Memorandum of Ethics

elaborated in the frame of the COST Action CA20108 Netskinmodels

This material provides background information for the interpretation of ethical aspects encountered in the fields of activity related to development, sharing and producing sophisticated cell-based and computational models of healthy and diseased skin.

It aims at facilitating the ethical and normative debate between representatives of research laboratories, hospitals, veterinary centers, industrial R&D departments, non-governmental organizations (NGOs), regulatory bodies and patients, nature and animal associations for identification, adjustment and perfection of ethical standards and norms, better adapted to daily priorities.

Aim of the Memorandum on Ethics (MoE), elaborated in the frame of the COST Action CA21108 – Netskinmodels, according to the Memorandum of Understanding of the COST Action (MoU), is to secure the conditions of co-development of products between academia (laboratories in biotechnology, chemistry, biology, computer science) and industries (chemistry, biology), defined in the regulatory acts with regards to background and foreground of Intellectual Property, technical innovations, biobanks etc.

Introduction

The contemporary progress in the different areas of medicine and the various life sciences is giving rise to a wide range of bioethical and research ethical dilemmas. As transnational cooperation in scientific activities intensifies, there is a growing need to develop universally applicable ethical guidelines in the field of biomedical ethics, research ethics and bioethics. This involves the promotion of universally shared ethical values and facilitating the ethical and normative debates between scientists, medical professionals, industrial partners, lawmakers and citizens.

Every culture, even the most critical of technological advances, must develop a response, be it supportive or antagonistic, to the emergence of new technologies, including biotechnology. The creation a favorable environment allowing the delivery of innovative and pathophysiologically relevant cell-based models recapitulating the complexity of the skin and skin diseases and the emergence of powerful in silico models by stimulating knowledge transfer within academic laboratories and between the latter and industrial partners is not possible without elaboration of a clear and exhaustive set of ethical norms, principles and values for applying them in the everyday scientific and industrial production.

The MoE elaborated in the frame of the COST Action CA20108 Netskinmodels recognizes the importance of taking international human rights legislation as framework and starting point for the development of bioethical principles. In addition to the basic documents on human rights, international legal instruments that are not human rights documents per se might also have impacts on the domain of bioethics. For instance, the TRIPS Agreement of the World Trade Organization has an important influence on conceptualizing the patentability of the human genome. Among many relevant instruments three especially important ones shall be singled out: (1) the Helsinki Declaration, (2) the Convention on Human Rights and Biomedicine of the Council of Europe, and (3) the International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO, that is recognized worldwide, especially among scientists and policy makers. Reference to instruments adopted outside the United Nations system is new in the UNESCO legal tradition. In the area of bioethics, the three mentioned instruments have special relevancy since they identify acknowledged principles and standards adopted at the international level.

Netskinmodels, by promoting interactions between industrial partners (chemistry, biology) and academic laboratories (biotechnology, chemistry, biology, computer science), is contributing to the development of sustainable and animal-free composites and reagents not only to respond to ethical requirements, but also to green-up the scientific practice that is currently relying on non-environmentally friendly oil-derived plastic products. According to MoU of the COST Action CA20108 Netskinmodels, the MoE contains the identification of such concepts as „*sustainable and ethical products*" and „*ethical and green products*", designed for the elaboration of 3D skin models, in the relation with the specific of the COST Action. Also, MoE, according to MoU, contains solutions to reduce plastic use via the development and validation of alternative composites, reagents and protocols (3Rs: Reduce, Reuse & Recycle). MoE is addressed to the

accessibility of unpublished data and on discoveries as well as on personal data, according to General Data Protection Regulation (GDPR) compliance, related to such categories as Confidentiality, Non-Disclosure, Data Use Agreements etc.

Use of Terms

- The term "*bioethics*" has had at least two different meanings, one broader than the other. The term was used for the first time by Potter (with a background in biology) in 1970. He advocated a comprehensive and global view of bioethics, as the moral analysis of the present and future of life. On the other hand, Hellegers (with a background in medicine) used the term "bioethics" for the first time in an institutional way for an academic field of learning and a movement regarding public policy and the life sciences. Bioethics in this view is a new way of approaching and resolving moral conflicts generated by a new concept of medicine. For the purpose of clarification of used term, the following definition is required to be identified: bioethics is a systematic, pluralistic and interdisciplinary field of study involving the theoretical and practical moral issues raised by medicine and life sciences as applied to human beings and humanity's relationship with the biosphere.

- Another term "*bioethical issues*" refers to the theoretical and practical moral issues raised by medicine and the life sciences in four distinctive areas: application to human beings, humanity's relationship with the biosphere, the availability and accessibility of scientific and technological developments and their applications.

- Life sciences are the sciences concerned with the study of living organisms. They encompass a broad range of disciplines that include, amongst others, biology, biochemistry, microbiology, virology and zoology. In recent years, many of these disciplines have increasingly focused on the characterization of the molecular events that define biological processes (often referred to as the "molecular life sciences"). Broadly speaking, life sciences include any study or research discipline that contributes to the understanding of life processes.

Relevant for the interpretation of the notion "*bioethics*" is the difference between the subject and object of ethics.

- The '*subject'* of ethics (the moral agent) is necessarily a human being. This flows from the characteristics of ethics (rationality and normativity). Ethics is a quintessential human activity. Human beings do not only develop ethical arguments but they are also the only entities that can act on the basis of such arguments. This does not imply that all human beings are moral agents (e.g. some lack rationality).

- The '*object*' of ethics (the moral patient) can extend beyond human beings. Ethical arguments can apply to entities that are unable to argue or to act on the basis of arguments, such as other species or the biosphere.

- The terms „*sustainable and ethical products*" and „*ethical and green products*" are designed for the elaboration of 3D skin models for creation of a favorable environment allowing the delivery of innovative and pathophysiologically relevant cell-based models recapitulating the complexity of the skin and skin diseases and the emergence of powerful in silico models.

Principles

(Bio)ethical principles appeal to human beings; they address human beings as the moral agents. However, at the same time, depending on the definition of bioethics, there can be a difference in moral objects. Ethical principles can apply to different '*objects*'. In medical ethics the moral objects are a specific category of human beings: health care providers and health care recipients. In bioethics the moral objects can be all living beings, present life, and even future life.

In the domain of bioethical questions consensus on specific issues will require balancing and weighing of principles. It is the nature of bioethics that several principles apply at the same time when confronted with a bioethical problem. If conflict occurs between principles, the assessment of the ethical dilemma should be based on carefully balancing the relevant principles, and on analyzing the arguments in order to determine which principle is overriding the other principles.

There is not an a priori hierarchy of principles. Confronted with a specific bioethical problem, all relevant principles need to be taken into account in order to reach a reasoned conclusion about the ethical solution.

Restrictions may be placed on the principles only in accordance with international human rights law, if they are prescribed by domestic law; and only when it is necessary in a democratic society in the interest of public safety, for the prevention of crime, for the protection of public health or for the protection of the rights and freedoms of others. In choosing between various restrictive measures, the principle of proportionality has to be respected because when restriction is necessary, rights derived from principles may be restricted only in the least restricted manner and proportional to the legitimate end of the restriction. possible by balancing the principles. The solution is reached because one of the principles overrides other relevant principles. However, in exceptional circumstances, the application of the principles set out in the declaration may be restricted. Even so, some limitations do apply since the restrictions should be consistent with international human rights law and should be prescribed by domestic law.

Ethical principles always require further interpretation since the norms implicit in principles have to be translated into concrete rules. Ancient ethical codes were often expressed in the form of an oath. One of the most well-known, the Hippocratic oath, has already defined some principles that have become the basis of early ethics teaching worldwide. However, modern bioethics is indisputably grounded in the values enshrined in the Universal Declaration of Human Rights. Other texts of different legal force have established rules for the protection of persons in the wider field of biomedicine. The principle-based approach encompasses various schools of ethics, including the deontological as well as the utilitarian theories. Furthermore, the rule–principal distinction was elaborated not only in ethics but also in legal theory. Rules are applicable in an all-or-nothing fashion, while principles do not operate in this manner. Principles have a dimension that rules do not have, the dimension of weight and importance.

Despite their general nature, principles can serve as sources of legislation. Moreover, in comparison with concrete rules, principles would better accommodate rapid advances and changes in the biomedical sciences.

In the ethics vocabulary a '*principle*' is a normative generalization that serves as a justification for particular prescriptions and evaluations of human actions. The notion of principle combines two meanings:

• principium: the starting point, beginning of an argument; in reasoning one has to start somewhere; a principle is the point of departure of a time of argumentation;

• princeps: the most important consideration, overriding other arguments or notions.

MoE make a distinction between the principles directly related to respect for human dignity such as respect for human rights and fundamental freedoms, beneficence and non-maleficence, autonomy, consent and confidentiality; the principles concerning the relationships between human beings such as solidarity, cooperation, equity, justice, cultural diversity; and the principles governing the relationship between human beings and other forms of life and the biosphere such as the responsibility towards the biosphere and the assessment of risks.

These principles represent different rational justifications for human actions. None of them provide an overriding justification. This is a major characteristic of ethics. If there were one fundamental principle, ethics would be quite simple because all human actions could be justified in terms of one principle only. What makes ethics complicated is that several principles apply and that one has to balance and weigh arguments continuously in order to determine the best course of action.

The rationale is to present the general principles in the following way: they determine the different obligations and responsibilities of the moral agent in relation to different categories of moral objects, gradually widening the range of moral objects, as follows:

- ***Human dignity: the moral object is the individual human being itself***

Human dignity is recognized as a core principle upon which other principles rest. Respect for human dignity flows from the recognition that all persons have unconditional worth, each having the capacity to determine his or her own moral destiny. Disrespecting human dignity could lead to the instrumentalization of the human person. Another feature of human dignity is emphasized in idea which states that interest and welfare of the human person prevail over the sole interest of science or society. Primacy of the human person has been expressed in various international documents, including the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine of the Council of Europe, adopted in 1997 and entered into force in 1999. The Convention states in its Article 2: "*The interests and welfare of the human being shall prevail over the sole interest of society or science*.". Of course, this principle should be balanced with other principles, such as the principle of solidarity and justice. Respect for human dignity has been cited frequently in various biomedical and legal contexts. The concept is frequently used in the Universal Declaration on the Human Genome and Human Rights.

- ***Equality, Justice and Equity***

Equality refers to the equal treatment of individuals in a similar situation while the term 'equity' refers to discretion, which serves as a corrective mechanism to formal equality by looking at the special circumstances. 'Justice' in the philosophical sense is a normative principle that refers to a judgement on the arrangement of institutions, society, groups of individuals, etc. A commonly definition of justice would be: treating equals equally, unequal unequally. Principles of justice are essential to the structure of a constitutional democracy. Fairness and due process are part of democratic legal systems and are closely related to the foundations of human rights. In addition to the general meaning, principles of justice play an important role in many decisions and practice in the field of bioethical issues, such as in allocating health care services and setting priorities in health care.

- ***Beneficence: the moral object is another human being***

The principles of beneficence and non-maleficence are sometimes stated separately, the two principles originating from the ancient maxim of 'do good' and 'do no harm' (primum non nocere) seem to be effectively treated in one single Article as the ethical imperative represents two aspects of the same claim.

- ***Respect for cultural diversity: the moral object is human communities***

Cultural diversity refers to the manifold ways in which the cultures of social groups and societies find expression. From the diverse forms taken by culture over time and space stem the uniqueness and plurality of the identities and cultural expressions of the peoples and societies that make up humankind. Respect for cultural diversity requires careful implementation. If ethical standards are dictated and simply copied in various legal systems without adequate interpretation, they may remain as mere legal transplants that will not function properly with other elements of bioethical norms in a given country. Therefore the existence of cultural diversity, the importance of cross-cultural perspectives and the principle of pluralism are recognized by the declaration. According to the UNESCO Universal Declaration on Cultural Diversity, diversity reflects the uniqueness and plurality of the identities of the groups and societies making up humankind. As a source of exchange, innovation and creativity, cultural diversity is as necessary for humankind as biodiversity is for nature.

- ***Non-Discrimination and Non-Stigmatization***

The prohibition of discrimination has been elaborated in various legal instruments and one of the most eloquent and pioneer statements can be found in Article 6 of the Universal Declaration on the Human Genome and Human Rights. This article introduced a new ground of discrimination and stimulated similar legal instruments worldwide to prohibit discrimination based on genetic characteristics. Discrimination, both in its direct and indirect forms treats a morally neutral and immutable characteristic (such as skin color, gender, genetic characteristics) as having a negative impact and, based on that illegitimate distinction, similarly situated individuals are treated differently. In addition to various forms of discrimination, stigmatization is also prohibited by the declaration. The history of medical research shows a disturbing pattern of discrimination against different groups: 'races', ethnic minorities, and women - even in the recent past. During the conceptualization of research and the establishment

of control groups, culturally, morally or legally problematic categories may be used, and the preemption of discriminative practices requires communication between the various disciplines. The elimination of discrimination has to be ensured in the different areas of health care, biomedical research and health policy formulation. Not only direct forms of discrimination, such as that which appeared in the often-cited Tuskegee Study, but also the various indirect forms should be eliminated. Discrimination may distort scientific progress. For instance, the routine exclusion of women from research trials led to the fact that many of the conditions specific to women remained unknown and that discoveries that were applicable to men were simply assumed to be applicable for women patients. Stigmatization often lingers even after the discriminatory laws and policies are abolished but it may also occur before discrimination is manifested in more direct forms. While prohibition of discrimination can be more easily targeted by legal instruments, elimination of the stigma requires a longer process of social transformation in which ethics and ethics teaching can play a predominant role.

- Autonomy and Individual Responsibility

Respect for personal autonomy is strongly linked to and derives from the notion of human dignity. Individuals cannot be instrumentalized and treated as means or goals; they should be granted the authority to make autonomous decisions in all aspects of their lives without doing harm to others. Respect for autonomy is not just a respectful attitude but it involves respectful action. However, autonomy, in this interpretation, is not simply an invested right but also has the dimension of responsibility towards others.

- Informed Consent

Informed consent is a fundamental element of contemporary bioethics. The right of individual self-determination has been the basis for court decisions in favor of informed consent of competent patients to health care procedures. Though the doctrine of informed consent is largely a creation of court decisions, it rests ultimately on moral foundations.

- Privacy and Confidentiality

Right to privacy guarantees a control over personal information in many ways. It restricts access to personal and medical information and it provides a claim of non-interference in various private spheres of the individual. Privacy extends beyond data protection, as certain private spheres of the individual that are not manifested in data processing can also be protected by the right to privacy. Confidentiality refers to a special fiduciary relationship, such as between researcher and research subject, or doctor and patient, and provides that the shared information shall remain secret, confidential and shall not be disclosed to third persons, unless a strictly defined compelling interest justifies disclosure under domestic law.

- Solidarity and Cooperation

This is based not only on the individualist concept of rights but also recognizes the importance of solidarity between individuals and across communities. Inequalities in access to health care worldwide increase the importance of including solidarity and equity among the basic principles. The idea of collective social protection and fair opportunity should be a governing principle in

policy decisions and it is an essential element of a population-based ethics. Furthermore, in the planning of health care systems special attention should be paid to vulnerable groups, such as to women, by providing access to reproductive health services and to children in guaranteeing their access to health care.

- Social Responsibility

There is a need for a new approach to social responsibility to ensure, whenever possible, that progress in science and technology contributes to justice, equity and to the interest of humanity. Five specific elements were singled out: access to quality health care, including sexual and reproductive health, access to adequate nutrition and water; reduction of poverty and illiteracy, improvement of living conditions and the environment, and the elimination of the marginalization and exclusion of persons on the basis of any ground, including gender, age or disability. Elimination of the marginalization and exclusion of persons on the basis of any ground, including gender, age and disability was recognized as different than elimination of discrimination. Marginalization may be a result of discrimination, although not necessarily. Marginalization of a group of individuals may have disadvantageous consequences in the field of health, such as insufficient access to information, to health services and to benefits of scientific development.

- Sharing of Benefits

Sharing of benefits often appears in various legal documents on genetic resources. In its Article 1, the UN Convention on Biological Diversity emphasizes "*fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding*.". Furthermore, Article 12(a) of the Universal Declaration on the Human Genome and Human Rights states that "*benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual.*". The International Declaration on Human Genetic Data devotes the Article 19 to the sharing of benefits and provides a useful tool for identifying various forms of benefits. We must go far beyond the scope of genetics including the sharing of benefits resulting from scientific research in general, using almost identical formulations to those used in the Declaration on the Human Genome and Human Rights.

- Responsibility towards the Biosphere

There is a need that was also expressed during the public consultations that a contemporary declaration on bioethics should extend its scope beyond human beings. It refers to the UNESCO Declaration on the Responsibilities of the Present Generations Towards Future Generations of 12 November 1997. Moreover, it recognizes that human beings are an integral part of the biosphere and that they have responsibilities and duties towards other forms of life. Although the principles apply to human beings, they have responsibilities towards other forms of life in the biosphere. The concept of human relations with the biosphere recently underwent substantial changes by the

recognition of interdependence between humans and their environment. Parallel to this recognition, the norms governing this field have been altered significantly. The preventive attitude in standard setting is more recent and therefore the public support for these preventive legal standards is not evident as the standards often require change of the already existing preferences in life style and in social and economic policy decisions. In order to promote such changes, the declaration includes this principle among the fundamental principles of bioethics. With regard to responsibility towards the biosphere, a special reference to future generations is made in the text to the safeguarding of interests in biodiversity and the biosphere that extend beyond the present generation.

Implementation

One of the conclusions of the MoE is that principles rather than rules or norms should be formulated, which would then provide a basis for developing specific legislation within the EU and would also stimulate ethics teaching at local and regional levels in the stats member of the COST. Formulation of principles will also guide future consensus regarding bioethical issues that are controversial today.

Another conclusion stress that the bioethics as a universal instrument must call for close attention to be paid to the importance of awareness raising: dissemination of information, education and consultation, as well as the promotion of public debates on biomedical dilemmas.

In the field of bioethics, standard-setting and political decision-making require interdisciplinary consultations and the widest possible involvement of the public.

MoE underlines the importance of individual consent, there are fields of research in which the acquisition of individual consent and the safeguarding of public involvement are not satisfactory. As biobanks are created in many developed countries, entire national populations are susceptible to becoming subjects of genetic research. On the other hand, the exploitation of genetic material from less developed countries requires the development of ethical guarantees.

The MoE distinguishes four target groups with whom regular dialogue should be maintained: persons affected by these decisions or practices, members of relevant disciplines, appropriate bodies, and civil society.

In situations of uncertainty, timely measures shall be taken to assess the risks involved. The assessment procedures should evaluate the ethical issues at stake. The outcome of the assessment can vary from accepting the development, regulating and monitoring the development, accepting a moratorium, or prohibiting the development.

The term ‘ethics committee’ is used in a broad sense as it embraces policy-making committees, quality assurance committees, peer-review committees, utilization review and risk management committees, scientific-review committees, and even intra-institutional committees. This reflects a current trend in which bioethics committees are beginning to accept a broader mandate, covering not only the ethical issues related to medicine and the life sciences, but also the ethical issues generated through the advances of science and technology in general. The declaration intends to reinforce the role of various ethics committees in the fields within the scope of the declaration, including the domain of research ethics and furthermore to strengthen the role of ethics committees in interpretation of the principles of bioethics. In this respect ethics and bioethics committees have an essential role in the implementation of the declaration.

The need for independent, multidisciplinary and pluralist committees has already been stated in many documents. The declaration emphasizes the importance of these criteria for assessment the ethical, legal and social issues related to scientific research projects and technological development and for the development guidelines and recommendations, in accordance with the principles set out in the declaration.

Transnational research is increasing due to international co-operation between the members of extensive research consortiums. Considering the cultural and legal diversity of the societies involved, different segments of research may be conducted in different countries. It is, however, essential that each of these countries be involved in the ethical assessment.

Today the international dimensions of health care are more significant than ever. In the field of international research co-operation, in the case of rare diseases which are neglected by health care systems at the national level, in the domain of the AIDS-prevention, ethical dimensions of health care frequently go beyond national frontiers.

Solidarity between and among individuals, families, groups and communities, with special regard for those rendered vulnerable, should be of special concern in decisions and practices within the scope of this declaration.

List of references to normative framework (to be completed):

1. European Code of Conduct of Research Integrity
2. European acts on Intellectual Property Rights
3. Directive 2010/63/EU on the protection of animals used for scientific purposes (European Parliament, 2010, Recital 10)
4. Cosmetic Directive 76/768/EEC
5. Cosmetics Products Regulation (EC) No1223/2009
6. Chemicals REACH Regulation (EC) 1907/2006.

List of other resources (guidelines) related to research ethics (to be completed):

1. European Charter of Medical Ethics. CEOM. https://www.ceom-ecmo.eu/en/european-charter-medical-ethics-67
2. Principles of European Medical Ethics. CEOM. https://www.ceom-ecmo.eu/en/view/principles-of-european-medical-ethics
3. Code of Medical Ethics. AMA. https://code-medical-ethics.ama-assn.org/
4. Guidelines for Stem Cell Research and Clinical Translation. https://www.isscr.org/guidelines/#guidelinestoc