrobial resistance has led to increasing interest in phage therapies, and various research projects are now in the clinical or preclinical stage. An example is a clinical trial in which 36 patients with a bladder infection caused by resistant or non-resistant Escherichia coli were treated with a cocktail of phages modified using CRISPR-Cas3 (LBP-ECO1).[420,428] In the United Kingdom, patients with cystic fibrosis and severe lung conditions suffering from heavy infections with antibiotic-resistant Mycobacterium abscessus are being treated with a cocktail of phages.[429,430,431] Some of the phages on these clinical trials have been genetically modified to increase their effectiveness. Although phage therapy is proving to be far from simple, more than half the patients appear to benefit from it.[431] No harmful side-effects have been found.

A final example is the use of CRISPR-Cas-based antimicrobial agents. In this case, a CRISPR-Cas system is inserted into antibiotic-resistant bacteria using a suitable vector (for example a bacteriophage). The CRISPR-Cas system can be directed to a specific piece of DNA or RNA from the bacterial chromosome or from a plasmid (a separate circular piece of DNA that often contains resistance genes) and cleave it. This results in the death of the bacterium or the loss of resistance genes, making the bacterium susceptible to antibiotics again.[432,433] This type of research is still largely in the preclinical stage.

5.6.2 Social aspects

Although most of the technological developments outlined above are still in the preclinical research phase, their potential significance for Dutch healthcare – and especially for global public health – is enormous. This is particularly true for patients suffering from life-threatening infections with resistant microorganisms. In addition, these biotechnological developments open up new possibilities to help combat the insidious global pandemic of antimicrobial resistance, which is estimated to have cost the lives of 1.27 million people worldwide in 2019.[417]

However, it is clear that the solution to the problem should not be sought only through technological innovations in the medical domain. The protection of public health against infectious diseases requires a much broader One Health approach based on the realisation that human health is closely bound up with that of animals, ecosystems and the environment. This broader approach – which has major implications for the way we practice agriculture, raise animals and interact with nature – is not new, but interest in it has grown rapidly in recent years in response to global developments, such as ongoing climate change and the COVID-19 and microbial resistance pandemics.[229] In 2021, major international organisations set up the Interdisciplinary One Health High-Level Expert Panel (OHHLEP), in which the Netherlands is also represented.[434] In 2017, the Netherlands Centre for One Health (NCOH) was established, in which Dutch universities, university medical centres and the National Institute for Public Health and the Environment (RIVM) participate.[435]

5.7 POLICY RELEVANCE

The rapidity of technological developments is forcing politicians and policymakers to make choices. Which developments and applications are desirable from a societal perspective and should therefore be given a free rein, or even government support? And which developments and applications are undesirable and should therefore be discouraged, curbed or at least kept at arm's length? These are often complex normative questions. Examples in the medical domain are germline modification and xenotransplantation (once both have been deemed safe enough for clinical applications), growing

embryos for research purposes and creating human-animal chimera (especially when brain tissue is involved). The following points deserve careful attention:

- In many cases, the dividing line is blurred rather than black and white: to what extent or for which purposes do we want to allow certain developments or applications? Germline modification for correcting severe genetic disorders, but not for human enhancement? Preimplantation genetic testing of embryos for certain genetic disorders has been taking place in the Netherlands for some time, but is used elsewhere for a much wider range of purposes, for example in the United States.
- It is important to consider developments in a broader context as well. Preimplantation genetic testing and germline gene editing cannot be seen in isolation from other technological developments in the area of human reproduction, such as the creation of artificial gametes, the ability to keep embryos in culture for longer and the progress made in neonatology that enables premature babies to be kept alive at increasingly earlier stages of their development. Together these developments raise questions about how far we as a society are willing to go with technologising human reproduction.
- Politicians making such normative choices should not only be informed by those directly involved, but also by ethicists, lawyers and dialogues with citizens (which has happened in some cases). Dissenters should be given room to make their own choices where possible. The government should also have an eye for minimising socioeconomic health disparities and make sure there is reliable and independent information available

To bring technological developments in line with the choices made, government oversight will be necessary on numerous fronts. A few examples:

- Wider introduction of a pharmacogenetic passport in clinical practice is currently stalled, mainly because of a lack of direction. It would be useful if the government took the lead or formally delegated responsibility to a suitable authority.
- Government direction is also necessary to make innovative but expensive cell and gene therapies cheaper and more accessible by working with all relevant stakeholders to explore new forms of public-private cooperation. Authorisation should also be looked into, because the new therapies are increasingly tailored to the individual patient and the current authorisation procedure for medicines is not designed for evaluating such therapies. A new evaluation system is needed to ensure that personalised therapies are both effective and safe.
- Government intervention in vaccine development is also needed. The new mRNA vaccines can be produced quickly using more or less standardised procedures in relatively small production facilities. This may open up possibilities for production of these crucial agents in the Netherlands (or within the EU), thus reducing dependence on foreign suppliers. Such strategic autonomy will be essential in times when demand is high (such as during a pandemic) and in times of geopolitical tensions.

Finally, politicians and policymakers are responsible for developing a balanced legislative and regulatory framework which will allow development of biotechnological applications that are considered desirable, while at the same time providing sufficient safeguards in the areas of safety, privacy and property rights. In the medical domain, this will require, among other things:

- revising the Embryo Act, at least if there is a political consensus for offering greater opportunities for research on embryos and animal-human combinations, for which preparations are already underway;
- further implementation of the new EU regulations for medical devices for in vitro diagnostics;
- greater clarity on which types of targeted genetic modifications do and do not fall under the GMO legislation.

International cooperation will often be necessary because much of the relevant legislation is EU law and the Netherlands is bound by international agreements, such as those in the Council of Europe.

6 WHAT MIGHT THE FUTURE HOLD?

The current applications in biotechnology and the trends described in the chapters of this report can be grouped into two categories: 'reading, understanding and characterising life' and 'adapting life'. The step to 'creating life' – the desirability of which remains disputed – has not yet been made. However, scientists are already working on several applications and developments in the grey area between modifying or making a new type of organism and creating life, and may in the more distant future succeed in breaking through the boundary to creating life. Besides the possibilities this would open up, it raises ethical and moral questions about the desirability of taking such a step and about the relation between humans and nature.[436] The next section discusses several examples of these new developments.

6.1 SYNTHETIC CELLS AND OTHER APPLICATIONS

In 2010 researchers built a synthetic cell by removing the DNA from the cell of the bacterium Mycoplasma capricolum and replacing it with a genome they had synthesised in the laboratory and which was based on the genome of the related bacterium *Mycoplasma mycoides*.[437] Since then the researchers have removed further 'redundant' genes to arrive at the minimum number of genes needed to allow the cell to grow and divide normally.[438] The synthetic genome is a stripped down copy of the *M. mycoides* genome, with fewer than 500 genes. By mapping the functions of the remaining genes the researchers are trying to learn more about how a cell works.[439] Alternatively, a bottom-up approach can be taken by building a synthetic cell from non-living building blocks. Several Dutch universities are working together in the BaSyC (Building a Synthetic Cell) research programme to assemble just such a synthetic cell.[440] Synthetic cells provide insight into the mechanisms of cell functioning and should serve as an ideal platform for producing biochemicals in cultivation reactors.

In 2017 Canadian researchers succeeded in recreating the horsepox virus, which no longer occurs naturally, from pieces of synthetic DNA.[441] The advantages of synthetic virology are that it avoids the need to keep and cultivate viruses in a laboratory, thus reducing the risk of infection, and makes it easier to induce mutations to investigate the function of genes in pathogenicity and such like.[442] Also, the ability to synthesise viruses and the increased power of artificial intelligence make the possibility of designing and building new viruses increasingly likely. There are already companies that offer services in designing and synthesising modified viruses.[443] Genetic information is somewhat similar to natural language; the bases code for the amino acids that make up proteins. Proteins contain recurring elements that have certain functions. Similar to ChatGPT for language, it is conceivable that in the future a programme will be developed that can use genetic elements (sequences) of viruses to build a new virus. Viruses are tailored to their host as they must evade the host's immune responses. Most computer generated viruses will not be able to do this, but as our knowledge increases it is possible that in a few years' time a whole new virus could be synthesised. This form of synthetic biology raises questions about safety and dual use. It is not clear to what extent applications like this will fall within the scope of the existing GMO legislation.

Scientists have succeeded in producing synthetic mouse embryos from stem cells in the laboratory, without the need for eggs and sperm.[444] This scientific breakthrough has nu-

merous implications and blurs the boundary between synthetic and natural embryos.[445] Cultivating animals or humans in artificial wombs will remain science fiction for some time to come, but some experts point to a possible future scenario in which reproduction has become a purely technical process and artificial reproduction, genetic screening and germline gene editing are used to eliminate diseases and select favourable traits. As Laurent Tellier, the CEO of the American company Genome Prediction, said: 'Sex is great, but it is not the best way to make a baby.' Or as the German philosopher Günther Anders put it, 'You'll be ashamed to have been born instead of made.'[446] These are scenarios for the distant future that are outside the scope of this Trend Analysis, but they nevertheless play a part in the debate about the development of reproduction technologies and germline gene editing.

Stem cells can also be used to make xenobots, biological entities that bear no resemblance to the organisms from which the cells originate. They can be made, for example, by combining individual stem cells from the African clawed frog (*Xenopus laevis*) in a petri dish in the laboratory.[447] The shape of these multicellular structures or 'organisms' can be varied by combining different types of stem cells based on computer models that predict which of these building blocks should be used. To the surprise of the researchers, xenobots have proved to be capable of replication when separate cells are added to them. The xenobots gather the cells together, which then form a new xenobot. Xenobots can also repair themselves when damaged. As xenobots can move by means of cilia on the surface of their cells, scientists hope that it will eventually be possible to use them for medical purposes or to clean up microplastics in the ocean. The researchers describe xenobots as organic robots with the characteristics of both a machine and an organism.[448] The experiments are not entirely uncontroversial because of the potential risks and ethical objections to creating self-replicating and self-repairing biological robots.[449]

Xenobiology investigates the possibility of replacing natural building blocks in microorganisms and other organisms, such as nucleotides in the DNA and RNA and amino acids in proteins, with synthetic variants that do not occur naturally.[450] The advantages of this are that the modified (orthogonal) organism would be completely biologically contained, because they could only grow in an environment where these unnatural building blocks are available.[451] These organisms could be made to produce new biochemical substances. In recent years nucleotides have been successfully replaced with synthetic analogues called xenobiotic nucleic acids (XNAs). Enzymes have also become available that can replicate the XNA and link them together. Many technological barriers still have to be overcome before orthogonal organisms become a reality, but should this ever be possible, a parallel living world would be created that has no connection to natural biology and ecology.

6.2 DEVELOPMENTS ARE MOVING FAST

The above-mentioned developments present opportunities, but also raise questions about safety and ethical boundaries. Researchers say that synthetic cells or organisms are too simple to have a chance of survival and that human and environmental safety is therefore assured. Synthetic cells are too fragile to survive outside culture conditions, xenobots can only replicate when single cells are provided and xenobiology is based on the principle that the unnatural components are not present in nature. These assumptions seem to be largely correct, but are based on current knowledge.

The developments outlined above are still in their infancy. But in recent years we have seen that developments in biotechnology sometimes move faster than expected. It is important that research into safety becomes an integral part of this type of innovative research, so that the safety of later applications can be assured without presenting unnecessary obstacles to research and innovation.[452]

The question is, who decides what is ethically acceptable, and how? What determines whether or not life is being created, and at what point and to what extent does a synthesised organism or cell structure obtain a moral status? It can be argued that this requires there to be a form of consciousness. Researchers point out that even if 'life' has been created, these simple structures cannot have any cognitive capacities. The same is said about brain organoids, because although they display electrical activity, the limited number of cells are too few to sustain consciousness. On the other hand, it is not clear how in these situations consciousness could be empirically determined to exist, and so consciousness would appear to be unsuitable as a criterion for determining moral status.[453] Given the questions raised by these types of initiative, and also by potentially controversial research, it is important to involve the public, social scientists and policy-makers at an early stage.

7 POINTERS FOR THE POLICYMAKING PROCESS

The world is facing major societal challenges. The United Nations has formulated 17 Sustainable Development Goals (SDGs) for a better world in 2030, varying from ending hunger, ensuring healthy lives and promoting wellbeing to stimulating sustainable economic growth. In the face of climate change caused by greenhouse gas emissions, loss of biodiversity and exhaustion of agricultural land we need to make the transition to more sustainable circular production in both agriculture and industry. There is also a need for affordable and accessible medical care. Achieving these goals will require societal changes as well as new technologies. Biotechnology is an enabling technology which has embedded itself in numerous sectors and fields of practice. This Trend Analysis shows that biotechnology can be one of the building blocks for achieving the UN goals. At the national level, biotechnology can contribute, among other things, towards government ambitions for the circular economy and the energy transition.

To exploit such opportunities, the 'biotechnological innovation ecosystem' must be in order. This ecosystem consists of diverse elements and actors, such as stakeholders, infrastructure, institutions, legislation that supports innovations while ensuring human health and environmental safety, funding for fundamental and applied research, and clear and shared policy and ethical principles (see Figure 1). The effective functioning and management of the biotechnological innovation ecosystem requires the coordinated engagement of the various parties active in biotechnology, such as government agencies, scientific institutions, the business community, NGOs, consumer and patient organisations, and citizen involvement.

Acceleration, diversification and convergence of biotechnology with other technologies

Since the previous Trend Analysis the convergence of biotechnology with computational technologies such as informatics, process automation and robotics has advanced. Big data, algorithms and machine learning (data sciences) have become an integral part of the biosciences and have radically changed the field. The number of commercial applications and companies is rising rapidly and trade is not restricted to biotechnological applications such as therapies, products or crops, but also include data (big data). The government should take the diversification of the field and the convergence of biotechnology with other fields of research and applications into account in its policies and decision-making. The current approach, which is focused mainly on specific sectors and applications within biotechnology without considering the wider linkages between technologies, is no longer adequate.

The biotechnological innovation ecosystem needs improving

The Dutch and European biotechnological innovation system urgently needs improving. The Netherlands is insufficiently prepared for the developments in biotechnology and the questions they raise, and is missing out on opportunities to make full use of the economic and societal potential of biotechnology. The previous chapters raised a number of negative developments. R&D activities in the agro sector have relocated abroad because EU regulations have not kept pace with developments, while products developed in the EU, such as meat and milk alternatives, are being marketed abroad first. Critical infrastructural elements, such as biofoundries and cloud services,

are absent or inadequate. In addition, it is unclear how consumer choice and coexistence with groups and sectors that want to remain free of certain biotechnological developments can be arranged. The ongoing integration and convergence of biotechnology with other fields raises questions about the shelf life of the current regulatory and assessment frameworks.

Fragmentation of initiatives and responsibilities impedes progress

One of the key messages of this Trend Analysis is that individual developments in biotechnology do not stand alone and cannot be seen in isolation. Many of the trends and topics covered in the Trend Analysis apply across the full scope of the application of biotechnology and are strongly interconnected.

The Dutch government has developed a number of initiatives to support biotechnology in the Netherlands, such as investing in research into cultured meat, gene and cell therapy, the building of a synthetic cell, and the National Growth Fund investment in the Biotech Booster aimed at exploiting economic opportunities. Also, in response to the previous Trend Analysis in 2016, a process of modernising biotechnology policy has been set in motion.

However, there seems to be a lack of alignment and coordination between the various initiatives and projects, and no clear goals have been formulated. In the Netherlands (and the EU), different applications of biotechnology are dealt with by different ministries, each of which concentrates on its own policy arena. As a result, no one is responsible for the development of biotechnology as a whole. The same goes for government efforts to meet the societal challenges. For example, the policy for the transition to a circular economy makes no reference to developments in biotechnology, even though this field has an important part to play in the transition.

This fragmentation and piecemeal approach is an obstacle not only to exploiting the social and economic opportunities, but also to preventing adverse social impacts and risks.

Vision and direction needed to develop the biotechnological innovation system

Individual developments in biotechnology do not stand alone, but should be understood within the context of the huge range of developments in biotechnology and their relation to developments in other disciplines. This wide range of development requires an *integrated approach* and government steering. The urgent questions arising from these developments are: how does the Netherlands want to make use of the possibilities of modern biotechnology to address societal challenges such as climate change, transitioning to a sustainable economy, and its strategic autonomy with respect to critical products such as medicines and vaccines? What is needed to ensure that biotechnology does indeed contribute towards meeting these goals? What do we want to prevent? And what is needed to ensure there are no undesirable applications or impacts?

COGEM and the Health Council of the Netherlands therefore argue for an *integrated long-term vision* on the direction of biotechnology to the benefit of Dutch society. The government should state which societal goals should be pursued with biotechnology and *take the initiative* in stimulating the development of biotechnology such that these goals can be achieved. This is not something that can be taken for granted if the development of biotechnology is left to the vagaries of the market. In addition, the government should work with other actors in the innovation system to prevent undesirable applications. The government's vision and approach can be laid down in a new com-

prehensive biotechnology policy document (*Integrale Nota Biotechnology, INB*).[g] Given the fragmentation of responsibilities for biotechnology within national government, the establishment of an interdepartmental programme directorate, such as that for the biobased economy and the energy transition, is strongly recommended.

Several points that should be considered when preparing a comprehensive, long-term vision are set out below.

Specific points and options for action

The Dutch government should take the lead so that the biotechnological innovation system is put in good order and maintained. This will require a cross-ministerial approach. The response to developments in nanotechnology, as expressed for example in the Government's vision document on nanotechnologies (*Kabinetsvisie Nanotechnologieën*),[454,h] may provide inspiration. Key aspects of a cross-ministerial approach should include the following:

Improving the research infrastructure

A new impetus in knowledge, innovation and methods that utilise science driven by big data and artificial intelligence can help the Dutch biotechnology sector maintain and expand its strong position. Good public-private research infrastructure is necessary for large-scale fundamental and risky research that can lead to groundbreaking innovations. The genomics research field is a highly competitive and evolving field. This field is essential for the development of the entire biotechnology sector and continuing support is needed for research and research facilities. Big data is highly important and contributes to all the different sectors and fields within biotechnology. The rapid growth in the vast amounts of data and the capabilities for analysis require data centres and cloud computing services. The government should coordinate the establishment and maintenance of such essential research infrastructure, because it exceed the limits of individual institutions and companies. *Biofoundries* are considered to be an important catalyst for industrial biotechnology, but the Netherlands does not have one. A national biofoundry facility for academic researchers and SMEs can make the Dutch biotechnology sector more effective.
A well-functioning labour market with sufficiently educated personnel is also a prerequisite for the development of the Dutch biotechnology sector. To ensure that the Netherlands can continue to compete with other countries it is important that the Dutch government intervenes to raise the quality and attractiveness of biotechnology study programmes.

Exploiting the economic potential

A major conclusion of the Biotechnology Trend Analysis 2007 was that the economic potential of the Dutch biotechnology sector was not being fully exploited, and this conclusion still stands.[455] Despite the Netherlands' strong scientific position, the presence of companies that develop and produce biochemicals, enzymes, medicines and vaccines, as well as the presence of numerous breeding companies and a considerable number of start-ups, the country's share in the global biotechnology sector remains modest. As also observed in previous Trend Analyses, a major barrier is the development of start-ups into medium-sized companies.[i] The absence of venture capitalists or their reluctance to invest makes it difficult to find sufficient capital, which

g The previous INB by five ministries (Agriculture, Nature Management and Fisheries; Health, Welfare and Sport; Education, Culture and Science; Economic Affairs; Housing, Spatial Planning and the Environment) dates from 2000 (TK 2000–2001, 27 428 no. 2).
h This vision addresses the following topics: opportunities (economic potential and opportunities for social applications), managing risks, ethical and legal issues, the research agenda, policy coordination, and public acceptance and communication. Based on a comprehensive and integrated approach to these topics, concrete policy actions were prepared and successfully implemented.
i HollandBio. De Biorevolutie Nederlandse innovaties voor een duurzame en gezonde samenleving.

means that commercial products are not marketed in the Netherlands and there is a risk of losing out to the international competition. A clear long-term government vision on biotechnology and an accompanying plan of action would increase the attractiveness of the Netherlands as a business location. Countries like Ireland and Belgium show how successful government policies for improving an innovation system can be. Numerous pharmaceutical companies have settled in Ireland, making the country the world's third largest exporter of pharmaceuticals.[456,457] The Irish biotechnology sector is growing rapidly and becoming increasingly important, in part thanks to links with the pharmaceutical industry.[458] With support from the Irish government, gene and cell therapy has become one of the pharmaceutical industry's main growth areas. In Belgium, the establishment in 1995 of VIB, the Flemish biotechnology research institute, has been an important driver of the growth of the biotechnology sector.[459,460] VIB does strategic research across the whole field of biotechnology. In stark contrast, the Netherlands Genomics Initiative (NGI), which brought universities, research institutes, companies and social stakeholders together, was discontinued in 2013 without any form of follow-up.

Fundamental research remains essential for innovation

Research funding for university institutions is heavily geared to valorisation and collaboration with the business community, which can jeopardise the position of university institutions as independent scientific experts. Curiosity-driven fundamental scientific research remains essential to sustain the flow of new technologies and applications, as demonstrated by the development of CRISPR-Cas and mRNA vaccines. Without the ongoing funding of this type of research, the Netherlands risks falling behind and becoming dependent on technological development and patenting in other countries.

Stimulating research on socially accountable biotechnological innovation

Given the divers views on the desirability of biotechnological developments and their responsible use, it is most important to stimulate research into the ethical, legal and social aspects (ELSA) and risks of biotechnology. Research from the perspective of 'responsible, research and innovation' (RRI) should also be encouraged.[j] An RRI approach not only explores ELSA from an outsider's perspective, but researchers from the social sciences and humanities work closely with scientists and technologists on biotechnology right from the outset. This approach not only investigates how biotechnology can be channelled in the right direction, but also critically examines the goals being pursued with biotechnology (and whether biotechnology in fact can deliver the best solutions) and what is needed to achieve these goals and to successfully embed applications in society. Stakeholder (and citizen) involvement is therefore essential. The way in which this approach has been used in the large-scale and long-term nanotechnology research programmes NanoNed and its successor NanoNextNL can provide inspiration.

Ethical principles underlying policy are indispensable

As we have stressed a number of times in this Trend Analysis, biotechnology can offer opportunities to take on societal challenges and strengthen the Dutch economy. An important ethical principle is that everyone should share in the benefits of scientific progress. At the same time, biotechnology raises complex ethical dilemmas and certain applications are not without risks to human health and the environment. What for one person may be desirable – or a question of individual autonomy – is unacceptable for another. Consider for instance, the use of germline gene editing and xenotransplantation. And where one person considers certain risks to be acceptable in the light of the benefits to society, another demands that risks must always be negligible. In such situations there are different, often conflicting, values at stake. Choices concerning

j Inspired by the international discourse on 'responsible research and innovation' (RRI).

the facilitation of biotechnological development are therefore ethical choices, which means that clear ethical principles are indispensable for a long-term vision. It is crucial that the government investigates which goals and associated applications can count on broad public and political support and which ones should be rejected.

Owning intellectual property rights is essential

The CRISPR-Cas patent landscape is unclear and complex. The commercial interests are big, and Europe and the Netherlands have little say in the matter. The patent situation that has developed is detrimental to Dutch companies and institutions because it can be a barrier to the use of gene editing by SMEs and for smaller applications. It would be helpful if Dutch organisations themselves could acquire a stronger patent position by researching other Cas proteins and CRISPR systems. Given the ground already lost to China and the US, this would require a financial injection for research. Patent constraints are currently experienced mainly in agriculture, but will probably become manifest in other areas as well.

Data protection versus open science

Exchanging data is essential for science and technological development. However, personal privacy must be guaranteed and the protection of intellectual property rights sometimes imposes restriction on the free exchange of research data and materials. Dutch researchers face dilemmas about how to deal with the various requirements concerning genetic, biometric and health data. The Dutch government is a staunch proponent of open science with free exchange and transparency of data, but valorisation of academic research, and with it the protection of intellectual property rights and of data on vulnerable patients, are also paramount. The EU and Dutch privacy legislation can be very restrictive for medical research and the exchange of data, both between Dutch institutions and internationally. European scientific academies have also sounded the alarm on this issue. What is needed is a single European data space and guidelines on how to reconcile the dilemma between open science and the protection of intellectual property rights. In 2022, the European Commission presented a proposal for establishing a European Health Data Space (EHDS) for medical data.

International cooperation between knowledge institutes is important for knowledge development and innovation, but the changing geopolitical situation, incidents of unwanted knowledge transfer and the influencing of research increase the complexity of cooperation. At the end of 2022 the Advisory Council for Science, Technology and Innovation (AWTI) made a number of recommendations on knowledge security and how to improve it.[461] According to the AWTI, knowledge security is the responsibility of government, in cooperation with the institutes.

Ensuring personal privacy

Genetic data are important for identifying the causes of diseases, developing new therapies and improving existing therapies, but they are also of increasing interest to the business community. There are internet companies that provide genome analysis services, (dubious) health advice and ancestry mapping for a fee, but it remains unclear what is done with the data obtained from their customers. Genetic data do not just concern the customer, but their direct families as well. The government faces the question of how to regulate these mostly foreign companies in the interests of ensuring the privacy of customers and preventing their genetic information from being freely traded.

Ensuring affordability and accessibility

New medical applications and medicines, such as gene and cell therapies and immunotherapy, hold great opportunities for healthcare, but these treatments are very costly. It is expected that the number of expensive treatments will continue to rise, and this in turn will require a review of the financing models. Alternative development mod-

els for gene therapies and drugs should receive government support. An issue that has to be addressed is equitable distribution. Expensive treatments must not become the preserve of wealthy patients. In addition, as the orphan medicinal products legislation appears to have the unwanted effect of driving up prices, there is a case for it to be reconsidered.

Modernisation of the legislation urgently needed

The legislation and licensing procedures are not keeping pace with developments. The EU debate about the revision of the GMO legislation in response to the new biotechnological techniques has been ongoing since 2002 and a decision is not expected before 2023. Meanwhile, countries outside the EU have revised their own legislation and trade conflicts and import problems are looming. The GMO legislation must therefore be modernised. The relevant EU directives and regulations are based on scientific insights from the last century and the Dutch GMO legislation is felt by scientists and businesses to be too complex. As biotechnology expands into other fields of practice, new stakeholders point out existing and new inconsistencies in the legislation and question the value of the GMO legislation for ensuring human and environmental safety

The EU regulations and licensing procedures for novel foods are too complicated or not suited to new products, such as industrially produced animal proteins and cultured meat. The regulatory framework for authorising medicines is not suited to assessing and approving personalised gene therapies. As the underlying genetic variability for a genetic disease can be great, therapies and medicinal products are geared specifically to a very small number of people – sometimes even individual patients. The authorisation procedure, which is designed to evaluate each individual products, is therefore unwieldy when applied to these treatments and therapies. The rapid pace of developments demands a more proactive response from the risk assessment agencies, which should align their assessment methods with the development of new applications.

National and international regulation of biotechnology

Dutch biotechnology policy is regulated largely at the EU level and by international agreements. For future policy it is essential that the Dutch government decides what should be regulated at the national level and what at the EU level or internationally. Despite the international context in which biotechnological developments take place, the government should consider what it wants to regulate and at what level. The European Union emphasises the economic harmonisation aspects, but given the issues of desirability and duty of care that are at stake it is important that the government – quite apart from the legal possibilities and limitations – has a clear picture of what it wants to be regulated nationally and internationally, and why. In any case, the government should make optimal use of its national policy freedom and the EU subsidiarity principle. Not everything should necessarily be regulated at the EU or international levels in future.[462]

Communication, education and participation require constant attentiont

The public have the right to transparency on the possible advantages, disadvantages and dilemmas posed by biotechnological applications. Reliable public information is not only needed to help people make informed decisions, but also to protect them against dubious promises by providers of genetic risk profiles on the internet. In addition, the rapid pace of developments means that society has an increasingly weak grasp of the potentials and consequences of biotechnology. Given the potential social ramifications of such developments, information is of great significance. In the interests of democratic citizenship, people must have access to knowledge that will allow them to make up their own mind about what is desirable and what is not. Communication and education – for example in secondary education – is indispensable. Considering the range of different and sometimes conflicting views on the desirability or otherwise of biotechnological applications, and on the underlying values, it is crucial that the Dutch public – and NGOs – are involved in determining the desired direction of biotechnolo-

gy development. Dissenting views should be taken seriously. In this regard, the Dutch government has initiated valuable initiatives, such as the DNA dialogue, donor animal dialogue and the study of public perceptions and values concerning modern biotechnology. In the light of the rapid development of biotechnology and the highly polarised debates in the past (for instance on the introduction of genetically modified crops), continued attention should be given to the provision of meaningful information, education and participation. The new national centre for science communication can play a facilitating role in this.

Closing remarks

The increasingly rapid advances in biotechnology are leading to unexpected developments and applications. Some are unwanted or controversial, such as when in 2018 the Chinese researcher He Jankui announced that the first genetically modified babies had been born. Other applications have been equally unexpected, but urgently needed, such as the arrival of mRNA vaccines against COVID-19 and the successes of CAR-T cell therapy in treating various types of cancer.

From a global perspective, attention should be paid to the availability and accessibility of biotechnological innovations. Various biotechnological innovations can help to improve healthcare, for example. However, it is not inevitable that the countries that could benefit most will be able to take advantage of the possibilities. The inflationary effects of intellectual property rights can price low and middle income countries out of the market, whereas they are the countries where some infectious diseases and genetic disorders have major impacts on public health. Biotechnology can also be disruptive and have a major impact on the primary production sector if certain raw materials are suddenly no longer needed. Against this background, differences between countries may persist or even be exacerbated by biotechnology, posing a threat to achieving the SDGs.

The fact that developments can be sudden and have far-reaching consequences for society, and that biotechnology can be a disruptive technology, mean that politicians and policymakers have to move quickly to define the ethical and legal frameworks within which these developments may take place. The development of biotechnology is an international phenomenon and subject to complex dynamics. Many developments are taking place in China and the US, while regulation, steering mechanisms and incentives are largely determined in the EU and room for national governance is limited. All this makes international consultation vital. EU decision-making on biotechnology has been exceedingly slow in recent years, partly due to opposing viewpoints between member states. Neither should the international context be a reason for passivity, and it is important that the Netherlands plays an active role within the EU to put developments in biotechnology on the agenda. Given the importance of biotechnology and the speed at which it is developing, the national leeway that is available should be used to the maximum.

A decision to take no action is also a choice that has consequences. Big technology companies are increasingly active in the digital 'pharma and healthcare market'. The core activities of these companies are being combined with the rise of big data, the linking of genetic data to other information and the use of smart algorithms to make predictions. These companies are capable of developing successful new applications that meet people's needs, and in particular those of patients and the pharmaceutical industry.[463] Giving these developments, a free rein can be advantageous, but at the same time it will give these companies a position of power that may later be difficult to control. The government must find a balance between ensuring the freedom to develop potentially useful applications and preventing often large private corporations obtaining potentially undesirable dominance.
Biotechnology must not be something that happens to us. Society – with the govern-

ment taking the lead – must decide what direction it wants developments to take. What is needed now are a clear vision and choices based on that vision.

GLOSSARY

Big data
The rapid collection of large amounts of data with a high degree of complexity and/or diversity.

Biofoundry
A facility in which genetically modified organisms are constructed and tested on a large scale with the use of robotics.

Biosafety
The set of measures to ensure human and environmental safety during work with pathogenic or genetically modified microorganisms in laboratories, etc.

Biosecurity
The set of measures to prevent misuse of biotechnology, for example for terrorism or warfare.

Biotechnology
Biotechnology is the application of science and technology to living organisms, or to parts, products and models of living organisms, with the purpose of altering or characterising living or non-living materials for the production of knowledge, goods and services.

CAR-T cell therapy
Medical treatment in which T cells (immune cells) are taken from cancer patients and genetically modified. They receive a modified receptor that recognises the tumour cells (CAR), and are then returned to the patient.

Cellular agriculture
A bundle of technologies in which bacteria, yeasts or cells grown in bioreactors are used to produce nutrients or foods.

Chimera
Organisms that contain cells from different genotypes (for example from different individuals) of the same or different species, such as human-animal combinations.

CRISPR-Cas
CRISPR-Cas is a system for making site-specific modifications in the genome of an organism by various means, including introducing point mutations, removing genes or parts of genes, and inserting new genes or DNA fragments at specific locations in the genetic material.

Enabling technology
An enabling technology is a technology that facilitates or supports another technology.

Enhancement
'Improving' human beings without a strict medical need.

Epigenetics
The study of irreversible and partially heritable changes in gene expression that are not associated with changes in the base sequence of the DNA. Such changes in expression may be the result of environmental influences.

Gene drives
Gene drives ensure that the inheritance of genes does not proceed according to the normal 50% Mendelian division, but that more, or even all, offspring have a certain gene or

sequences. This leads to the rapid spread of the gene throughout the population. There are both natural and CRISPR-Cas-based constructed gene drives.

Gene editing (site-directed mutagenesis)
Making site-specific changes such as mutations, deletions and insertions in the genome.

Gene therapy
Gene therapy involves introducing genetic material (DNA or RNA) into the somatic cells of an individual and bringing it to expression to treat a disease.

Genetic modification
Genetic modification is altering the genetic material (DNA or RNA) of an organism in a way that is not possible by natural reproduction or by natural recombination.

Genotype
The genetic make-up of an organism, as recorded in its DNA.

Germline (genome) modification
The modification of genetic material in gametes (reproductive cells) or fertilised egg cells, after which all the cells of the embryo carry the modification, which can then be passed on to the following generations.

GMO
Genetically modified organism.

Informed consent
Carefully considered assent. A statement of voluntary permission to carry out a treatment, such as an extensive diagnostic intervention, operation or participation in a scientific study, having been fully informed of the value of the treatment and the risks involved.

Marker-assisted breeding or marker-assisted selection
A plant breeding technique which makes use of DNA sequences (marker sequences) that are known to be located near to the gene or section of genetic code associated with the desired trait. It can be used in the laboratory to select young plants that possess the marker sequence, and therefore also the desired trait, before the trait is expressed in the phenotype.

Novel foods
New foods and ingredients that have not previously been sold in the European Union (EU).

Organoids
Three-dimensional mini organs grown in the laboratory. They are grown from pluripotent stem cells and can be used to study the functioning of healthy and diseased organs, the effects of medications and the influence of genetic defects.

Pharmacogenetics
Pharmacogenetics is the study of genetic variation (variations in the DNA of a human or patient) that can influence the response to medicines and side-effects.

Phenotype
The observable characteristics or traits of an organism; the result of the genotype in combination with environmental factors.

Precision breeding
Gene editing in plants. This term was originally used for marker-assisted breeding, but is now more frequently used for gene editing in plants.

Sequencing
Sequencing is the process of determining the order of the bases (A, C, T/ U and G – adenine, cytosine, thymine/uracil and guanine) on the DNA or RNA which carries an organism's genetic information.

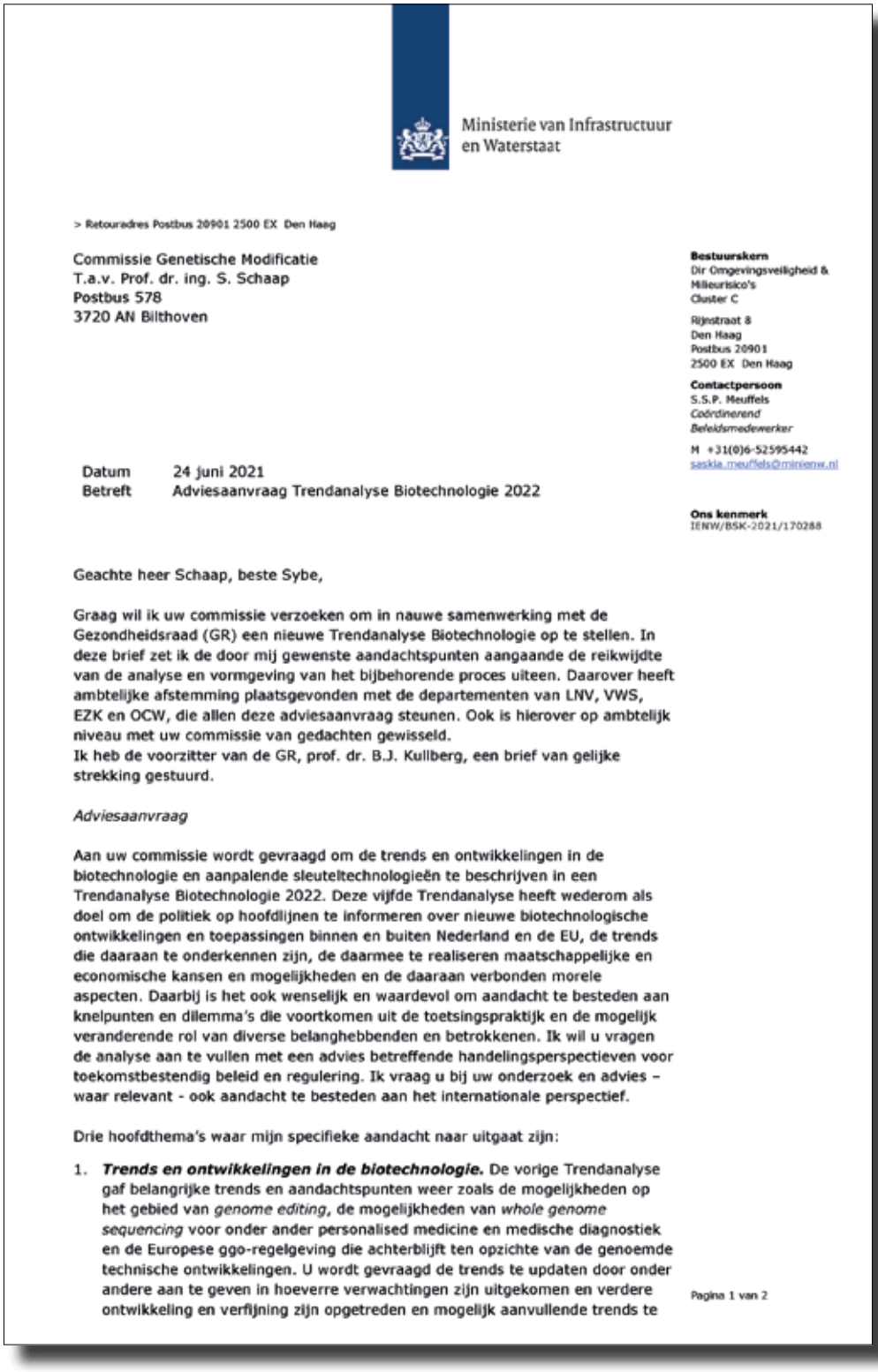
Xenobiology
Xenobiology is the investigation of the possibility of replacing natural building blocks of microorganisms and other organisms, such as nucleotides in the DNA and RNA and amino acids in proteins, with synthetic variants that do not occur naturally.

Xenobots
Living structures built of stem cells and designed using genetic algorithms.

Xenotransplantation
The transplantation of organs from one species to another species, for example from an animal to a human.

X-omics
X-omics is a collective term for various fields of research in cell biology and refers to the study of the whole: genomics maps the DNA code, *epigenomics* is the study of how genes are regulated without the DNA sequence being changed, *transcriptomics* studies the expression of genes in RNA, proteomics is the study of all proteins, and metabolomics is the study of all metabolic products.

APPENDIX A. REQUEST FOR ADVICE



Ministerie van Infrastructuur en Waterstaat

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Ons kenmerk
IENW/BSK-2021/170288

Datum 24 juni 2021
Betreft Adviesaanvraag Trendanalyse Biotechnologie 2022

Geachte heer Schaap, beste Sybe,

Graag wil ik uw commissie verzoeken om in nauwe samenwerking met de Gezondheidsraad (GR) een nieuwe Trendanalyse Biotechnologie op te stellen. In deze brief zet ik de door mij gewenste aandachtspunten aangaande de reikwijdte van de analyse en vormgeving van het bijbehorende proces uiteen. Daarover heeft ambtelijke afstemming plaatsgevonden met de departementen van LNV, VWS, EZK en OCW, die allen deze adviesaanvraag steunen. Ook is hierover op ambtelijk niveau met uw commissie van gedachten gewisseld.
Ik heb de voorzitter van de GR, prof. dr. B.J. Kullberg, een brief van gelijke strekking gestuurd.

Adviesaanvraag

Aan uw commissie wordt gevraagd om de trends en ontwikkelingen in de biotechnologie en aanpalende sleuteltechnologieën te beschrijven in een Trendanalyse Biotechnologie 2022. Deze vijfde Trendanalyse heeft wederom als doel om de politiek op hoofdlijnen te informeren over nieuwe biotechnologische ontwikkelingen en toepassingen binnen en buiten Nederland en de EU, de trends die daaraan te onderkennen zijn, de daarmee te realiseren maatschappelijke en economische kansen en mogelijkheden en de daaraan verbonden morele aspecten. Daarbij is het ook wenselijk en waardevol om aandacht te besteden aan knelpunten en dilemma's die voortkomen uit de toetsingspraktijk en de mogelijk veranderende rol van diverse belanghebbenden en betrokkenen. Ik wil u vragen de analyse aan te vullen met een advies betreffende handelingsperspectieven voor toekomstbestendig beleid en regulering. Ik vraag u bij uw onderzoek en advies – waar relevant - ook aandacht te besteden aan het internationale perspectief.

Drie hoofdthema's waar mijn specifieke aandacht naar uitgaat zijn:

1. ***Trends en ontwikkelingen in de biotechnologie.*** De vorige Trendanalyse gaf belangrijke trends en aandachtspunten weer zoals de mogelijkheden op het gebied van *genome editing*, de mogelijkheden van *whole genome sequencing* voor onder ander personalised medicine en medische diagnostiek en de Europese ggo-regelgeving die achterblijft ten opzichte van de genoemde technische ontwikkelingen. U wordt gevraagd de trends te updaten door onder andere aan te geven in hoeverre verwachtingen zijn uitgekomen en verdere ontwikkeling en verfijning zijn opgetreden en mogelijk aanvullende trends te

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identificeren. Daarnaast wordt u gevraagd om nieuwe trends of producten voortkomend uit de technologische ontwikkelingen of aan biotechnologie verwante ontwikkelingen (denk bv aan kunstmatige intelligentie) weer te geven en de mogelijke spanningen die deze (technologische) trends oproepen ten aanzien van regulering en maatschappelijke acceptatie.

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2. ***Maatschappelijke opgaven en economische aspecten.*** Biotechnologie is een sleuteltechnologie, een zogenoemde enabling technology, die het mogelijk maakt om maatschappelijke uitdagingen aan te pakken. Dit heeft ook een grote economische waarde. Graag zie ik in de trendanalyse aandacht voor de bijdrage van biotechnologische toepassingen aan de grote maatschappelijke opgaven en uitdagingen van deze tijd op medisch, industrieel en agrarisch vlak. En hoe dit in relatie staat met het waarborgen van de veiligheid voor mens en milieu. Er kan bijvoorbeeld gedacht worden aan de ontwikkeling van vaccins voor de bestrijding van de COVID-19 pandemie en het inzetten van deze technologie voor bestrijding van andere ziektes en aandoeningen, of de inzet van biotechnologische toepassingen voor het realiseren van de *UN Sustainable Development Goals* en de doelstellingen uit de Green Deal.

3. ***Draagvlak maatschappij.*** Er zijn verscheidene onderzoeken uitgevoerd naar de uiteenlopende opvattingen van burgers over biotechnologie en haar toepassingen, bijvoorbeeld uw onderzoek uit 2019. Kennis over maatschappelijke waarden en de publieke perceptie is van belang om zicht te hebben op randvoorwaarden waaronder ontwikkelingen aanvaardbaar kunnen zijn. Recente ontwikkelingen, zoals bijvoorbeeld de COVID-19 pandemie, de bijdrage van biotechnologie aan de eiwittransitie of de onlangs gepubliceerde studie van de Europese Commissie aangaande de status van Nieuwe Genomische Technieken kunnen hierbij interessante thema's vormen.

Proces

U wordt gevraagd het initiatief te nemen om het proces te organiseren om te komen tot de oplevering van een nieuwe Trendanalyse medio 2022. In het bijzonder vraag ik u nauw samen te werken met de Gezondheidsraad. Ik vraag de voorzitter van de Gezondheidsraad, eveneens per brief, om hun medewerking bij de Trendanalyse. Uiteraard staat het u vrij om ook andere adviesorganen en wetenschappelijke instituten te betrekken. Daarnaast acht ik het van belang dat op enigerlei wijze belanghebbende organisaties en burgers worden betrokken om de impact van de biotechnologische ontwikkelingen op de samenleving te kunnen beoordelen. Indien IenW ondersteuning kan bieden bij de vormgeving en realisatie hiervan, dan bied ik graag medewerking vanuit mijn departement aan.

Via deze weg hoop ik u voldoende geïnformeerd te hebben en ik zie uit naar de Trendanalyse Biotechnologie 2022.

Hoogachtend,

DE MINISTER VAN INFRASTRUCTUUR EN WATERSTAAT,

drs. C. van Nieuwenhuizen Wijbenga

APPENDIX B. MEMBERS OF THE PROJECT COMMITTEE

The Biotechnology trend Analysis was prepared by a joint project committee of COGEM and the Health Council of the Netherlands consisting of the following members:

- Prof Marianne de Visser (Chair)
- Prof Martina Cornel (Community Genetics & Public Health Genomics, Amsterdam UMC)
- Prof Susana Chuva de Sousa Lopes, (Anatomy & Embryology, LUMC)
- Prof Ellen Moors (Copernicus Institute of Sustainable Development, Utrecht University)
- Prof Jack Pronk (Industrial Microbiology, Delft University of Technology)
- Prof Paul Struik (Centre for Crop Systems Analysis, Wageningen UR)

Observer:

- Saskia Meuffels MSc (Ministry of Infrastructure and Water Management)

The project committee was supported by a writing team consisting of:

- Harrie van Dijk PhD (Health Council of the Netherlands)
- Virgil Rerimassie LLM MSc (Health Council of the Netherlands)
- Frank van der Wilk PhD (COGEM)

APPENDIX C. CONSULTED STAKEHOLDERS AND EXPERTS

Fifty organisations were approached, of which eight responded with substantive replies (VIG and FIDIN made a joint response):

- Association BVF Platform (Dutch Biological Safety Officers Platform)
- Dierenbescherming (Dutch Society for the Protection of Animals)
- HollandBIO
- Natuur en Milieufederatie Noord-Holland (North Holland Nature and Environment Federation)
- Nederlandse Biotechnologie Vereniging (Dutch Biotechnology Association)
- Plantum NL (Dutch industry association for the seeds and young plants sector)
- Platform Bioeconomie
- VIG (Dutch society for innovative medicines) and FIDIN (Dutch industry association for veterinary pharmacy)

Consultees:

• Prof Britta van Beers	VU Amsterdam
• Prof Roel Bovenberg	University of Groningen
• Bernice Bovenkerk PhD	Wageningen UR
• Prof Martien Groenen	Wageningen UR
• Prof Henk-Jan Guchelaar	Leiden University Medical Center (LUMC)
• Timen van Haaster MSc	HollandBIO
• Prof Björn Heindryckx	University of Ghent
• Niels Louwaars PhD	PlantumNL
• Prof Patricia Osseweijer	Delft University of Technology
• Prof Marcel Reinders	Delft University of Technology
• Prof Rogier Sanders	Amsterdam UMC
• Monique van Vegchel MSc	PlantumNL
• Daniël Warmerdam PhD	ZonMw

APPENDIX D. OECD DEFINITION OF BIOTECHNOLOGY

The OECD developed both a single definition and a list-based definition of biotechnology. This (indicative, not exhaustive) list-based definition serves as an interpretative guideline to the single definition.

The single definition is:
The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.

The (indicative, not exhaustive) list-based definition of biotechnology techniques is:

- **DNA/RNA:** Genomics, pharmacogenomics, gene probes, genetic engineering, DNA/RNA sequencing/synthesis/amplification, gene expression profiling, and use of antisense technology.
- **Proteins and other molecules:** Sequencing/synthesis/engineering of proteins and peptides (including large molecule hormones); improved delivery methods for large molecule drugs; proteomics, protein isolation and purification, signaling, identification of cell receptors.
- **Cell and tissue culture and engineering:** Cell/tissue culture, tissue engineering (including tissue scaffolds and biomedical engineering), cellular fusion, vaccine/immune stimulants, embryo manipulation.
- **Process biotechnology techniques:** Fermentation using bioreactors, bioprocessing, bioleaching, biopulping, biobleaching, biodesulphurisation, bioremediation, biofiltration and phytoremediation.
- **Gene and RNA vectors:** Gene therapy, viral vectors.
- **Bioinformatics:** Construction of databases on genomes, protein sequences; modelling complex. biological processes, including systems biology.
- **Nanobiotechnology:** Applies the tools and processes of nano/microfabrication to build devices for studying biosystems and applications in drug delivery, diagnostics, etc.

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Colofon
This is a joint publication of the Netherlands Commission on Genetic Modification (COGEM) and the Health Council of the Netherlands, supported by the Netherlands Scientific Council for Government Policy (WRR).

March 2023

Design: Avant la lettre, Utrecht
Infographics: Linsen Communicatie
Translation: Derek Middleton, Text Compilation · Editing · Translation