TREND ANALYSIS BIOTECHNOLOGY 2016

SUMMARY

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COMMISSIE COGEM GENETISCHE MODIFICATIE

Scientific advances in biotechnology have taken off in recent years. New techniques and applications develop in rapid succession, and more and more biotechnology products reach the market. Biotechnology is also becoming tightly integrated into other sectors and fields of research. It has become a mainstream technology across the whole range of life sciences. These developments offer new opportunities and avenues for innovation, the economy, food production, health care, and other areas. These developments, however, also have a major impact on policy, legislation and how we think about biotechnology. They raise ethical questions and societal dilemmas about admissibility, regulation, ownership and how to deal with international differences and approaches.

It would be impossible to cover all the developments in biotechnology in this trend analysis. By necessity therefore this analysis is restricted to eight trends which are typical of biotechnology and the major dilemmas and questions for society which they bring to the policy and political arenas.

The first two trends - Next Generation Sequencing and CRISPR-Cas – constitute the driving force behind recent developments in biotechnology. They provide a strong impetus for the other trends described here: the development of specific medicines, tools and therapies tailored to individuals or diseases (e.g. personalised medicine, gene therapy, 3D bioprinting), new techniques in agriculture (e.g. RNAi) and interventions in the ecosystem (e.g. genetically modified insects). Eventually it may even be possible to design organisms and fashion nature as we see fit (i.e. synthetic biology).

1. NEXT GENERATION SEQUENCING (NGS): THE NEW STANDARD

Sequencing is the process of determining the base sequence in the genetic material (DNA or RNA) of micro-organisms, plants, animals and humans. The speed and scale at which DNA sequences can be determinded has increased exponentially in recent years, while the cost has dropped dramatically. Sequencing is now widely used in medicine in genetic diagnostics and will increasingly be used for screening as well. This is why it is very important for professionals and the public alike to be made more generally aware of the facts about genetics, as well as its benefits and limitations. The discussion about NGS is mainly about the interpretation, communication, ownership, use and storage of the large amounts of data that NGS techniques generate.
The increased opportunities for genome sequencing raise questions about the limits between generating and sharing data to support knowledge acquisition and possible medical applications on the one hand, and privacy, intellectual property rights and costs, on the other hand. Because the nature and the impact of the data to be obtained cannot be ascertained in advance (like incidental findings) the classical method for 'informed consent' is no longer adequate. In addition, the information obtained often goes beyond just the individual concerned. How should we for instance handle the rights of (underage) family members not to know (or rather, to be informed of) their genetic risk factors?
These considerations may make it necessary to review the present legislation and regulations, such as the Special Medical Procedures Act (WBMV), privacy legislation, and patent legislation, etc.

2. CRISPR-CA S9: DOCTORING WITH GENETICS

CRISPR-Cas9 is a revolutionary new, cheap and simple technique by which the genes of micro-organisms, animal, plants and humans can be very precisely modified. This opens doors to new types of research, products and treatments.

The ability to make specific changes in the genome, however, also blurs the distinction between products of genetic modification, classical mutagenesis and 'natural' products or organisms. This undermines the legal basis of the EU legislation on genetically modified organisms (GMOs) which is based on this distinction.
CRISPR-Cas9 joins the growing list of 'novel techniques' where it becomes unclear whether the products fall under the EU GMO legislation or not, and if so, whether they should be exempted. Clarification from the European Commission about these techniques has not been forthcoming so far. The speed at which CRISPR-Cas9 has spread in the scientific community, the breadth of the areas in which this technique is applied - not only in the agro sector but in the medical sector too - and the vast opportunities and economic interests at stake in this technology make it extremely urgent that decisions are made.
The new opportunities presented by this CRISPR-Cas9 technique also raise ethical questions about the admissibility of certain applications, including germline modification, the genetic modification of monkeys to serve as a disease model for humans, and interventions in the ecosystem to deliberately exterminate a species. These ethical questions also urgently require political and policy decisions.

3. PERSONALISED MEDICINE: CUSTOMISED PREVENTION, DIAGNOSTICS AND THERAPEUTIC TREATMENTS

Personalised medicine is about the use of preventive and other treatments that are tailored to the physical (genetic) disposition, lifestyle and environment of the individual patient or a specific group of patients. *Next generation sequencing* gave a new impetus to the possibilities of and the discussion on *personalised medicine*. There are high hopes for applications in the area of cancer treatment based on the genetic characteristics of tumours, as well as in other areas. Although personalised medicine offers clear advantages, such as customised therapies with better results and fewer side effects, it challenges the present healthcare system in the Netherlands and elsewhere by raising such questions as: how can the opportunities presented by personalised medicine be effectively implemented without making concessions to careful research into safety and efficacy (i.e. smaller groups of patients) or transgressing privacy? How can we ensure that healthcare remains affordable as the number of 'personal' medications grows, given that their narrow field of application makes them very expensive? Various authorities are investigating whether reviewing admittance procedures and changing the approach to classical clinical studies could offer solution to the demand for a more individual approach in healthcare.

4. GENE THERAPY: PROMISE FULFILLED

In gene therapy, genetic material (DNA or RNA) is introduced into the living cells of an individual and expression is induced to treat a disease. The number of clinical studies has increased in recent years, promising results have been obtained in clinical studies in cancer, immune system and blood diseases, and elsewhere, and the first gene therapy products have been brought onto the market. The nature of gene therapies and the risks associated with them vary widely. Some new methods and techniques, including the use of replicating viruses to combat tumours, harbour potential risks which require additional measures, while other types of gene therapies carry little or no risk. Under the present Dutch legislation all gene therapy treatments are subject to the same licensing procedures and safety assessments. A shortening of the licensing procedures for gene therapy treatments which constitute no risk to third parties or the environment could provide an important impetus to support innovation in the Netherlands and to capitalise on the potential offered by gene therapy. Other than

this, the same problem occurs with gene therapy as with personalised medicine, i.e. small patient numbers and ensuring that healthcare remains affordable.

5. NEW TECHNIQUES: SILENCING GENES WITH RNA

While the legal status of various new plant breeding techniques have been the subject of discussion in the EU for many years now with no decision taken, new techniques are continually being developed. One of these developments is the use of RNAi technology. RNA interference (RNAi) is a process in the cell regulating gene expression or combating viruses. RNAi makes it possible to block gene expression without changing the DNA. RNAi has become an important research tool to study the function of genes and now also has practical applications in the development of therapeutic drugs, as well as in agriculture.
The first insect-resistant GM crop based on RNAi technology is already on the market. RNAi technology can also be used in conventional crops in the form of RNA sprays to control pests or influence plant characteristics. Weed resistance to herbicides can be overcome by adding RNAi molecules to the herbicide. The use of RNAi in the form of sprays or herbicide additives does not appear to be covered by the EU GMO legislation. It is possible that residual genetic material (such as RNA) associated with genetic modification may be present on food and other products. Even if the presence of this material constitutes no risk to humans or the environment, this could prompt a public debate on the principle of freedom of choice.

6. GENETICALLY MODIFIED INSECTS: INTERVENTIONS IN THE ECOSYSTEM

Corporations and scientists are investigating whether GM insects could be used to control infectious diseases or curb pests in agriculture. Several countries around the world have already conducted field trials. These developments offer opportunities for public health and possibilities to curtail the use of insecticides, but they also face objections from opponents in relation to safety, possible impact on ecosystems and biodiversity, or economic damage.
A number of infectious diseases have proliferated strongly in recent years, spreading to other countries and regions. Many of these viruses, e.g. zika, chikungunya and dengue, are insect-borne. Field trials with GM mosquitos to combat dengue have already been carried out abroad and it is expected that such field experiments will also be carried out in the Netherlands Antilles (St. Eustatius and Saba). The situation concerning the legislation and licences for such experiments in the Caribbean region of the Kingdom of the Netherlands is unclear. The Dutch Decree on Genetically Modified Organisms does not apply to the BES islands[1] and The Public Housing, Spatial Planning and Environmental Protection Act BES (Wet VROM BES) includes nothing about GMOs. The use of GM insects to control infectious diseases requires that the Dutch government takes the necessary steps to safeguard careful risk assessment, proper risk management and provide a means for stakeholders' and citizens' involvement.

7. 3D BIOPRINTING: TAILOR-MADE BODY PARTS

3D bioprinting is a multidisciplinary field applying technology, biology, chemistry and mathematics to generate one or more types of living tissue, structures or biomedical implants with the aid of 3D printing techniques. In the past, the use of 3D printing in the medical

1 The Dutch islands of Bonaire, St. Eustatius and Saba in the Caribbean sea.

sector lay mainly in the construction of custom-made implants and models, but is moving towards implants covered with living cells and biocompatible implants containing living cells. Work is being done, for example, on printing soft tissue (e.g. skin, cartilage) and bone tissue for reconstructive surgery. 3D bioprinting has, until now, been mainly used in research and pre-clinical testing, e.g., for making disease models and for testing medicines or cosmetics. Especially European companies are interested in the latter because animal testing for cosmetics is no longer permitted.
The field is still in its infancy and faces major technological challenges. A special facility has been built in the Netherlands and a specialist training course set up. 3D bioprinting will, in the future, raise questions about legislation, ownership and liability. Are the products produced in this way medical products or implants? How and under what legislation will the safety assessments be carried out? And where does the liability lie? To whom do the products belong when they have been made from donor cells or when the patient's own body cells are used? There are also the ethical and societal matters of the admissibility of this technology and its meaning in terms of how we view the human body.

8. SYNTHETIC BIOLOGY: FROM CLOTHING TO VACCINES

Synthetic biology is the collective term for the design, redesign and construction of new biological molecules, cell components and systems, for the purpose of incorporating non-natural systems into natural systems for useful applications. Synthetic biology is used, for example, for the production of industrial and other raw materials and fine chemicals, for the development of systems for drug delivery or for synthesizing vaccines. It is a multidisciplinary field which focuses on making genetic changes to existing cells or organisms (the top-down approach) on the one hand, and the design and construction of new cells (the bottom-up approach) on the other hand.
The term 'synthetic biology' covers a large number of widely differing applications and techniques and it is difficult to provide a conclusive definition. The current applications may be considered as a form of genetic modification, but this will change in the future. Given the breadth of applications and the speed of developments, instituting legislation and policy specifically for synthetic biology would be both undesirable and virtually impossible. It is important to be able to respond flexibly to new developments. This requires a different method of governance in which, instead of formulating direct legislation, consideration is given, on a case by case basis, to whether legislation or regulation is necessary and what existing frameworks are available for this. National and international cooperation and exchange of information between stakeholders is important to value the potential of the technology while at the same time addressing issues related to biosafety, biosecurity, intellectual property, sustainability and public acceptance.

Points to consider

The trends indicate that biotechnology offers promising opportunities and is of great economic importance to the Netherlands. At the same time, however the rapidly advancing technical possibilities raise questions and present dilemmas. Some of these questions apply to all these trends and are gaining in urgency due to the spread and assimilation of biotechnology into a whole range of applications:

Ethical questions: new biotechnological opportunities such as personalised medicine, gene therapy, and next generation sequencing in diagnostics and screening raise ethical questions about privacy, ownership, right on self-determination, autonomy, and questions about the cost to society versus individual benefits, and the boundary between treating diseases and enhancement (i.e. changes for which there is no direct medical reason). The most

obvious example is germline (i.e. genome) modification. Its clinical use is banned almost everywhere in the world at the moment, but now that it appears to becoming technically possible to prevent genetic disorders from being passed on to offspring in this way, this ban will be open to question. This makes it necessary to discuss desirability and ethical admissibility, as well as potential application areas. Establishing ethical boundaries and weighing the values and interests of the various stakeholders is primarily a political task.

Safeguarding the public knowledge position: The government is faced with the challenge of exploiting the opportunities offered by the new technologies while at the same time upholding safety while remaining cognizant of the ethical and societal aspects involved. The independence of publicly funded research, however, is at odds with the growing levels of public-private cooperation. It is important to have access to in-house expertise and scientific knowledge and data from sources other than just national and international companies. Only then can the government be recognized as an autonomous negotiating partner that can play a constructive role, e.g., in drawing up safety standards and test methods.

Intellectual property: the ever increasing speed with which large volumes of data are becoming available on biological material, DNA and cellular mechanisms has intensified the discussion on intellectual property. The rise of patent law in plant breeding has been at the expense of plant breeders' rights and is closely linked to the arrival of biotechnology in this sector. By gathering and analysing patient genetic data and material more insight has been gained into the origins and course of diseases and new, more targeted diagnostics and treatments have been developed. This also raises questions about protecting the privacy of patients and possibly family members, and whether ownership rights are based on the data or the biological materials. This could, for example, weaken the willingness to contribute to biobanks.

Legislation and regulations: the EU GMO legislation is based on the distinction between genetic modification and non-genetic modification, known as conventional techniques or applications. Genetic modification and its products are covered by comprehensive legislation, regulations and safety assessments while the products of conventional and other biotechnological or exempt techniques are not subject to these same rules. In view of the high costs involved in safety assessment studies, there are major consequences if an application is subject to GMO legislation. Only very large companies can afford such high costs and therefore avoiding the GMO legislation has become a 'driver' for innovation.
The scientific dividing line between genetic modification and other biotechnology techniques, however, has become increasingly blurred, such that there is often little or no distinguishable difference between the products themselves and 'natural' products. This undermines the legal basis for the EU GMO legislation and invalidates the approach used thus far - in which each technique is assessed to determine whether the products are subject to the GMO legislation. The EU legislation is in need of reform to provide citizens, consumers and companies with clarity. It would seem to be unavoidable that more emphasis will have to be placed on an integrated approach, focused more on the consequences of introducing a product than on the techniques used to create the product.
The focus of the present GMO legislation on just the safety aspect is also not helpful in settling the debate on genetic modification, because this ignores the need for a risk-benefit analysis. An analysis in which the risks of biotechnology applications are weighed against the benefits or value would more closely meet the wishes of patients and consumers and the pursuit of a single assessment framework for the safety of a range of applications and technologies.

The international context: the possible consequences of technological and biotechnological developments in terms of Dutch legislation, policy or society, must be viewed in the international context. Many things can be regulated at national level, but it will always be

necessary to take the international context into account. Legislation, which is unfavourable, can lead businesses to relocate their research & development (R&D) to another country, international differences in the legal definition of a GMO are important when concluding trade treaties such as the Transatlantic Trade and Investment Partnership (TTIP) or when importing and labelling GMOs, and patients can go abroad for medical treatment. The international context is inevitable but, at the same time, does not have to dictate terms to the Netherlands. In the national context it will be necessary to think about what political and policy course the Netherlands wishes to pursue, because making no decision means that the international context will be leading.

Political bodies therefore need to make clear decisions about how to deal with the ethical aspects, the Netherlands public knowledge position, intellectual property and the fundamental principles under legislation and regulations in force.