

principles of the *ijtihad* from which these fatwas originated.

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The Ethical Dilemma of Human Germline Editing

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1. Introduction

Gene editing provides us with the ability to design and edit genomes of biological entities giving them new properties. A new technology named the CRISPR/Cas9 system allows for fast and inexpensive gene editing (1). A piece of RNA, called guide RNA, contains a set of bases which are complementary to the target sequence on the DNA. The Cas 9 enzyme will follow the guide and will make a cut across both DNA strands. The affected cell then recognizes the DNA damage and tries to repair it; this is the point where scientists can use DNA repair methods to introduce a genetic mutation (2).

Deliberately manipulating the human germline for the avoidance of severe inherited diseases has generally been viewed as acceptable, whereas for 'enhancement' of human capabilities in some cases it has been deemed ethical, but in others not. A disease is any disturbance to the structure or function of the body. There are various types of diseases, ranging from metabolic to inflammatory, from neoplastic to degenerative, and of course,

there are also genetic diseases (3). If there was a way to prevent one of these diseases, should further exploration be encouraged? Assuming a solution is found, would it be acceptable to use the technology for human enhancement? Or are the ethical differences too great to overcome?

Should a temporary or permanent global ban on human germline editing be introduced and, if so, on what basis? Is there an ethical difference between using gene editing for the avoidance of severe inherited diseases or for 'enhancement' of human capabilities? Since the genetic changes made in the DNA of gametes and embryos will impact and will be inherited through the generations, a broad range of discussions on the prospect of enforcing a global ban due to the implications of this technology has begun (4).

2. Offside effects

Regarding the CRISPR/Cas9 technology, one of the concerns that have developed is regarding its accuracy. In theory, it will bind to the target sequence and no other region. However, when working with enzymes that cleave the chains of nucleotides, such as CRISPR/Cas9, there are off-target effects towards other locations in the genome that share similar arrangements with the destination (5). Since the side effects will be an issue, there have been cultural strategies (6) and chemical molecules (7) that have been reported to increase the efficiency of genome editing. Further examination is required to test the possible detrimental effects on cells or embryos exposed to such conditions.

However, in the meantime, bioinformatics has developed a predictive scoring system that identifies determinants that influence Cas9 efficiency towards targets, which should improve outcomes by decreasing the mosaicism rate (when the genetic makeup of some cells varies from others)(8).

3. Human embryos, a requirement for the development of research in the field

The concern regarding the inability to predict the consequences of such a procedure highlights the need for more data on the safety of such interventions, and techniques that could increase the efficiency (9). The preferred solution to discarding affected embryos would be using non-viable embryos. These embryos may result from In Vitro Fertilization, but consent from the donor couple must first be obtained.

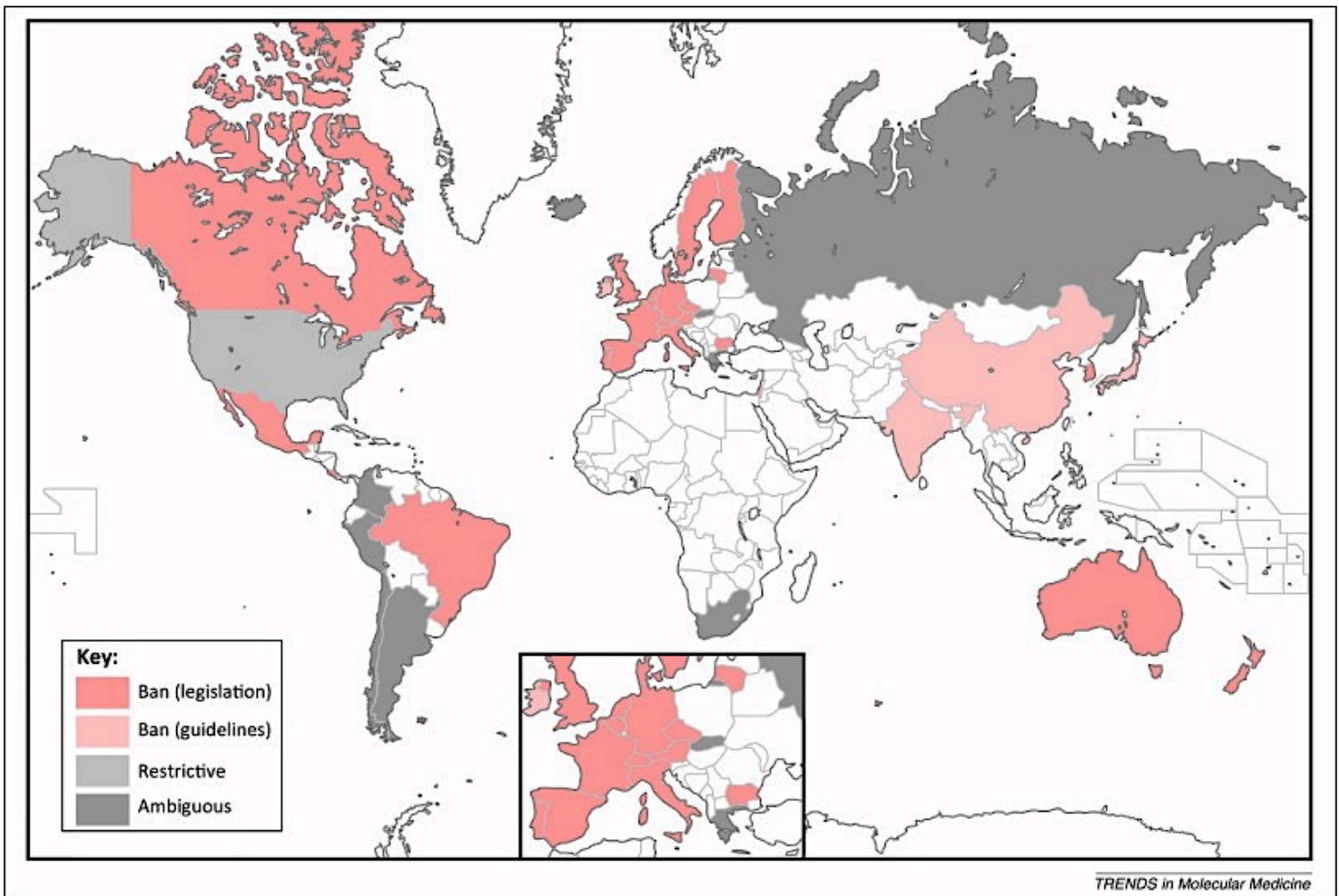


Figure 1: “An international regulatory landscape regarding human germline gene modification. Thirty-nine countries were surveyed and categorized as “Ban based on legislation” (25, pink), “Ban based on guidelines” (4, faint pink), “Ambiguous” (9, gray), and “Restrictive” (1, light gray). Non-colored countries were excluded in this survey.” (14)

Likewise, adult somatic cells give rise to human induced pluripotent stem cells, therefore lessening the ethical concerns. Recent discoveries have reported that human induced pluripotent stem cells can differentiate into male germ cells with the use of bone morphogenetic proteins. There is no record of hiPSCs differentiating into human oocytes, but the scientific community is hopeful in the data to come from current experiments on mice (7). Further research must be conducted on the viability of induced germ cells to determine if they can successfully undergo fertilization and produce viable embryos.

Therefore, a necessary component in the preclinical stage assessment may be using embryos created from human embryonic stem cells as a comparison tool to ensure the reliability of embryos formed using hiPSC's. However, to obtain embryonic stem cells, the destruction of the embryo ensues after cell extraction (10). The moral

dilemma here is whether the duty to prevent future suffering is greater than the obligation to respect the value of a potential human life. There is a broad range of views concerning whether or not the embryo has the status of a person; this has created a barrier to further discovery due to current restrictions in various countries.

4. Varying national laws

Many countries or states have different ethical policies regarding the use or creation of a human embryo for research. In some countries, where there is an overabundance in cryopreserved embryos originally intended for In Vitro Fertilization, researchers are permitted to utilize them with informed consent from the donor parents and by meeting guidelines of institutional review boards (11). Of the countries that allow using embryos for research purposes, there is a restriction to the culture period: 14 days or until the primitive streak forms (7).

In some countries, using germline gene modification is prohibited until gene correction is enhanced (China, India, Ireland, Japan). The US National Academy of Sciences and the National Academy of Medicine have come out with a report (February 2017) outlining several criteria to allow germline editing clinical trials to continue (12). The

rules include that the benefits must outweigh the risks, a risk of damage to the human embryo will prohibit advancement (13), and the objective ought to be the prevention of a severely debilitating disease. In contrast, the UK does not ban the use of human embryos for the sake of reproductive research as long as the HFEA (regulator in the UK responsible for overseeing the handling of embryos and gametes in research and fertility treatments) approves (14).

5. Making a distinction

The Liang Study used non-viable tripronuclear zygotes with a debilitating disease to investigate the use of CRISPR/Cas9 gene editing on human cells to improve data on clinical applications of this technology (15). This study underwent a public outcry; people were calling it the making of 'designer babies' (16).

Some individuals may find it more morally appropriate to administer genetic interventions in one case over another. Interventions for genetically healthy persons are enhancements, whereas in the latter case they are considered therapy. Some may say that enhancement expresses dissatisfaction; conversely, some see it as an opportunity to improve. However, the concept of improvement is not morally contentious as we do many activities in our lives to improve ourselves, some of which being: education, research, and fitness.

Each person is entitled to relief; we see that the distinction solely focuses on the etiology rather than the degree of suffering (17). A physician's professional responsibility to choose the optimal treatment that promotes quality of life, and respecting an individual's reproductive autonomy are valid reasons to move forward with germline interventions (18).

6. Addressing influential factors

There are two aspects to a disability: the medical aspect and the social aspect. Society often categorizes individuals with impairments as disabled, which prevents them from taking part in everyday life (19). Disabilities are more often acquired through an individual's environment rather than inherited; meaning that the social aspect of a disability is a valid concern that ought to be prioritized to encourage people with disabilities to live ordinary lives (20). On the other hand, individuals with medical disabilities, in which their body is impaired in some sort due to a genetic abnormality, can benefit tremendously with this technology. The ethical, legal and social framework that will result from the broad adoption of these technologies must be considered. The ever-occurring question when addressing human germline editing for severe inherited diseases is:

what is seen as a 'severe' genetic disease? Ethical discussions must take place as anticipatory governance; we cannot have a future stall in technological advancement due to a lack of dialogue in our current time (21).

7. Establishing an ethics committee dedicated to human germline editing

Before considering clinical applications, there should be a committee in place for each country that permits the practice of germline modifications. The research group at the Francis Crick Institute obtained approval from the HFEA in regards to conducting experiments involving CRISPR/Cas9 editing of human preimplantation embryos (22).

The UK Health Ministers appoint HFEA members based on guidelines (the 'Nolan' guidelines) that ensure appropriate merit. Also, members of the HFEA have a broad range of expertise to maintain an objective view. Members range from professions in the field of medicine to the field of law and from philosophy to religion (22). Further, the fertility clinics and research centres ought to adhere to the ethical rules and safety protocols established by the UK government. Regular inspection of these locations by the HFEA will ensure compliance. Further, adherence to the ethical rules and safety protocols set by the UK government will be enforced by the HFEA through regular inspection of UK fertility clinics and research centres (22).

Knowing that technical concerns will eventually be resolved by additional scientific research, moral considerations must be the point of focus of public debate (10). Countries should establish an ethics committee to tackle the ethical dilemmas according to the ethical rules placed by the country's government. After careful consideration of the ethical and social implications of such a technology, a country will then be able to establish policies better suited for their values and beliefs.

8. Just distribution scheme

The ethics committee dedicated specifically to the editing of human genomes will need to develop policies that will be the sole source of consolation when it comes to ethical puzzles to avoid misuse by certain individuals or organizations.

To address the concern of 'designer babies,' we should discourage inventions that promote positional advantage and rather posit a just distribution scheme. Neither race nor sexual orientations are conditions that require genetic intervention. If genetic engineering is used to alter an unborn child's skin color, sexual orientation or sex, the parents risk advancing discriminatory

attitudes. Therefore to ensure just distribution, genetic interventions ought not to increase discrimination or racism (23).

Treatment for genetic diseases often requires intervention at a single particular locus, whereas phenotypic traits often result from the interaction between several genes and the environment, making it difficult to influence these complex traits through germline modification without a greater understanding of epigenetics (16). The increased difficulty may result in only a 'select few' being able to afford the intervention, making genetic enhancement morally unacceptable as a factor involved in the ever-increasing gap between the rich and the poor. Genetic alterations ought not to be restricted to a particular sect of society to coincide with the just distribution scheme.

9. Conclusion

Research towards improving the specificity and reducing the off-target effects of the CRISPR-Cas9 system is developing towards a safe level that will eventually permit clinical applications in human patients. In light of the considerable number of countries that are ambiguous, or are awaiting further developments in the technology (14), establishing a temporary global ban is appropriate. This temporary global ban will result in the countries with the ethical policies in place, to lay pressure on the countries undecided on the issue at hand. Due to the global demand, rather than continuing to remain without an opinion, this temporary ban will provide the incentive for countries to focus on the ethical, social and evolutionary implications of this biotechnology, resulting in legislation based on their country's values.

Any discovery that seeks to fulfill medicine's ethical mandate to help the sick will generate pressure to move from the lab, towards the human body (9). Should a country support human germline editing, they ought to establish a plan of conduct to prevent abuses of this technology. When it comes to administering human germline editing to those who are considered to have normal body function and to those of whom are considered impaired, the distinction is in the etiology. Conducting this technology with the aid of a just distribution scheme is recommended to ensure proper allocation of skills. With ongoing reassessment and public participation preceding any heritable germline, the ethical concerns that arise will be acknowledged, and the technology will be able to move towards clinical trials.

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Circus animals - how much is 'unfair'?

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1. Introduction

In early 2017, eleven out of the thirty-two retired circus animals that were kept in a facility near Bucharest, Romania were killed in a fire (Popescu 2017). The public debate moved quickly from the regrettable accidental death of the poor beasts to the general subject of circus animals. A petition entitled "We put an end to the exploitation of wild animals in circuses" (Magor 2017) asking for a ban on the use of wild animals in circuses collected 62,096 signatures by February 7th. On January 29, the General Council of the Bucharest Municipality released a draft decision to ban animal performances in the State Circus. Also, the animals belonging to the State Circus are to be relocated by an NGO (Klodnischii 2017).

The use of animals for organized entertainment goes back to Antiquity. Ancient Greek and Roman territories, Egypt, India, Assyria, Babylon, or China have all known the practice of keeping wild animals for display and games. In the Roman Empire, thousands of local and exotic animals were captured and shipped in poor conditions to the Capital and other large cities. At destination, the animals participated in *venations* (demonstrative hunts taking place in the arena), parades and other types of entertainment. In late antiquity, Roman arena games had to transform, due to diminution of resources. Animals in *venations* were no longer hunted on the spot but preserved for return shows. Also, circus-type performance of tricks by the animals became encouraged (Mackinnon 2006). In modern Europe, arena shows were re-discovered by Philip Astley who started a riding school in 1768, with his

famous performances at Astley's Royal Amphitheatre in London including acrobatic riding (Frost 1881).

2. The underlying reasons

Why do people enjoy animal encounters and performances? More than a few hypotheses were formulated on why we cast a special status upon certain creatures, represented mainly but not exclusively by pets (Serpell 1996). Beyond the endless speculations on the origin of this behavior one element stands: in many cultures, some animals are regarded as special and even personalized and 'befriended'. People give them names, include them in their social world, exchange lots of affection with them and often comment on their human-like attitudes. In contemporary Europe pets can get clothes and accessories and be buried in cemeteries, as humans do. One might also find this fact interesting that from Aesop's fables to contemporary books (animation movies or video games) the public is attracted by and even accepts moral criticism from characters represented by anthropomorphic animals (Dunn 2011). *Why* do people exhibit such attitudes remains unclear, with 'humanization' being identifiable as an aspect rather than the cause of those peculiar interactions between humans, and animals. Yet, it is easy to observe that circus animals are also valued for traits that are alien to their normal behavior in the wild and rather human-like. Circus is a display of the unnatural, but this unnatural is attractive as it is rooted in 'humanization' of the animals. Circus animals are clever unusual beasts that are able to learn and perform. They are trained to react in ways that seem 'human' in terms of determination, coordination and performance, which attracts, amazes and amuses the audience.

Many continue to seek spectacular animal encounters in spite of the efforts of various organizations to educate the public on animal welfare that might have led to some success in terms of concern over the animals in circuses and disapproval of animal performances (Wells & Hepper 1997; The Scottish Government 2015; Zanola 2007). During the last years, a stand has as well been taken by various Western travel brands and tour operators against exploitation of wild animals (such as elephants, tigers, and snakes) in the form of travel attractions such as riding or various types of performance. Still, the demand for animal attractions is increasing and new markets are developing in the world (Baran 2016). Also, animals continue to be present in some circuses.

Are those speaking against animal circus performances merely 'obsessed' by animal rights? The July 2013 newsletter of the World Circus

Federation (Fédération Mondiale du Cirque 2013) seems to promote this perspective, whilst celebrating the legal victory of one renowned circus company against animal rights organizations and calling circus fans to organize some sort of a counter-movement in support of maintaining animal performance in circuses. The Federation quotes a pro-circus student activist: “... taking the circus away would be unfair to the public, the circus performers, and above all, the animals that circuses strive to take great care of and preserve for generations to come”.

As it can be easily observed, the quoted argument is centered on a term pertaining to ethics that can inherently bear a highly variable content, depending on whom do you ask about its significance: *unfair*. In this context, one might want to try and understand *what* is actually *unfair* and *to whom* when it comes about animals in circuses.

3. The unfairness

Violence tends to be generally viewed as *unfair*. It has been argued that violence and cruelty once used in taming and training of circus animals has gradually been replaced with less brutal methods. Yet, the training tools and methods that should be employed for corrective non-violent purposes are still used by some in a harmful way, so that the animals get wounded both physically and psychologically (Humane Review 2012; Kharb 2013; Zoocheck 2016). The case of trainers Roger and Mary Cawley (a. k. a. Mary Chipperfield), fined for cruelty to animals became widely known (BBC 1999). The undercover footage *Elephants in Circuses: Training and Tragedy* (PETA 2007) revealed to the world certain tamers' shockingly brutal perspective. As for the law suit so proudly mentioned in the World Circus Federation's newsletter, a legal analysis published by Beverage (2010) reveals a series of details about how animals were abused and convincingly argues that the 'victory' of the entertainment company was rather technical, due to 'ambiguities and counterproductive provisions' in certain laws and their regulatory schemes. Also, circuses have been recurrently cited by the United States Department of Agriculture for neglect and abuse of animals (Bradshaw 2007).

Furthermore, not only physical violence but also harming a living being by forcing it beyond its natural limits tends to be generally considered *unfair*; failing to provide proper shelter, food and water to an individual, be it human or non-human constitutes a basic example. Again, how far can therefore humans push animals so that we decide that it is *unfair*? Even circus animals that are not subject to brutal treatments remain creatures

deprived of a free natural life, convinced to learn tricks by methods that may be less unpleasant than the old-fashioned ones but are still unpleasant, and obliged to observe a strict schedule for our liking only.

Ecological and behavioral research has established that there is a deep unavoidable contradiction between wild animals' nature and circus life, as none of the wild species employed in circus performance meets the 'ideal' of having low cognitive function, low ecological and social needs, such that it would be proper for living in an artificial environment that bears the characteristics of a circus (Iossa *et al.* 2009). As their feeding, social and reproductive behavior are altered and limited by the specific living conditions, the conclusion that circus animals live an 'inevitably impoverished life' comes natural (Harris *et al.* 2006). Hand-rearing, training and performance, as well as frequent travelling affect them (Bekoff *et al.* 2015). They are exposed to risk factors and develop various health problems and abnormal behaviors related to 'circus life', with all that such existence implies (Rose *et al.* 2006; Animal Defenders International 2009; Hopster & de Jong 2014; Macháčová *et al.* 2015; Dorning *et al.* 2016).

The amount of *unfairness* has been certainly considered sufficient by some professional veterinary organizations so that to express negative opinions on the welfare of animals in circuses and eventually recommend that the use of wild animals for performance be banned (e. g. British Veterinary Association 2012; Federation of Veterinarians of Europe 2015; Veterinary Ireland 2016).

Worldwide, a number of regions, counties, municipalities, and states have banned totally or partially the use of animals in circuses. Such bans are in effect in Argentina, Austria, Australia, Belgium, Bolivia, Brazil, Bosnia and Herzegovina, Bulgaria, Canada, Chile, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, El Salvador, Estonia, Finland, France, Greece, Hungary, India, Iran, Ireland, Israel, Latvia, Malta, Mexico, the Netherlands, Norway, Panama, Paraguay, Peru, Poland, Portugal, Republic of Ireland, Singapore, Slovenia, Spain, Taiwan, UK and USA (Robinson *et al.* 2015; Dorning *et al.* 2016; Animal Defenders International *Circus bans*). Steps are now taken for enacting more bans in the UK (Ares & Cromarty 2016).

Public authorities may ban the use of wild species in performances, simultaneously advancing solutions for rehabilitation of the rescued circus animals. A very good example is represented by India, which in 1998 banned the use of lions, tigers, leopards, bears and monkeys and by 2004 the Central Zoo Authority reported rehabilitation of 314 lions and tigers from circuses. Confiscated

animals are sheltered in lifetime-care facilities established in the off-display area of the zoos (Gupta & Chakraborty 2005).

Over time, circus has had to adapt and cope with various challenges and changes in the society and it managed to survive and continue to be numbered among the forms of entertainment valued by many generations (Loring 2007). The contemporary world might also accommodate to viewing the animals in circuses not as some sort of inherited cultural commodity but as valuable living beings belonging to the realm of nature that we now so much struggle to learn to respect and protect, as G. A. Bradshaw (2007) so powerfully put it “animals are not defined by their circumstances but affected by them”. Circus can very well exist and entertain the public without animal performances. In *cirque nouveau*, which combines traditional circus arts with elaborate scenography into a thematic show of human artistry, sound and light, the art of entertainment has shown new performances that keep attracting the public for more than thirty years now.

We have the power to destroy and the power to build, the power to enslave and the power to set free, the power to force other living beings to serve us and the power to force our egoistic wishes to make room for kindness and compassion. What shall we choose, for this world, which is not only ours but also future generations’?

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Bioethics, Law, and Society: Joint AUSN, Center for Ethics of Science and Technology, and Eubios Ethics Institute Conference 24-26 June 2017 at the International Peace Park@kaeng Krachan, and Chulalongkorn University, Bangkok, Thailand. *Organizers: Center for Ethics of Science and Technology, Chulalongkorn University, Thailand, American University of Sovereign Nations (AUSN), USA, the International Peace and Development Ethics Centre, and Eubios Ethics Institute.*

Social Work, Human Security, Ethics and Human Ability, 1 July 2017, UKM, Kuala Lumpur, Malaysia. *Organizers: UKM; American University of Sovereign Nations (AUSN), USA, Asia-Pacific Forum on Ethics.*

Intensive courses on research ethics and bioethics in the Philippines:

Catanduanes State University, Virac, 6 July 2017

Bicol University, Legapzi, 7-8 July 2017

University of San Jose-Recoletos, Cebu, 10-12 July

Visions of Social and Ethical Change in ASEAN, and Beyond, 17 July 2017 (9:00-17:00) Chulalongkorn University,

Bangkok, Thailand. *Organizers: Center for Ethics of Science and Technology, Chulalongkorn University, Thailand, American University of Sovereign Nations (AUSN), USA, Youth's UNESCO Club, and Eubios Ethics Institute.*

Joint AUSN-Bangladesh Society of Bioethics Intensive Bioethics Training Course, 15-16 July 2017 in Dhaka, Bangladesh.

International Bioethics Roundtable: Bioethics Across and Between Continents and Peoples for the Betterment of All AUSN, Arizona, USA, 2-5 September 2017

Eighteenth Asian Bioethics Conference: The Future of Bioethics and Healthcare (ABC18), 25-28 October 2017 in Seoul, Republic of Korea, followed by a **Joint AUSN-Gangneung-Wonju National University Intensive Bioethics Workshop (ABA Satellite meeting)** 29-30 October 2017 in Gangneung, Korea.

The Eleventh Kumamoto University International Bioethics Roundtable: Philosophy and practice of bioethics across and between cultures, 18-19 November 2017, Kumamoto University, Japan.

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