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A conceptual framework for the ethics of synthetic biology

Mette Ebbesen's *research interests are ethical assessment of biomedicine, molecular biology and nanotechnology. Having a background in molecular biology, ethics, as well as philosophy she performs this ethical assessment from an interdisciplinary approach. She is director and associate professor at Center for Bioethics and Nanoethics at Aarhus University, Denmark and employed at the project iPSYCH.*

Svend Andersen *is professor of ethics and philosophy of religion in the Institute of Culture and Society, University of Aarhus. He is the founder of the Centre for Bioethics and Nanoethics in that university and a former vice chairman of the Danish Council of Ethics. His research covers a wide area in ethics, both theoretical and applied, and has issued in a number of articles in bioethics.*

Finn Skou Pedersen *is professor of molecular retrovirology at the Department of Molecular Biology and Genetics at the Faculty of Science and Technology of Aarhus University. He received his basic education in biochemistry and biology at Aarhus University and the University of Copenhagen and his current interest in viral replication and gene transfer goes back to a post-doctoral period at Harvard University.*

Abstract

Synthetic biology is an emerging and promising interdisciplinary field of research. Synthetic biology deals with the design of new biological units, devices to build artificial life, or the redesign of existing natural biological systems with possible applications within many diverse areas such as energy, environment, food, and medicine. In this way, synthetic biology may help solve some of the challenges the world is facing in the 21st century. However, it is of

the utmost importance to consider, at an early stage, the ethics of new emerging technologies such as synthetic biology and nanoscience. In this article, we argue that analogues can be drawn between nanoscience and synthetic biology. Firstly, we show that the ethical principles of beneficence, nonmaleficence, respect for autonomy, and justice are important for nanoscience, and we reveal that these principles are part of the bioethical theory of the American ethicists, Tom L. Beauchamp and James F. Childress. Secondly, we argue that analogues can be drawn between the ethical problems of nanoscience and those of synthetic biology, and thirdly, we conclude that the theory of Beauchamp and Childress can also be used to analyze ethical issues of synthetic biology. In this article we use an oncolytic poxvirus for delivery and expression of transgenes in tumors as an example to illustrate how to use Beauchamp and Childress' theory to analyse ethical problems of synthetic biology.

Keywords # 1 Synthetic biology, # 2 Ethical assessment, # 3 Ethical framework, # 4 the four principles of biomedical ethics.

Introduction

With its visions of designing and constructing new biological parts, devices and systems, as well as re-designing existing, natural biological systems for useful purposes such as pharmaceuticals and energy, synthetic biology has been declared one of tomorrow's emerging fields (www.syntheticbiology.org). Researchers within the disciplines of physics, chemistry, molecular biology, biology, biological modeling, engineering, and information technology interact in a truly interdisciplinary setting across traditional disciplinary boundaries to develop the fundamental concepts of synthetic biology. Scientists conduct basic research such as the synthesis of DNA sequences as bricks (so-called Biobricks) designed to fit into cells, they explore the possibility of combining DNA sequences, genes, cells, and cell parts with electrodes, metal surfaces, and nanofibers. The area of synthetic biology has many potential applications with societal impact, at present the applied activities within synthetic biology are mainly focused on energy, cleaning of chemical pollution, and the development of new pharmaceuticals with fewer side effects.

Synthetic biology focuses on the design and construction of new biological systems which cannot be found in nature. It is a field of

science and engineering that currently includes a number of subfields such as for example:

- "Engineering DNA-based biological circuits, including but not limited to standardized biological parts;
- Defining a minimal genome/minimal life (top-down approach);
- Constructing so-called protocells, i.e. living cells, from scratch (bottom-up approach);
- Creating orthogonal biological systems based on a biochemistry not found in nature; and
- Gene and genome analysis" (Schmidt, 2009).

A concrete example of research into synthetic biology is the idea to use a bottom-up approach to design a protocell called 'The Los Alamos Bug' from non-living organic and inorganic materials by Rasmussen et al. (2003, 2004). The vision is to build a protocell consisting of three entities: Genetic material, a metabolic system, and a nano-container. The metabolic system envisioned to be implemented is supposed to form the components of the container which self-assemble into an aggregate in water, and this aggregate contains the metabolism and the genes. Furthermore, it catalyzes gene self-replication and metabolic processes. The design of this protocell is much simpler than biological cells and it allows the design of containers of few nanometers in diameter (much smaller than existing cells) (http://www.istpace.org/Web_Final_Report/WP_1_artificial_cells_conception/the_los_alamos_bug/index.html). To illustrate that the design of the protocell is simpler than biological cells, it can be mentioned that instead of RNA, Rasmussen et al. (2003, 2004) seek to use non-biological molecules such as peptide nucleic acids (PNAs), since these are simpler to couple with the lipid layer and easier to synthesize than RNA. Also, instead of biological ribozymes, they plan to use simple short oligomers which can self-replicate without enzymes by a ligation mechanism. Rasmussen et al. (2004) originally used computer simulations to predict the life cycle of the protocell. By now experiments in the laboratory have demonstrated the light-driven metabolism to synthesize lipids. However, the other parts of the life cycle have not yet been demonstrated in the laboratory (Rasmussen et al., 2004).

Whereas synthetic biology in general offers many visions, it also offers perils such as the accidental release of redesigned organisms or the re-engineering of microorganisms or living systems with the purpose to harm by terrorist organizations (Serrano, 2007). According to the Austrian biosafety scientist Markus Schmidt, "Synthetic biology is developing rapidly as a new branch of biotechnology, with many anticipated benefits and a high impact on society. As a result, the societal aspects of this discipline, as well as its possible risks, are becoming increasingly prominent. It is therefore crucial that the societal dimensions develop side by side with the field" (Schmidt et al., 2009). Helge Torgersen has studied the societal dimensions of synthetic biology and suggests comparing the introduction of synthetic biology with the introduction of nanotechnology in the early 1990s. Both disciplines "belong to the set of converging technologies … as they are novel, assumed to become key enabling technologies and to provoke concerns regarding public acceptance" (Torgersen, 2009).

Along the same lines, we argue in this article that analogues can be drawn between ethical issues of synthetic biology and ethical issues of nanoscience, biotechnology, biology, and healthcare, which have been analyzed for years in several ethical studies. From these reflections a knowledge base has been developed which can serve as the foundation for ethical analyses of synthetic biology. We argue that basic ethical principles as presented in the bioethical theory of principles of the American ethicists, Tom L. Beauchamp and James F. Childress, constitute a promising framework for ethical reflections on synthetic biology (Ebbesen et al., 2006; Beauchamp & Childress, 2013). However, it is still being debated what approach to use in the analysis of ethical issues of synthetic biology. The British professor of the sociology of scientific knowledge Steven Yearly (2009) doubts that Beauchamp and Childress' approach is a profound way to analyze the ethics of synthetic biology. However, as we will see later in this article, we find that he declines the use of Beauchamp and Childress' approach by citing an article that misinterprets their theory significantly in philosophical terms.

Several researchers agree that the ethics of synthetic biology does not need a quite new ethical methodology. Rather, as we shall argue below, existing ethical methodologies need to be used in new technological contexts (Parens et al., 2008; Schmidt et al.,

2008). Furthermore, Ainsley Newson, a senior lecturer in biomedical ethics at the University of Bristol, points out that founding the discipline of ethical analysis of synthetic biology offers the opportunity of shaping this discipline as an interdisciplinary field, where ethicists learn from law and social science and vice versa. According to Newson, this would provide a rich reflection on synthetic biology (Newson, 2011). We find this an interesting perception, and suggest that this interdisciplinary approach should be even broader, including researchers from science and health science as well, since synthetic biology includes these fields. This would provide ethicists the opportunity to be updated with news about science in the field and it would provide scientists the opportunity to gain insight into ethical reflections.

We begin with a discussion of the ethics of nanoscience and subsequently draw analogues to that of synthetic biology. First, we present some ethical aspects of nanoscience, and by showing that these ethical issues resemble ethical issues of biotechnology, biology, and healthcare, we argue that ethical issues of nanoscience are not new and unique. Next, we examine which basic ethical principles are at stake in nanoscience and demonstrate that these principles are part of the bioethical theory of Beauchamp and Childress (Ebbesen et al., 2006). Then, we present some predicted ethical issues of synthetic biology and illustrate that these are similar to ethical issues of biotechnology, biology, and healthcare. As with nanoscience, we examine which basic ethical principles play a role within synthetic biology and show that these are included in Beauchamp and Childress' theory, which therefore can be used to analyze ethical issues of synthetic biology. Lastly, we present the bioethical theory of Beauchamp and Childress and show how it can deal with the ethical problems of synthetic biology by using an oncolytic poxvirus for delivery and expression of transgenes in cancer cells as a model system. The focus of this article is the practical ethical issues of nanoscience and synthetic biology, rather than the, admittedly, important foundational ethical issues of these fields, such as the relation between human and nature, the relationship between human and artificial life, and the moral status of designed artificial organisms.

Ethics of nanoscience

Fifteen years ago, the nanoscience era started, research into nanoscience advanced rapidly, and the field attracted much visibility and funding (http://www.nano.gov/about-nni/what). Researchers within physics, chemistry, biology, molecular biology, and medicine took a more interdisciplinary approach and focused their work on research fields which required input from more than one discipline, for instance, biocompatible materials such as implants, chemical synthesis, and gene delivery by nanoparticles to cells.

In 2003, however, researchers from the University of Toronto Joint Centre for Bioethics in Canada cautioned that there was a scarcity in ethical reflections on nanoscience (Mnyusiwalla et al., 2003). These authors conducted a survey of databases and found a shortage of publications on the ethical and social implications of nanoscience. From this they concluded that reflections on ethical issues of nanoscience lagged behind research into nanoscience itself, which was developing fast. However, in Ebbesen et al. (2006), we disputed this conclusion. We questioned whether the fact that there was a shortage of published articles on the ethical dimensions of nanoscience implied that the ethical issues of nanoscience had not yet been analyzed. We proposed that the ethical aspects of nanoscience are analogue the ethical issues of biotechnology, biology, and healthcare, which have been reflected upon by ethicists at least since the 1970s. From these reflections a knowledge base has been developed which functions as a foundation for ethical analyses of nanoscience. Furthermore, we argued that basic ethical principles, such as the bioethical theory of principles of Beauchamp and Childress, are a promising approach for ethical reflections on nanoscience (Ebbesen et al., 2006; Beauchamp & Childress, 2013).

Below in figure 1 we have listed some examples of ethical issues of nanoscience which are pointed out in the general literature (Ebbesen et al., 2006). Furthermore, we have drawn analogies to known ethical issues of biotechnology, biology, and healthcare to argue that these ethical issues of nanoscience cannot be considered new and unique (Ebbesen et al., 2006).

Ethical issues of nanoscience	Analogues to known ethical issues of biotechnology, biology, and healthcare
Uncontrolled proliferation of self-replicating nanosystems	Dispersal of gene-modified organisms (GMOs)
Toxicity of nanoparticles	Dispersal of GMOs Toxicity of asbestos
Biological warfare and terrorism	September 11th (anthrax powder)
Invasion of privacy as a result of the creation of genetic databanks	Biobanks in healthcare in general (for instance the storage of blood samples)
Enhancement of human capabilities	Enhancement of human capabilities by gene 'therapy'
Costs and research priorities with regard to nanoscience	Costs and research priorities with regard to biotechnology
Access to nanoscience and nanotechnology	Access to biotechnology and healthcare in general
Patents, ownership, commerce of nanoscience	Patents, ownership, commerce of biotechnology

Figure 1. Ethical issues of nanoscience and analogues drawn to known ethical issues of biotechnology, biology, and healthcare (Ebbesen et al., 2006).

In figure 2 we have examined which ethical considerations and basic ethical principles are at stake within nanoscience (however, we do not claim that the list is complete). As demonstrated by red marking in figure 2, the ethical issues of nanoscience fall into three categories: 1) Risk-benefit analysis, 2) Informed consent, and 3) Fairness. In the following, we will show how the four basic ethical principles of nonmaleficence, beneficence, respect for autonomy, and justice are at stake in these three groups of ethical issues.

Ethical issues of nanoscience	Ethical considerations	Basic ethical principles
Uncontrolled proliferation of self-replicating nanosystems	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence (not harming)
Toxicity of nanoparticles	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence

Ethical issues of nanoscience	Ethical considerations	Basic ethical principles
Biological warfare and terrorism	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence
Invasion of privacy as a result of the creation of genetic databanks	Informed consent	Respect for autonomy
Enhancement of human capabilities	Who should be offered access to enhancement? Fairness	Justice
Costs and research priorities with regard to nanoscience	Fairness	Justice
Access to nanoscience and nanotechnology	Who should be offered access to nanoscience and nanotechnology? Fairness	Justice
Patents, ownership, commerce of nanoscience	Fairness	Justice

Figure 2. Ethical issues, ethical considerations, and basic ethical principles of nanoscience. However, we do not claim that this list is complete and covers all ethical concerns and ethical principles of nanoscience (Ebbesen et al., 2006).

1) Risk-benefit analysis

According to Beauchamp and Childress, a risk-benefit analysis is an evaluation of possible risks in relation to possible benefits, hence a ratio between the probability and magnitude of an anticipated benefit and the probability and magnitude of an anticipated harm (Beauchamp & Childress, 2013, p. 232). This often leads to a judgment about the tolerability of the risks under assessment. Within ethics, a risk-benefit analysis is essentially a balancing of the **principles of nonmaleficence and beneficence**. The concept of nonmaleficence has been explained by the concept of harm, and according to Beauchamp and Childress, "significant bodily harms and other setbacks to significant interests are paradigm instances of harm" (Beauchamp & Childress, 2013, p. 152). They focus on "physical harms, especially pain, disability, suffering, and death, while still affirming the importance of mental harms and other setbacks to one's interests" (Beauchamp & Childress, 2013, pp. 152-153). In biomedicine and healthcare the concept of benefit often means something positive such as health or quality of life.

2) Informed consent

Informed consent is based on the assumption that the person in question has the capacity to act intentionally, with understanding, and without controlling influences determining the action. Generally, the justification of informed consent is to protect autonomous choice and hence the **principle of respect for autonomy** is the basis for the practice of informed consent (Beauchamp and Childress, 2013, pp. 102, 114-15).

3) Fairness

The term fairness is usually closely connected to the concept of justice. This includes the fair distribution of goods in society which is particularly important if goods and services are in short supply. Here, valid **principles of justice** can be used to determine how social burdens and benefits ought to be allocated (Beauchamp & Childress, 2013, p. 249). Hence, there are good reasons to claim that the basic ethical principles at stake within nanoscience are nonmaleficence, beneficence, respect for autonomy, and justice. These principles are part of the bioethical theory developed by Beauchamp and Childress (2015), which we have argued constitutes a profound approach for the analysis of ethical issues of nanoscience (Ebbesen et al., 2006).

In the next section, we will draw analogues to the ethics of synthetic biology and subsequently return to the use of the bioethical theory of Beauchamp and Childress to analyze ethical issues of synthetic biology.

Ethics of synthetic biology

During the last years, the ethical dimensions of synthetic biology have got some visibility. For instance, the funding agencies try to integrate ethical considerations of synthetic biology as part of scientific research by requiring ethical analysis as part of applications for funding. This has been done in the UK where four research councils have funded seven scientific networks incorporating ethical reflections. Also, the European Commission's Seventh Framework Program funds a project called SYNBIOSAFE having an ethical component. And lastly, the National Science Foundation in the US finances projects incorporating ethical reflections from the beginning (Calvert & Martin, 2009). Furthermore, the American Presidential Com-

mission for the Study of Bioethical Issues has analysed the ethics of synthetic biology and formulated certain directions and principles to ensure that synthetic biology can be developed in an ethically responsible manner (Presidential Commission for the Study of Bioethical Issues, Dec. 2010). Unfortunately, according to a scorecard, only seven of the eighteen recommendations of the presidential advisory panel have actually been implemented (Pittman, 2012).

In figure 3, we have listed some predicted ethical issues of synthetic biology, which appear in the general literature (Schmidt et al., 2009; Schmidt, 2009; Serrano, 2007; Caplan, 2009; Presidential Commission for the Study of Bioethical Issues, Dec. 2010; Synthetic Biology. Introduction to a Debate). Furthermore, we have drawn analogies between the predicted ethical issues of synthetic biology known ethical issues of biotechnology, biology, and healthcare, in the figure.

Ethical issues of synthetic biology	Analogues to known ethical issues of biotechnology, biology, and healthcare
Protection of employees working with biotechnological processes (design of DNA, artificial cells etc.)	Protection of employees working with biotechnological processes
Runaway proliferation of self-replicating artificial (non-natural) systems	Dispersal of GMOs
Possible toxic nature of designed artificial systems dispersed in the environment	Dispersal of GMOs Toxicity of asbestos
Misuse for weapons or terrorism	September 11th (anthrax powder)
Costs and research priorities of synthetic biology	Costs and research priorities with regard to biotechnology
Access to synthetic biology	Access to biotechnology and healthcare in general Priorities with regard to healthcare
Risks associated with test of new treatments (for instance based on self-replicating systems)	Dispersal of viruses used in gene therapy
Patents, ownership, commerce of synthetic biology	Patents, ownership, commerce of biotechnology

Figure 3. Predicted ethical issues of synthetic biology and analogues drawn to known ethical issues of biotechnology, biology, and healthcare (Schmidt et al., 2009; Schmidt, 2009; Serrano, 2007; Caplan, 2009; Presidential Commission for the Study of Bioethical Issues, Dec. 2010; Synthetic Biology. Introduction to a Debate).

In figure 4, we have examined the ethical considerations and basic ethical principles at stake within the ethical issues of synthetic biology.

Ethical issues of synthetic biology	Ethical considerations	Basic ethical principles
Protection of employees	Health impact Private sphere / informed consent	Beneficence Nonmaleficence Respect for autonomy
Self-replicating artificial (non-natural) systems	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence
Toxic nature of artificial systems	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence
Misuse for weapons/ terrorism	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence
Costs and research priorities with regard to synthetic biology	Fairness	Justice
Access to synthetic biology	Who should be offered access to synthetic biology? Priorities with regard to healthcare Fairness	Justice
Risks associated with test of new treatments (for instance based on self-replicating systems)	Environmental impact Health impact Risk-benefit analysis Informed consent	Beneficence Nonmaleficence Respect for autonomy
Patents, ownership, commerce of synthetic biology	Fairness	Justice

Figure 4. Ethical issues, ethical concerns, and basic ethical principles of synthetic biology.

As in nanoscience, the ethical considerations of synthetic biology fall into three groups: 1) Risk-benefit analysis, 2) Informed consent, and 3) Fairness (figure 4). And as explained above, the following

basic ethical principles can be found from these three ethical considerations: Nonmaleficence, beneficence, respect for autonomy, and justice. These ethical principles are part of several ethical theories. Here, we follow Beauchamp and Childress' theory because this theory contains all the relevant principles and has been critically developed by the authors through the last thirty years.

The principles of biomedical ethics of Beauchamp and Childress

The nature of morality

Beauchamp and Childress argue that the four basic principles of respect for autonomy, beneficence, nonmaleficence, and justice form the foundation of a common morality across cultures. According to their theory, everybody committed to morality knows the general norms of not to steal, to tell the truth, not to kill, and to rescue persons in danger. These are examples of norms found in the common morality. Since the norms or rules are cross-cultural, we can judge cultures by use or according to these rules. So, the common morality has a normative force and all human conduct can rightly be judged by its criteria. This means that if persons do not live up to the demands of the common morality they are immoral. Beauchamp and Childress not only justify the common morality normatively, they also justify it empirically by saying that the common morality can be demonstrated by empirical research. The purpose of such an empirical study would be to investigate whether cultural or individual differences emerge over our most general norms. Only persons committed to morality should be included in the study. Beauchamp and Childress suggest that it would be reasonable to expect that all persons committed to morality accept the principle of nonmaleficence (it would be unbelievable that any person committed to morality would reject this principle). All persons included in the study should thus be screened first to demonstrate whether they accept the principle of nonmaleficence (Beauchamp & Childress, 2013, pp. 305-308).

According to Beauchamp and Childress, the general principles of the common morality form the framework of our most abstract obligations. These principles can be specified into more specific rules and still more specific norms. There is a transparent connection between principles and rules. For instance, the principle of respect for

autonomy can be specified into the rule of respecting the privacy of others, which can be specified into the norm of keeping personal information private and confidential (figure 5, next page). A rule can be justified by more than one principle; hence there is not a linear connection between rules and principles (personal communication with Beauchamp).

General principles	More specific rules	Still more specific norms
Respect for autonomy	Tell the truth Respect the privacy of others	To tell about a health condition if discovered in research Disclose material information in medical research Keep personal information private and confidential
Nonmaleficence	Do not cause pain or suffering of others	Do not turn patients away from a hospital when seriously ill Avoid as much pain and suffering as possible
Beneficence	Prevent evil or harm from occurring Help those who have disabilities Balance benefits, costs, and risks	Use public health measures to protect from disease Protect subjects in research against excessive risk Seek improvements in the quality of the environment
Justice	Give equal consideration under the law	Provide equitable access to healthcare of appropriate quality Provide compensation for injury caused to research subjects

Figure 5. Principles, rules, and norms of the common morality (Personal communication with Beauchamp).

Beauchamp calls the universal system of principles, rules, and norms which constitutes morality wherever it is found 'morality in the narrow sense'. From this view there is no difference in morality in China, Japan, Italy, and USA. Persons from these cultures committed to morality do defend the same general principles, rules, and norms. However, at the same time Beauchamp defends moral pluralism, since differences in morality are present in the way he calls 'morality in the broad sense'. The diversity of moral positions is connected to the implementation, specification, and balancing of the universal system of principles, rules, and norms. Beauchamp

writes: "Morality in the broad sense recognizes divergent and even conflicting moral positions created by different philosophical, religious, or cultural commitments […] here the many conflicting social codes across societies show significant dissimilarities of belief, but not so many dissimilarities that morality in the narrow sense is called into question" (Beauchamp, 1997, pp. 25, 27).

The general principles of the common morality

According to Beauchamp, the four basic principles of the common morality are useful for dealing with complex cases of biomedicine. In figure 6, a short formulation of the four principles is presented.

The principle of respect for autonomy

- "As a negative obligation: Autonomous actions should not be subjected to controlling constraints by others" (Beauchamp & Childress, 2013, p. 107).
- "As a positive obligation, this principle requires both respectful treatment in disclosing information and actions that foster autonomous decision making" (Beauchamp & Childress, 2013, p. 107). Furthermore, this principle obligates to "disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision making" (Beauchamp & Childress, 2009, p. 107).

The principle of beneficence

- One ought to prevent and remove evil or harm
- One ought to do and promote good (Beauchamp & Childress, 2013, p. 151).

The principle of nonmaleficence

"One ought not to inflict evil or harm", where harm is understood as "thwarting, defeating, or setting back some party's interests" (Beauchamp & Childress, 2013, pp. 152-153).

The principle of justice

Beauchamp & Childress argue that a single principle cannot address all problems of distributive justice (Beauchamp & Childress, 2009, p. 250). They defend a frame-

work for allocation that incorporates both utilitarian and egalitarian standards. A fair healthcare system includes two strategies for healthcare allocation: 1) a utilitarian approach stressing maximal benefit to patients and society, and 2) an egalitarian strategy emphasising the equal worth of persons and fair opportunity (Beauchamp & Childress, 2009, pp. 288, 293).

Figure 6. The four basic principles of the common morality.
A brief formulation of the four ethical principles: the principles of respect for autonomy, beneficence, nonmaleficence, and justice (Beauchamp & Childress, 2013; Ebbesen, 2009).

These principles are prima facie binding in the sense that they are to be followed in every situation if they are not in conflict with other principles. This means that none of the principles is absolute. If two or more principles conflict they first need to be specified making them adequate for the actual case at hand. According to Beauchamp, "Specification is defined as a process of reducing the indeterminateness of general norms to give them increased action guiding capacity, while retaining the moral commitments in the original form" (Beauchamp, 2003, p. 269). Specification is a way of narrowing the scope of the norms, for instance by specifying where, when, who, why, how, and by whom the action has to be performed or eluded (Beauchamp, 2003, p. 269). The result of specification may be that the conflict of the principles is eradicated. If not, the principles or the specified norms have to be balanced. When principles are balanced, one principle is infringed by another. Balancing is about the weight and strength of the principles (Beauchamp & Childress, 2013, pp. 19-20). Beauchamp & Childress list six conditions which constrain balancing and which must be met to justify the infringement of one prima facie principle by another (figure 7). When prima facie principles are specified and balanced, moral diversity may occur and this is what Beauchamp calls 'morality in the broad sense'.

1. "Good reasons can be offered to act on the overriding norm rather than on the infringed norm".
2. "The moral objective justifying the infringement has a realistic prospect of achievement".
3. "No morally preferable alternative actions are available".
4. "The lowest level of infringement, commensurate with achieving the primary goal of the action, has been selected".
5. "Any negative effects of the infringement have been minimized"
6. "All affected parties have been treated impartially" (Beauchamp & Childress, 2013, p. 23).

Figure 7. Conditions constraining balancing. Conditions that must be met to justify infringement of one prima facie principle by another (Beauchamp & Childress, 2009; Ebbesen, 2013).

The bioethical theory of Beauchamp and Childress is subject of serious debate, and several ethicists have discussed their 'principlist' approach and given suggestions for improvements (DeGrazia, 1992; Holm, 1995; Strong, 2000; King & Churchill, 2000; Rendtorff and Kemp, 2000; Rauprich, 2008). During the six editions of their work, Beauchamp and Childress have incorporated some of these suggestions. However, it is not our task in this article to go into this debate.

Sociologist John Evans made a survey exploring how bioethics became institutionalized in the USA from 1980s into the 2000s. Evans observed that participants in the ethical debate specifically used the principle-based approach of Beauchamp and Childress and he criticised them for focusing specifically on autonomy (Yearley S, 2009). Based on this focus on autonomy, Yearly is critical regarding the use of Beauchamp and Childress' theory to analyse ethical issues of synthetic biology. However, an approach focusing primarily on autonomy is not in line with Beauchamp and Childress' theory, since in this theory the four principles are prima facie binding and hence, all four principles must be considered from the outset.

Analyzing ethical issues of synthetic biology

To illustrate how Beauchamp and Childress' theory can be used to analyze ethical issues of synthetic biology, we present a case where an oncolytic poxvirus has been engineered to replicate selectively in cancer cells and used as a vehicle for delivery and expression of transgenes in tumors (Breitbach et al., 2011; Cripe et al., 2015). This platform technology based on oncolytic viruses is an example of a synthetic product within biotechnology.

Breitbach et al. (2011) and Cripe et al. (2015) chose to use vaccinia, a large double-stranded DNA containing poxvirus, for intravenous delivery and expression of transgenes in tumors. These transgenes could for instance express therapeutic proteins or siRNAs (capable of silencing oncogenes). Vaccinia has biological properties which makes it appropriate for managing these tasks. Firstly, vaccinia is intravenous stable and spreads to distant tissues. Secondly, it spreads fast and is motile within tissues. Thirdly, it often deposits in tumors, and lastly, vaccinia replicates dependent on the EGFR/Ras (epidermal growth factor receptor) pathway signalling, which is generally activated in epithelial cancers (Breitbach et al., 2011).

The oncolytic poxvirus (JX-594) was tested in a phase I clinical trial to investigate the dose-related fashion of tumor-specific infection, replication, and expression of transgenes. Twenty-three patients with advanced treatment-refractory solid tumors were selected for the trial and they underwent a single intravenous infusion of JX-594. JX-594 was mostly well tolerated; the most common side effects were flu-like symptoms lasting up to 24 h (Breitbach et al., 2011). Breitbach et al. (2011) obtained biopsies 8-10 days after intravenous infusion and reported cancer-selective and dose-related JX-594 delivery and replication in tumors. Furthermore, new tumor outgrowth in the time after infusion was not as frequent in patients treated with high doses as in to patients treated with low doses (Breitbach et al., 2011). Recently, a phase 2 dose-ranging study of Pexa-Vec in 30 patients with advanced liver cancer demonstrated increased survival in high dose Pexa-Vec versus low dose (Cripe et al., 2015). Moreover, intratumoral dose escalation has been found to result in antitumor avtivity at high doses (Cripe et al., 2015).

The first step in an ethical case analysis is to identify which ethical concerns, values, and principles are at stake in the actual case at hand. Therefore, in figure 8, we have presented ethical issues of

using cancer-targeted oncolytic poxvirus JX-594 for transgene expression in clinical trials. Generally, we believe that the following ethical concerns are important in all clinical trials: Informed consent of research subjects, expectations of therapeutic effects, risk analysis of side effects of testing new methods, equitable access to clinical trials, and adequate compensation should be paid to research subjects. Furthermore, this tumor specific oncolytic poxvirus is specifically designed to self-replicate in cancer cells expressing the EGFR/Ras pathway signaling. Thereby, this system exemplifies the ethical concerns of 'uncontrolled spread of self-replicating artificial systems', mentioned earlier. And lastly, employees should be protected against virus infection. As illustrated in figure 8, ethical principles of beneficence, nonmaleficence, respect for autonomy and justice are important in the case at hand. The second step in the ethical analysis is to collect relevant clinical information (technical or scientific information) to perform a risk-benefit analysis regarding the risk for 'uncontrolled spread of self-replicating artificial systems' and regarding possible side effects for research subjects. The third step is to consider whether some of the principles do conflict and whether they need to be specified or balanced.

In this article we have performed step one in the ethical analysis, hence we have identified which ethical considerations and basic ethical principles are at stake. We have not performed step two – to collect clinical information to make a risk-benefit analysis – and step three – to specify and balance ethical principles – since these steps require detailed information regarding the specific case at hand.

Ethical issues	Ethical considerations	Basic ethical principles
Protection of employees	Health impact Private sphere / informed consent	Beneficence Nonmaleficence Respect for autonomy
Uncontrolled spread of self-replicating artificial (non-natural) systems	Environmental impact Health impact Risk-benefit analysis	Beneficence Nonmaleficence
Informed consent of research subjects in clinical trials	Informed consent	Respect for autonomy

Ethical issues	Ethical considerations	Basic ethical principles
Expectations of therapeutic effect	Beneficence	Beneficence
Side effects of testing new methods in clinical trials	Risk-benefit analysis	Beneficence Nonmaleficence
Provide equitable access of research subjects to clinical trials	Fairness	Justice
Adequate compensation should be paid to research subjects	Fairness	Justice

Figure 8. Ethical issues, ethical concerns, and basic ethical principles of synthetic oncolytic viruses used in clinical trials.

Conclusion

In this article we have outlined a conceptual framework for the analysis of ethical issues of synthetic biology. Firstly, we showed that the ethical aspects of nanoscience are not new and unique since they are very similar to ethical issues of biotechnology, biology, and healthcare, and that basic ethical principles of nanoscience are part of the bioethical theory of Beauchamp and Childress (Ebbesen et al., 2006). Secondly, we explained that the ethical issues of synthetic biology are similar to ethical issues of nanoscience, biotechnology, biology, and healthcare. We concluded that the principles of beneficence, nonmaleficence, respect for autonomy, and justice are important for synthetic biology and pointed out that these are part of Beauchamp and Childress' theory. However, we do not claim that there could not be other principles to use. We argued that the theory of Beauchamp and Childress can therefore be used to analyze ethical issues of synthetic biology by going through the steps in an ethical analysis using oncolytic poxvirus as a vehicle for delivery and expression of transgenes in tumors as a model case.

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