On the Future Advances in Engineering and In-Vitro Culture of Human Embryos

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Recently, two embryologist laboratories have independently and jointly reported that they have teamed up and successfully cultured human embryos in-vitro beyond the previous technical obstacle, as well as the widely and also generally accepted moral and legal limit, of the implantation stage[1,2]: i.e. DPF day 14 (days post fertilization). Although this new model system can offer many interesting new insights into human development, it also represents an ethically highly complex and controversial issue. Another big break with recent ethical taboos and widely accepted standards, and hence R&D constraints, has also occurred recently, as Chinese scientists for the first time genetically manipulated human 3PN [tripronuclear] zygotes [which are the 'remaining' lower quality zygotes, while 2PN zygotes are used for human IVF, in-vitro fertilization], and also the resulting embryos, using a relatively new and powerful genome editing CRISPR/Cas9 technology, which is yet still in its very biomedical and methodological infancy (nevertheless, this method is already used manifold, likely due to a "keyword derived grant success effect"). Both, in-vitro culture and human engineering have very far-reaching implications: Already today, it is of highest particular importance to mention that the way is about to be paved for new in-vitro "embryogenic engineering strategies" emerging in the future, which will plan to also make use of human embryo in-vitro culture methods (for method prediction see Fig. 1) instead of the pretense to only try to get clues for rational design of better stem cell differentiation protocols. Rational design can be predicted today to not find all major clues due to inherent embryonic complexity. The use of an ECM matrix is only a natural exception, as it doesn't correspond to the highly regulative auto-patterned embryonic development - but enables it here from the outside. Hence, one can already predict today that "embryo cultures" will be used as additional stem cell differentiation protocol in the future to yield all cell types of the body, rsPSCs[3], and even various precious adult stem cell precursors, and embryonic organs[4] - that could be subsequently grown in-vitro, or in-vivo xenografts (in this case organ growth). This discussion shall review and add some crucial new points to this debate.

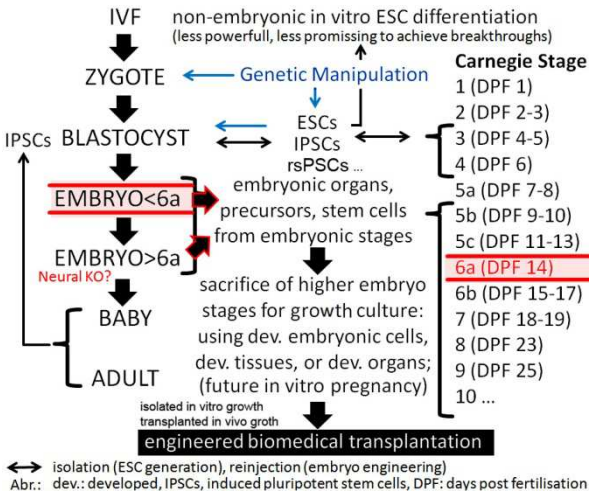

Fig. 1 Prediction of potentially emerging embryogenic in-vitro methods that would also require an extension of the Carnegie 6a limit, causing unseen ethical issues.

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Carnegie 6a: The Day-14th Rule

So then, human embryos were cultured in-vitro beyond the implantation stage using a simple growth media and a widely used and simple implantation matrix, which bears a standard complex mix of ECM proteins[1,2,5] (matrigel) to substitute for basal membrane signaling. This new procedure thereby allows a natural self-organizing autonomous growth of the hereby attached embryos, or also pluripotent stem cells, likely enabled by a critical cell mass, a blastocyst cave structure, geometrically, cellular polarity/structure and via signaling, e.g. of the basal membrane with integrins (β1)[5]: a cell to matrix signal, anchor and mobility, and informative interaction hub. Moreover, at this point, the advanced in-vitro protocols of the two new publications also indicate that these culture methods seem to already allow today - or very soon - yielding even much higher human embryonic stages in-vitro. In fact, the fallen technical hurdle puts all "too-curious" scientists on "a collision course" - but also makes any future control of it much more difficult. In between the lines, the studies indicate the potential of a technical feasibility far beyond day-14 that may be astounding but is not allowed by many and relevant national laws[6] and international guidelines of today[6], and this prospect is also prohibited to be tested in experiments (so how can we finally know and not guess?). Nevertheless, the in-vitro culture potential has already become another key reality and technological point of argumentation in the global debate about a potential shift of the allowed embryonic time limit. Initially, the 14-day DPF day-14 time limit was implemented internationally by 12 countries as three of the authors have also briefly reviewed here[6]. But already today, they conclude and strive for revisiting and extending the international "14-day rule" - but why so fast and so early, one might wonder? Where does the necessity arise for a fast change, from "competition"? A motivational driver usually is the scientific kudos. Hence, it is very likely that functioning protocols already exist and the hidden R&D potential behind these new embryo culture strategies promises more of it - if they were allowed ethically and legally (the R&D limit seems to be already the day-14 limit). In fact, already today, the day-14 rule is not taken as serious by scientists, as the legislator could have originally meant or intended it, potentially indicating some standard erosion. However, it really makes in fact very much sense to technically look at the developmental stage[6] and not the day post fertilization (DPF). Hence, it would be at least technically better (without giving a moral connotation) to define a specific developmental stage and not a specific DPF, also due to the different timing that can occur in-vitro, which was also found before in the "in-vitro differentiation speed" of embryoid bodies derived from embryonic stem cells (ESCs)[7]. Since it is not possible to arrest development at this stage, instead of the 14-day DPF stage, it were better to use the developmental stage defined term "Carnegie Stage 6a" that corresponds to the primitive streak, body plan, and the axis formation

stage, as well as individuation, and distinct pattern formation, while a spatio-temporalization takes place alongside with a process called germ layer pre-specification, including differentiation into the neuro-ectoderm making the prospective brain/CNS. Hence, the distinctly defined sub-stage term ”Carnegie 6a” not only makes very much sense from a legal-political, but also from an embryologic and scientific point of view.

Additional Points for the Ethical Debate

The “day 14 guideline”, which was, however, implemented in the real-world laboratories as “Carnegie 6a” and in the studies, should be thus legally adjusted, like the international guidelines to “Carnegie 6a”, even if such would be further extended one day for a specific but highly controlled purpose. The Carnegie 6a or day 14 DPF line was also intentionally drawn[6] close to the point when the very early neural progenitor cells of the prospective CNS/PNS first develop in the neuroectoderm (a precursor blastodermic layer of the embryo). The basic logic behind most of our ethical decisions stems from a widely unexpressed belief and assumption that the “functioning nervous system” and “cognitive self” would entitle us to “human rights” - and, as it also seems, not one of the other cell types of our body (a neurocentric ethical and senior anthropocentric minted logic). Hence, today, our non-neural body belongs, somehow, like a biological property, to our respective and functioning CNS/brain, and is used and owned by it every moment, also in most relevant legal contexts. But, it cannot exist independently without our body and has achieved to bear the human rights comprising the legal rights that its biological assets of the individual remain undamaged and “free”. This dominating argument of partial cognitive neuroscience originally stems from the idea that our perception, feeling, consciousness, thinking, and so on, is a key prerequisite for our self and being, and thus of our human rights that are more legally-bureaucratically termed “moral status” these days and also in this debate. This is, for example, why our medical systems may treat a diagnosed “brain-dead patient” as “clinically dead” (moral status of a dead), which self-allows the medical practitioner to even stop all life-support, like machines, even if only cognition is somehow deeply impaired (with some exceptions still given).

“Can you really give a human embryo the moral status of a dead human person?”

The answer is no and indicates that the entire idea behind giving a “moral status” is misleading due to the multidimensionality of the dilemma. But this also doesn’t mean that a final conclusion is reached here - also due to the multidimensionality of the same dilemma. Additionally, that “no final conclusion is reached” doesn’t mean that this is a final conclusion that is reached about this topic in any way and that a line can or cannot, or should or should be not drawn somewhere in the sand. However, it can be concluded that all dimensions and facts and all contexts have to be considered

in a well-weighted and unbiased but at the same time also political manner - which is in fact also a dilemma - and that the answer can be still either yes, no, or in between, i.e. in the sand. Thus, this is actually where the discussion should start and not where it ends. From the previous example, we may derive that the functioning of the human brain/CNS is also in our health care system the underlying defining feature for the steady admission of "human rights" and the "human right to live". Whenever it comes to such definitions, we can find that the overall functioning of the CNS can be in fact defined "quite differently". Functioning is more ambiguous than often and widely anticipated. Hence, until today very many inconsistencies in this CNS-derived logic, justification, jurisdiction, and ethical rationale of human rights still exist, as "functioning" can be defined and technically assessed in many different ways, also in the "human embryo ethics standards and stage limit debate". What might seem to some of us maybe like somewhat "scientifically irrelevant philosophic thinking", nevertheless, finally drives all of our hard-fact decisions, laws and also standards about this methods and thus also science. For instance, also the basis of the "moral status" that we admit to embryonic life and other life, for instance, a "potential extra-terrestrial life" or to animals of this planet. The mentioned inconsistencies also persist here, and once again due to the ambiguous definition of "functioning". To also give some example for this ambiguity: (1) what if we are not very intelligent relative to extraterrestrial life [would our brains maybe start to claim our right to live differently?], or a real-world down to earth example (2) about 65 billion animals with very high cognition, with intelligence, and also a very complex CNS are still mass slaughtered per year, as their CNS does not seem to entitle them to specific or equivalent rights" - according to our CNS that defines functioning via a higher and more anthropocentric type of quality in cognition. "Quality of cognition and thinking" is likely to be much biased since it is always defined by a thinking that entitles itself (there is not "one measure or way" to test it). A more specific comparison in this context might be the nationally highly related and often debated legal time limit on human abortion. Many countries orient on the Carnegie 6a stage, i.e. the 14-day rule, but "much later legal limits" are also found with up to 90 days, for example in Italy, or even up to "full viability reached by the biologically independent child", e.g. in the Netherlands, which can be up to ca. 160 days, or week 22. This very late stage corresponds with an already very much developed human embryo, brain, and individuality. One could also easily argue that an already "functioning brain" can be diagnosed depending on how it is de facto tested and assessed (ambiguity and qualms increase with stage). That week 22 might be in fact a limit set too late, is also seen by many professionals from the medical field, and the fetus and brain may even feel pain already before week 20[8] There are in fact reasons to speculate that a "preliminarily functioning" brain is very likely

to be found yet in much earlier stages. These facts and ambiguities should be better researched (if this is ethically and technically possible) and they still need to be better understood. That "a line is drawn in the sand" - as it was stated by the three authors[6] - is correct, but it cannot be used as an argument *per se* to shift this line in one or the other direction. "Arguments can be found" to draw the line at very many stages starting from stage 0 - as a human life frame has an ethical value that can be in fact weighted differently. By trend, some religious people might weight it 100%, less-religious scientific people might see it close to 0%, as only some cells that do not think or feel, and there would be also a very high somatic cell turnover every day; but these somatic cells would not team up to generate a new human life (generation of IPSCs[9] are an artificial exception to this rule that only happens in the laboratory). Still, this situation indicates the existence of multiple relevant dimensions and that a more complex ethical issue is given here, which needs to find a way to integrate all scientific, technological, societal, social, ethical, religious, medical, cultural, criminal, philosophical, and human rights questions, and all of the related or respective contexts, by carefully and exactly weighing in all of the manifold contemporary and future associated risks and opportunities, and how they would really turn out to transmit de facto in the realm of possibility of the real world. Additionally, today's "attainable feasibility of controlling" of such embryogenic procedures to avoid potentially undetectable breakings of the law should be also better considered. Future long-term strategic implications and "nash equilibria" should be also kept in mind.

Advances in Manipulation of Human Life

For the first time in history, human embryos are genetical modified, somatically and also (very likely) in their prospective germline[10]. Also, many additional genetic, epigenetic, cytosolic, and other molecular modifications are already thinkable today. February this year (2016), the UK's HFEA[†] allowed - also for the first time in history - to genetically engineer human embryos in a so-called western country, which is facilitated by further advancing genome editing methods like CRISPR/Cas9[11–13]. As a result, human embryos are already routinely modified and engineered using the "remaining 3PN zygotes" from IVF procedures. This first report about this strategy published by Chinese scientists in 2015 demonstrates the feasibility to genetically manipulate human zygotes and embryos[10,14]. Noteworthy, these scientists were still facing several significant difficulties with the method and indicated that the "fidelity and specificity" of their protocols must be still further improved a lot for all potential clinical applications (low efficiency, high-risk off-target effects, mosaic editing)[10].

Mosaic Editing, Allele Complexity & More

The notion of the Chinese report of mosaic editing, post-human zygote manipulation, reveals how we can estimate the state of the

[†] Human Fertilisation & Embyology Authority, London, UK

recent methodological affairs[10]: The CRISPR /Cas9 method is still very much in its testing phase. The mosaic phenotype is also known from inducible homologous recombination in ESCs and embryos (not shown) or CRISPR methods in other mammalian systems[15], i.e. mouse embryonic stem cells and the early embryos. By only looking at the particular methodological and genetic risks it becomes already fully apparent that human genetic engineering is not justifiable today and there is still a long way to go while adverse genetic effects are better researched in mice. The genetic manipulation of the human germline bears too many uncontrollably high risks.

Embryology-driven ESCs Methods

It has become clear that the most powerful embryonic stem cell protocols are likely to go "the specific route of embryology" - although differentiation not always has to take this strict path and can also sometimes take "alternative, more artificial routes" (e.g. in the engineered non-embryogenic cellular ESCs in-vitro differentiation protocols). Despite this ambiguity, it is still argued today that the only and best way of rational design of the differentiation protocols for human, mouse, and maybe all mammalian stem cells, is to "learn from embryology to resemble it in-vitro in the stem cell differentiation cultures". This is also a key argument and the last outlook given by the recent reports[1,2]. However, this argument might be used to put regulators and populations mind at ease - and there is an even later and more far-reaching outlook to be given, which is actually already much thinkable today and "not unrealistic" but even "likely to happen in the future": technically, as one could easily agree, the best way to resemble something is, in fact, to do it exactly the same way. Thus, the best way for regenerative medicine stem cell research to resemble embryology could be to enable embryology itself in-vitro - and the new reports indeed show a new and high method potential and maybe hidden affinity for such embryogenic strategies and approaches[1,2]. To best resemble embryology in vitro, future scientists could thus enable or simply (only requires IVF plus growth culturing methods - differentiation would go its programmed way) perform embryology in-vitro, and the reports and demands to extend the day 14 Carnegie 6a limit are probably only the very first step in doing so, and many steps alike are about to follow. Hence, the kudos-drive will prepare the society for sequentially higher staged limits of embryo experiments fueled by the promise of salvation of new embryogenic tissue and organ transplantation medicines. Hence, these developments have to be also seen in the emerging context of potentially arising goals of the emerging future applied embryo engineering research. Nevertheless, most researchers, even the leading experts in the field, still did not fully mention the big picture or the future potential and risk of these methods, as it can seem, including these very latest breakthrough reports[1,2] (05/2016). Already today, aside from IVF, the use of blastocysts also provides another technically feasible "embryonic vehicle" to perform all steps of differentiation within

embryologic contexts (Fig.1). Embryonic in-vitro culture is a promising scientific field on the other hand for all sorts of R&D purposes: (1) to better understanding in a "model system" human (early) embryology and development (the model system is not only a model it is the subject itself), (2) for rational design of cellular in-vitro differentiation protocols, but also (3) of human genetic and other types of engineering, and (4) of embryo in-vitro culture techniques to harvest primordial cells and organs[4] that could be grown in-vitro and as xenografts for regenerative medicine, rejuvenation, and new organ transplantation. Approach 3&4 both bears high ethical risks of (I) e.g. human embryo culture for scientific commercial and additional purpose; or (II) potential non-human and human chimera biohazards e.g. with ESCs, IPSCs[9], rsPSCs[3]; or (III) genetic engineering, (IV) germline manipulation, and additional thinkable biohazard of human engineering. Simplified, with other words and highlighting the real implementation risks: in the future, one could, for example, start to sell in-vitro differentiation products that were secretly generated via embryo-methods and hidden embryo manipulation techniques and alike. Such powerful embryo methods could theoretically fully escape public control and could comprise engineered and chimeric human life forms that can bear the potential of genetic ethical and utterly devastating human individual and societal disaster. Maybe that is also a reason why this was not mentioned in the R&D outlook of the recent reports[1,2], which is only the very beginning of such potentially emerging embryogenic technologies. But still, these coherences and potential risks must be explained to the public and policy makers at some point, somewhen, and also somewhere: that's why they are claimed here to start a discussion.

"All potential risks must be explained to the public and policy maker"

Another potentially high risk of these new opportunities also stems from a high level of uncontrollability that also arises especially from those risks that are not on the regular and public map of our understanding. The right legal measures should be taken and must be found in the future based on a full understanding of all possibilities and risk potentials, contexts and dimensions, which is the initial idea of this discussion here. Now that embryos can be cultured in-vitro, a longstanding technical hurdle was somehow easily taken and more technical hurdles can be predicted to potentially fall if a publication and procedure is allowed. Today, there is already a significant risk and moral issue that arises whenever (1) human or humanoid embryos are cultured or whenever (2) ESCs are differentiated into human and chimeric non-human blastocyst-derived embryos (e.g. mouse[16], swine, monkey, and so on) in order to generate "precious primordial stem cells", or "rsPSCs[3]-like cells", which by the way also work in ethically controvertible inter-species pluri- or multipotent stem cell xenografts[3], tissues, and organs[4] in-vitro and in-vivo (see

brief summary prediction in Fig.1), and (3) genetic manipulations of the germline, etc. These risks should be much better controlled to prevent a potential misuse today, also in light of the feasibility of late stage chimeras and the "incentives of organ generation".

"Human embryo xeno-chimera disasters and genetic hazards must be prevented."

For some readers less familiar with the topic, it might seem 'counterintuitive' that stem cell science could now choose to go embryonic, as the authors have just identified new culture ways to go in-vitro, and in-vitro methods would advance fast - seemingly. Nevertheless, they, in fact, only assured a new in-vitro way to go embryonic in-vitro to undergo it's in-vivo stages in the absence of "external" maternal tissues mimicked here[1,2].

"The embryonic path could be seen as the fast and easy lane of differentiation into all body tissues, organs, and cells".

This embryonic fast-track comes along with high potentials: high opportunities and also high moral and human risks. The in-vitro advances are in fact on the extra-embryonic side of in-vitro development: the blastocyst's implantation while the program of self-organization of the human embryo devoid of maternal tissue[1,2] is running best in the embryo context. Put simple, as mentioned also in my thesis, the high level of inevitable self-organization is based on an "anticipated auto self-patterning mechanisms of ESCs" (embryonic stem cells) in the blastocyst, later the so-called epiblast cells that form the primitive streak embryo that forms a critical mass that in turn interacts in the blastocoel with the blastocyst's basal membrane and geometric cellular structure. Hence, to fully resemble embryogenesis one can start with IVF (zygotes; fully feasible) or a blastocyst stage (partially feasible engineering; usually chimeras; but method potential generally given), while it is still thinkable that optimal in-vitro protocols could be found to circumvent this approach one day, which not necessarily has to be "fully reflecting the underlying embryology" (i.e. resembling the embryonic molecular-genetic sequence of cellular states), but can be also found via engineering and screening strategies.

"If scientists will one day make use of this emerging embryologic differentiation method, and if they want to grow e.g. a human eye, the embryo that they will have to sacrifice for that will also have a highly developed human brain and stage, causing an unseen bioethical dilemma"

Blastocyst Stage "Embryonic Vehicles"

Today, it is technically still not possible - or unthinkable - to rejuvenate embryonic stem cells into a zygote or into multicell-embryonic stages (Carnegie 0-2, see Fig.1). This would allow for in-vitro blastocyst development, a powerful embryonic stage vehicle for a full embryonic program induction. Additionally, it is still also not possible to create a blastocyst

in-vitro (ca. Carnegie 2-3), which would be another technical producibility breakthrough as the blastocyst is still the key vehicle for many embryonic stem cell strategies and to "go embryologic" in engineering protocols. Yet, also recently, new technically promising reports indicate that this could be feasible one day[17]: for instance human ESC-derived trophoblastic spheroid implantation models[17] could maybe become a next further advancement. Although ESCs could technically give rise to trophectoderm (TE) cells, so far, a functional blastocyst has not yet been engineered from scratch, in early 2016; but the point is: it could work one day. Then, blastocysts filled with ESCs could be developed into embryos in-vivo and -vitro. So what has in fact happened here to ESC biology is that it starts favoring to "also go the embryonic route", which means taking real embryos instead of finding tremendously complex in-vitro ESCs protocols (e.g. for entire organs[4]), while stem cell progenitors seem more feasible to be found in-vitro without embryogenic protocols. Knowingly or not, as this strategy was not mentioned in all the reports, which only conclude to focus on the rational design of ESC in-vitro protocols while forgetting about the potentially evolving embryogenic protocols[1,2]. The technical reason for the embryogenic need in the protocols is that the early stages of ESCs, especially the ones around the "Carnegie 6" stage, all have to go through a spatio-temporal signaling attached-blastocyst auto-patterning phase, which is also likely to be geometrically and structurally primed, and via cell polarity and signaling [5] also with the basal membrane e.g. mainly integrin β1[5]. The early ESCs stages have to deal with the auto pattern formation program that happens best in a natural context and the "framework of the blastocyst" - and only a partial semi-auto-patterning can be observed with ESCs alone[18] in vitro (not a full functional embryo formation - only a resembling of embryonic patterns). All ESCs and embryoblast self-organization is, in fact, expectable from their described nature and from all what we know today about their biology - but it is still a legitimate new point that was made in the experimental findings that now clearly seem to validate the predominant previous views. With other words, "ESCs need to undergo an independent bottleneck of priming" and self-patterning within a spherical or flattened spherical/disc like stage: and the best way to enable all development lines at once seems to be the original embryonic development - and the very high early interdependence of all tissues could make this a requirement.

***Embryologic cell fate interdependence makes the "embryogenic protocols" a potential future requirement for the* creation of complex organs and tissues.**

For example, during development, one early tissue sends important key cues and signals to its adjacent tissues of a different cell fate tissue, organ, cell type, function, and future. This is an important method aspect of future R&D that has been seemingly forgotten here, like how to deal with the unseen

complex ethical issues and dilemmas of human embryo generation and (mass) destruction, manipulation, and engineering? How to prevent human xeno-chimerism and human genetic hazards or embryo crimes? Can potential future biomedical opportunities outweigh all of these high risks? The new methods establish a new deep dilemma and divide. It is already very clear today that it requires new ways to regulate and control these biomedical procedures with human life: i.e. human early life would have to be destroyed to cure another older human life, a new biomedical phenomenon of the more traditional "passed down senior domination" in human societies. Like everywhere, like also in science where the senior scientists dominate our views and finding and junior scientists like me have it difficult to publish (due to publication costs only senior faculty networking peers) like any of such concerns or "future technology predictions" (Fig. 1).

A human science-fiction nightmare becomes more reality - but a biomedical dream of regenerative medicines too.

Also, patient-specific IPSCs[9] grown in-vitro could also give rise to patient specific organs using spare part clones of themselves and alike. Ways will be found to sacrifice the remaining embryo "at the earliest Carnegie stage possible (approach)" due to the high moral issues, while stem cells, organs[4], and primordial tissues are isolated and could be grown elsewhere. Non-neural embryo culture (conditional CNS KOs) will be found as an optional (but still problematic) alternative (a human embryo generated without a brain would maybe have a different legal "moral status" in the future, but there would be a rudimentary brain/CNS leftover, a possibility that would cause highest ethical concerns). "Tomorrow" this would be maybe nothing that the population could fully agree with, hence it will be maybe an in the details kept biomedical secret that nobody will be able to check privately without a permission that nobody is granted except some "established seniors" (like it is already today in science to some extent). It could be also an ongoing subject of a "systematic censorship", and so on. Also, animals could be theoretically cultured this way one day (CNS-less), and then electrically enervated to build up muscle - but to escape this dilemma? But what would you think, if an "alien species" or a "genetic slave driver" would do exactly the same with us, or to us? We would most probably reject this idea, wouldn't we? Such theoretical questions could probably help to reveal a more unbiased understanding. An opportunity-risk-dilemma will likely always be inherent all of these methods. The more valuable the tissues, cells, and organs[4] gained, the later the embryonic stages by trend, the higher the ethical dilemma and moral issues that will arise not only from its misuse but also from its use: hence, opportunities will try to outcompete the risks.

Embryo Policy Dilemma

Contemporarily, it might be alarming to see that the two most and widely agreed upon,

axiomatic and broadly incontrovertible moral standards, taboos, and also legal-political regulations about human life, are breaking away so easily and quickly, and nobody seems to be able to stop this development, which now widely becomes a new normality and reality. This trend is much in line with the globally observable reduction of moral and democratic standards, and also in this case due to the international technology race and a predominant game theoretical thinking found worldwide: "The: if we won't do it, someone else will do it thinking". E.g. due to a lack of international standards, which could be maybe called a "global UN standard deficiency". To be more specific, only some years ago, the human germline was a totally agreed upon, and totally untouchable, taboo for all scientists in many countries. It is now falling so quickly, so unnoticed, seemingly like in a salami swindle. What might be good for scientific progress bears the societal costs of "potentially uncontrollable misuse". China and also the UK will now officially and routinely culture and also modify human embryos[11,14] and an international law still remains elusive and seems, like all urged for international laws, very infeasible today - despite their need. Hence, a reform of the UN might be proposed also from this frontier to make it more capable of acting.

Let's think of real world examples: Would you allow destroying an early embryonic human life - and up to which embryonic stage - e.g. to give back sight to a blind?

So far, by now the US and many other countries have moved to resist and block these trends at least to some significant extent of measures[19] to embark on the quest for finding the best contemporary solution for the dilemmas.Additionally, many top expert scientists have urged to fully prevent germline manipulation[20] due to inherent and uncontrollable risks, but also to prevent all of the hidden and unknown risks. There is still too many details and risks that are not fully understood[10] and once a genetic disaster has spread - it could be difficult to stop it.

Thus, any potential genetic poisoning of the human gene pool via the germline must be prevented systematically.

Experimenting with human life is always a very difficult moral issue: e.g. embryo manipulation, but also our clinical trials. The reader should please notice that all of these futuristic new "embryogenic methods and human genetic manipulations" are potential trends that are not all going to happen in the next decades but some could. The point is that they can become a bigger reality one day, in a more distant future, which will be prepared for maybe already today, and some methods already today work to some extent. Additionally, the moral and ethical questions of the problem are also much predicated on the adverse societal context and all of the risks of this technology - again including the point that hidden violations of the law seem to become much more feasible over time. Also, several potential violations cannot be

systematically screened for today: e.g. human embryonic stem cells could be propagated indefinitely in laboratories, just secretly, like HeLa cells, of which scientists have generated more than ca. 20 tons until today (of HeLa in 2014). So, how to prevent a misuse here? Human ESCs (hESCs) could be also injected into blastocysts to give rise to engineered, modified, chimeric and non-chimeric embryos even in medium-cost labs all around the world. The same holds true for the abundance of human zygotes (3PN, 2PN, 1PN) that could be easily miscounted or also accounted differently and transported frozen around the globe. This indicates that "a lack of controllability already exists today". How should that get any better in the future with all of the new methods evolving? "Should that happen via an obligatory human life surveillance officer in all embryo laboratories and clinics, in all countries?" That could be probably too expensive. Later on, genetic germline modifications and new embryo production techniques are also very difficult to be found or detected. Although these opportunities and risks might be still much "like dreams and nightmares of the future", it seems to be obligatory already today, to think them through, to prevent fatal situations and technological nash equilibria from forming before it is too late for a prevention strategy.

Future Implications and Moral Issues

Finally, the added and reviewed points of risk are briefly summarized here: (1) the risk to human life and the society from human embryo culture; (2) the risk of human genetic, epigenetic, somatic, germline, and other modifications, or otherwise engineered human life forms; (3) risk to human life from embryonic in-vitro culture; (4) risk of "human xeno-chimera embryo biohazards" and life-forms [genetic, cellular, neuronal, late-stage, etc.]; (5) risk of moral hazards stemming from embryogenic production, in-vitro human spare parts (6) neuronal KO and semi-KO and all sorts of neuro-manipulation, genetic manipulation of human behavior (7) genetic slavery or genetic divide (8) long-term social-genetic risks: a society that is further subdivided into rich and poor could drift in an irreversible "genetic discrimination nash equilibrium"; (9) risk of genetic manipulation, screening, asymmetric information, the general risk that the public is not well informed by the media and news; this also includes censorship, and policies to not explain it to the public and media, scientific and journalistic self-censorship; and (10) other future social structure risks: only a society with fair hierarchies and free political structures, a fair foundation of human rights, fair wealth and information distribution, and fair sustainable standards for all, could be able to best manage all of the high societal scientific and biomedical quality standards, R&D and human-genetic and -embryogenic controls that are needed as a prerequisite to only "ethically" and "socially beneficial" make use of generally all technologies that have emerged or will - in a common human future.

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