Genetic Engineering Transgenesis:Advantages, Assessment of Risks and Ethics

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ملخص

تعرَّف الهندسة الوراثية بتعديل المنظومة الو راثية للخلية و يعرَّف نقل الجينات بنقل الجين أو سلسلة من ألـ DNA إلى كائن حي بطريقة صناعية. ولهذه التقنيات فوائد علمية بحتة في الدراسات الجينية والفسيولوجية مثلا، ولها أيضا فوائد تطبيقية في التحسين الوراثي.

نقل الجينات ليس بالضرورة ضاراً بعْينه باعتباره نقل قطعة من الـ DNA مماثلاً في ذلك للتبادل الطبيعي للمادة الوراثية، ومع ذلك فالأمر يقتضي لكل حالة على حدة اتخاذ كافة الإجراءات الكفيلة بالتحقق الكافي من هوية الـ DNA المُدْخَل ومنتَجه وأثاره في الكائن المعدَل وراثياً. من الممكن مثلاً أن يسفر الإدخال عن إتلاف جين آخر أو عن تفعيل ضار لجين آخر. من المخاطر الممكنة التي لا بد من تقييمها السُّمية والتحسُّس إضافة إلى الأخطار البيئية كالانتشار غير المسيطر عليه للكائنات المعدَّلة وراثياً، وتأثير ذلك على توازن الأنواع إضافة إلى احتمالات مزيد من تنقلات الجين المدخَل بين الأنواع بطرق وعواقب غير متوقَّعة. تناقش هذه الورقة بعض التقنيات لتحقيق ذلك كتقنية "مبدأ التكافؤ الشامل" وتقنية «البصمة الأيضية».

في ضوء فعالية تقنيات الهندسة الوراثية ونقل الجينات ينبغي أن نمضي قدُماً فيها ولكن مع إجراء ما يمكن من احتياطات الأمان للكائن الحي المعدَّل وراثياً ولبيئته وتوازنها وللإنسان خليفة الله في الأرض والمُستأمن عليها. ففي الوقت نفسه الذي نؤمن أن الخالق جل وعلا قد سخر لنا ما في الأرض، فإنه علَّمنا أنه ما مِن دابة في الأرض ولا طائر يطير بجناحيه إلا أُممٌ أمثالنا!

SUMMARY

Genetic engineering is defined as modification of the cell genome and transgenesis is defind as transfer or introduction of a gene or new DNA sequences into an organism by artificial means. These technologies have important fundamental (e. g. for genetic and physiological analysis) and biotechnological applications (e. g. in breeding).

Transgenesis mimics what is going on in nature and, therefore, is not harmful. Transgenic risk therefore has to be assessed on a case by case basis, depending firstly on the nature of the genetic construct introduced and secondly on the insertion's consequences (as it may inactivate a coding gene or activate another gene which may have dangerous effects). Assessment should consider the toxic, allergic and ecological risks, in addition to unpredictable effects of transgenesis on the equilibrium of species and the horizontal transfer of DNA to other species. Some techniques that would make this possible, such as the principle of "substantial equivalence" and the technique of "metabolic foot-printing," are discussed in this paper.

Transgenesis is an efficient technique, and thus its benefits should be obtained. However, all the necessary precautionary measures should be taken. This should ensure safety not only for the genetically modified organism but also for other species including the human being and consequently the environmental equilibrium. Humans are responsible for this planet and are considered as its "trustees". At the same time since God authorized us to get benefit from the universe; we are instructed to respect all the creatures as they are "nations like us"!

Introduction:

Biotechnology is the use and or manipulation of living organisms to improve, modify or produce important products or processes for agricultural, industrial, medical and environmental purposes. Genetic engineering and transgenesis are powerful biotechnological tools. The former entails the modification of the cell genome; the latter the transfer or introduction of a gene or new DNA sequences into an organism by artificial means. The introduced genetic material is limited and well-characterized. In either case, the modified cells or organisms express and transmit a new genetic trait. In genetic engineering, different mutagenesis techniques can be used to modify the genetic composition of DNA. However, in transgenesis we have to obtain the desired gene from a donor organism using restriction enzymes, and then making a construct by ligating it into a vector that will be introduced into a living cell, be it that of an animal, plant or bacterium. These cells should be able to perform a new function encoded for by the introduced gene.

Not surprisingly, people are divided into different camps over biotechnology. Opponents note that the long-term results of these new technologies remain unknown. We do not know that their effects might not be deleterious, and if so if they would be reversible. However, proponents argue that transgenesis has an exceptional importance in our life because of its many applications (Niemann et al., 2005). For them, transgenesis and genetic engineering rank among the top four scientific advances of the 20th century, similar in significance to unlocking the atom, escaping the Earth's gravity and information technology revolution. They note that to meet the needs of an ever increasing global population, man has to employ techniques that have to be both rapid and efficient. Genetic engineering and transgenesis proved to fill these requirements.

However, in both genetic engineering and transgenesis, we do not

create cells or organisms. We just manipulate created material; i.e. cells and organisms that already exist. But that is no more than we should expect. In the Holy Koran. Creation is a characteristic of God, not man:

The Bee::

أَفَمَنْ يَخْلُقُ كَمَنْ لَا يَخْلُقُ ۗ أَفَلَا تَذَكَّرُونَ (١٧)

17. IS THEN HE WHO CREATES LIKE ONE THAT CREATES NOT? WILL YE NOT RECEIVE ADMONITION?

Pilgrimage:

يَا أَيُّهَا النَّاسُ ضُرِبَ مَثَلٌ فَاسْتَمِعُوا لَهُ ۚ إِنَّ الَّذِينَ تَدْعُونَ مِنْ دُونِ اللَّهِ لَنْ يَخْلُقُوا ذُبَابًا وَلَوِ اجْتَمَعُوا لَهُ ۖ وَإِنْ يَسْلُبْهُمُ الذُّبَابُ شَيْئًا لَا يَسْتَنْقِذُوهُ مِنْهُ ۚ ضَعُفَ الطَّالِبُ وَالْمَطْلُوبُ(٧٣)

73. O MEN! HERE IS A PARABLE SET FORTH! LISTEN TO IT! THOSE, ON WHOM, BESIDES ALLAH, YE CALL, CANNOT CREATE (EVEN) A FLY, IF THEY ALL MET TOGETHER FOR THE PURPOSE! AND IF THE FLY SHOULD SNATCH AWAY ANYTHING FROM THEM, THEY WOULD HAVE NO POWER TO RELEASE IT FROM THE FLY. FEEBLE ARE THOSE WHO PETITION AND THOSE WHOM THEY PETITION!

The Criterion:

وَاتَّخَذُوا مِنْ دُونِهِ آلِهَةً لَا يَخْلُقُونَ شَيْئًا وَهُمْ يُخْلَقُونَ وَلَا يَمْلِكُونَ لِأَنْفُسِهِمْ ضَرًّا وَلَا نَفْعًا وَلَا يَمْلِكُونَ مَوْتًا وَلَا حَيَاةً وَلَا نُشُورًا (٣)

2. HE TO WHOM BELONGS THE DOMINION OF THE HEAVENS AND THE EARTH: NO SON HAS HE BEGOTTEN, NOR HAS HE A PARTNER IN HIS DOMINION: IT IS HE WHO CREATED ALL THINGS, AND ORDERED THEM IN DUE PROPORTIONS.

3. YET HAVE THEY TAKEN, BESIDES HIM, GODS THAT CAN CREATE NOTHING BUT ARE THEMSELVES CREATED; THAT HAVE NO CONTROL OF HURT OR GOOD TO THEMSELVES; NOR CAN THEY CONTROL DEATH NOR LIFE NOR RESURRECTION.

Two additional points should be made here. Transgenesis has taken place between different species since the beginning of life but using natural means (e. g. crosses by wind, insects...). These events even if of low frequency, would have transferred complete genomes between different species. The artificially-made transgenesis is much more limited than the natural transfer of complete genomes. Further more, the very idea that biotechnology approaches the mystery of creation follows from the idea that everything in an organism is inscribed and dictated by its DNA sequences. But this is not true. There is also epigenetic inheritance--traits transmitted by mechanisms not directly involving the nucleotide sequence of a genome. Epigenetic inheritance includes modification of chromatin by DNA and histones methylation/ demethylation and also by histones acetylation/deacetylation. Clearly, environmental influences and random phenomena can play a significant role during development. That's why Dolly died after suffering from diseases that were not experienced by her "mother". Dolly lived less than her "mother". Epigenetics can explain also the difference between even the identical twins. Epigenetic variations might help explain why one identical twin acquires a genetically based disease, such as schizophrenia, but the other does not, despite their identical genomes. Creation is too much complex to be just determined by the DNA sequence. It's an issue of the extra power of God!

This is not to pretend that there are no ethical issues in applying the techniques of genetic engineering and transgenesis to human beings, but that apart there is no reason why they should not efficiently provide reservoir of technologies for the pharmaceutical, industrial, agricultural and environmental industries.

Aims of the Study:

1. Understanding the new technologies of genetic engineering and transgenesis, their principles, applications and drawbacks.
2. Assessment of the ethical impact of these technologies.
3. Making a religious assessment of these technologies.
4. Attributing technical and ethical responsibilities to human beings.

Hypothesis:

Faith in Islam implies that the Holy Koran and the authentic Prophetic Sayings are authoritative. In this paper, the advantages and disadvantages of the new technologies of genetic engineering and cloning will be weighed and assessed in the light of the Holy Koran and the authentic Prophetic Sayings. If the advantages dominate with no clear contradiction, then these technologies can be approved with the necessary precautionary measures and ethical principles that are also extracted from the Islam sources and human good sense.

Methodology:

This paper will neither concentrate on the methods of genetic engineering (chemical or physical induced mutations, knock out, PCR mediated mutagenesis...) nor on the methods of transgenesis (e. g. microinjection and the use of stem cells). Instead, the applications of transgenesis will be reviewed and the responsibility of human beings to manage these techniques and to ensure safety for themselves and their environment will be discussed. The discussion will be guided by the scientific results and texts extracted from the Holy Koran and Prophetic Sayings.

Fundamental and Biotechnological Applications:

(A) Basic Research:

Transgenic animals can serve as models for the study of gene function and mechanisms of genetic action. If the gene is known, a hypothesis explaining its role or defining its control mechanism is evaluated.

Furthermore, systemically knocking out laboratory animal and plant genes can provide us with banks of knocked-out animals and plants, which should be important in highlighting the functional role of a specific gene and its interactions with other genes.

In addition, transgenesis is the validation method for genetic and physiological analysis, as in vivo regulation studies. In this case

deletions are made in the regulatory sequences of the gene, which can be constructed, with a coding reporter sequence in order to examine the importance of each of those deletions (Ghareeb et al., 1998)

(B) Biotechnological Applications:

Human beings are confronted with the problem of ever increasing population and ever decreasing cultivable lands and available space for animal production. We need to multiply the present production by 3.5 to offer enough food to 10 billion human beings in 2050. In addition, in agriculture, up to 40% of the harvest may be lost as a result of different diseases. Introduced animal resistance for example can reduce the use of antibiotics, is simpler for farmers, reduces cost, reduces transfer to human and makes animals enjoy a better quality of life. To do that, we have to look for revolutionary plant and animal production and protection technologies like transgenesis, which seems to be vital.

The applications of these biotechnologies are varied--from giving a new character to plants (like resistance to herbicides and pesticides), to the design of bacteria able to decompose the oil spills, or (in other cases) able to produce pharmaceutical products like growth hormone; proteins able to dissolve blood clots in heart attack therapy; insulin; blood clotting factor VIII (highly important in decreasing bleeding); antithrombin (a blood thinner) and many other vital compounds.

Transgenic animals are invaluable in breeding, for desired traits can be selectively introduced between species regardless of the classic mating barriers. This is of utmost importance for production of vital substances for nutritional, pharmaceutical and industrial purposes using the living cells and organisms as "new factories". This biotechnology can, therefore be considered as a nature-mimicking bio-technique. It mimics what is going in nature since the onset of creation and, therefore, is not offensive per se.For example, transgenesis technology has been applied to fish. Fish growth hormone genes have been transferred to various fish species (trout, salmon, carp, catfish, tilapia and loach) that show considerably accelerated growth, 2-fold in most species, 7-fold: in salmon (Devlin et al., 1994) and 35-fold in loach (Nam et al., 2001).

Study of Human Diseases:

A major application of transgenesis is gene therapy which can be defined as the correction of a genetic deficiency in a cell by the addition of new DNA and its insertion into the genome. The study of human diseases represents also one of the important applications of transgenesis. Studying human diseases can be facilitated by making animal models for human diseases. These animal models can be done by adding, inactivating or modifying human genes in animals like mice, rabbits, rats etc

The number of known human diseases of genetic origin is estimated to be about 8,000. These diseases, which vary in severity and could be lethal, still await non-classical treatment or cures. Transgenic animals supply us with invaluable models for human diseases on which symptoms might be better assessed and studied. On such animals, different therapeutic strategies can be applied like evaluation of the therapeutic effects of chemical compounds. After a sufficient level of validation, results might be extrapolated to human diseases.

An example of animal models for human genetic diseases is the muscular dystrophy syndrome. It was found that LAM2 gene coding for laminin isoform, when knocked out in mice, leads to human muscular dystrophy syndrome, which is not contracted normally by mice. Then it was found that ransfer of agrin gene leads to formation of neuromuscular junctions, which restores muscle function (reviewed by Houdebine, 2003). Transfer a completely different gene suppresses the pathology (Moll et al., 2001). Thus, using transgenic animals, models were prepared for both the disease and its treatment.

The use of animals in medical research is not new, but transgenic research is additionally necessary because, animals do not naturally contract many human diseases. This is because of the lack of receptors for human pathogens on animal cells. Creation of animal models capable of contracting human diseases can be achieved by transgenic animals expressing a human pathogen receptor. This strategy has been validated for several human diseases. For example transgenic rabbits expressing the human CD4 gene in T-lymphocytes are sensitive to HIV infection (Dunn et al., 1995). Furthermore, sensitivity can even be improved by

another HIV receptor, CCR5 (Cohen, 2001). Many other examples can be cited in the explosive domain of creation of a transgenic animal models for research on human diseases as the human papilloma virus (Souders et al., 2007), prion diseases (Moore and Melton, 1997), atherosclerosis (Iritani et al., reviewed by Houdebine, 2003), oncogenes and cancer (Bartek and Lukas, 2001), mammary tumors (Geng and Sicinski, 2001; Schwertfeger et al., 2001), Alzheimer's disease (Chapman et al., 2001), etc.

It is hoped that transgenesis can be used to treat many human diseases through the extraction of cells from the patients and introducing reparatory or healthy genes in these cells. The prepared nucleus can be taken and introduced into an enucleated oocyte. This oocyte can develop in vitro where embryonic cells can give rise to differentiated cells (e.g. neural, muscular, and hepatic). These functionally differentiated cells can be re-implanted and used to treat the patient.

Pharmaceuticals Production:

One of the major applications of recombinant DNA technology is the production of pharmaceuticals as human growth hormone (Goeddel et al., 1979), enzymes (Van den Hout et al., 2001), blood factors (Wood et al., 1984), vaccines (Davis et al., 2001), antibodies (Holliger and Hudson, 2005), structural proteins (Heine and Boyle, 1993). One notable example is insulin. Instead of the traditional method of extraction from pig pancreas, insulin is produced since 25 years from bacteria in which the human insulin gene was cloned (Johnson, 1983). The insulin hormone produced from the transformed bacteria is highly pure and identical to the native human insulin.

Antibodies are prepared from animal cells in which gene constructs for the two chains of antibodies are introduced (Hotta, 2004).

More interesting, however, the possible modifications on milk, which represent 30% of the protein consumed in developed countries, are to treat the problem of undigested lactose and to ameliorate it to be more adapted for industry (e.g. cheese production). Over expression of K-casein in mouse milk is expected to reduce micelle size and enhance milk stability (Bosze et al., 2001). Another approach would be for cow milk is to contain human rather than cow proteins in order to decrease

allergenic effects and increase digestion and to make it more nourishing and growth enhancing. In many cases, transgenesis seems to be the only way to achieve the mentioned objectives (Houdebine, 1998; Pintano and Gutierez-Adan, 1999). Or again: recombinant proteins in milk (Simmons et al., 1987) can be obtained by milk protein gene promoters fused to the coding region. Using this approach, experimental secretion of more than 100 foreign proteins in milk of rabbit, goat and cow is already performed.

Important Limiting Elements:

Even though, transgenesis and biotechnology possess an extraordinary potential, our use should balance enthusiasm with caution. Rather than issuing a blanket condemnation of the technology, we should proceed to make a rational assessment of risks on case-by-case basis. The precautionary measures to be taken depend on plant or animal species or variety, culture conditions, ecosystem, use (food, industry...), nature of genetic construct being introduced, insertion consequences (e.g. inactivation of a coding gene or activation of a silent gene) and possible deleterious effect.

Bio-safety problems are real. The danger degrees to experimenters, environment are variable and necessitate appropriate precaution: scarifying of genetically modified organisms (GMO) if and when necessary, confinement of GMO, using of filters, grids, cages, autoclaving, safety hoods, glove boxes, special clothes to avoid intentional and unintentional dissemination of GMO into the environment. Transgenesis has to be controlled and organized in order to obtain more and better products without harming or drastically influencing the environment (Devlin et al., 2006).

For the manipulation of human zygotes, an ethical problem arises, however. Can we rightly manipulate zygotes and orient them to fabricate specific differentiated cells, tissues or may be entire organs on demand? Is a zygote a human being from the first moment (fertilization)? Religious texts can provide insight on this point. The authentic Prophetic Saying reported by Muslim [2645] informs us that a differentiation burst takes place on the 42 day of the fetal life. Furthermore, another authentic Prophetic Saying reported also by Muslim [2643] instructs that the

spirit is blown in the fetus on the 120 day of the fetal life. Does that mean that we can manipulate zygotes before day 120? I prefer to leave this question open to be answered by religious and scientific references, but note that there is a basis for discussion and decision-making.

In the case of human transgenesis, there are ethical problems arising from its complexity and novelty. However, even for transgenesis of other living organisms (e.g. animals and plants), we have limits and risks of gene therapy as the complex effects and side effects of pharmaceuticals are not fully known. Guidelines are not yet standardized for these new techniques. We are even limited by technical advances. Risks are still real.

Transgenesis Risks for Human Consumers:

The nature and location of the transgene might lead to altering the nutritional properties and safety of the human food in addition to possible toxicity and allergenecity of the foreign gene. Emergence of animal virus favored by transgenes is also a possible danger of transgenesis (reviewed by Houdebine, 2003).

Competent authorities must therefore undertake an assessment of possible consequences. These include toxic risks (gene product and modification of metabolism), allergic risks (range of molecular weight

of allergic proteins, analogy with allergic proteins...etc), ecological risks (propagation of transgenic plants and animals, effects on biological equilibrium, horizontal transfer of DNA, potential selective advantage and other risks) transgenic rapeseed which can survive and produce plants as much as a decade after it was sown (D'Hertefeldt et al., 2008). Evaluation of chemical risks is an important safety element, which can be done by comparison of the analytical profiles of known toxic substances or by using experimental animals.

To assess the possible risks for human consumers, two approaches have been proposed (a) metabolic foot-printing described by Henriques et al., 2007. It's based on all the known chemical substances and (b) substantial equivalence (Novak and Haslberger, 2000). This last is a principle of assessment for safety where transgenic sources of food are compared with non-transgenic ones (the parent organism only or different varieties of the same species) known to be safe (Catchpole et al., 2005, Konig et al., 2004, Kuiper et al., 2001).

Transgenesis and Animal Welfare:

Is transgenesis a violation of nature's laws? Is it designing new organisms just to make them suffer? Objectively, transgenesis induces animal suffering during collection of embryos for microinjection, embryo transfer to recipient females implicating surgery or scarifying animals. "3-R rule" has been suggested to limit animal suffering, as we cannot eliminate this suffering unless we all become pure vegetarians.

This rule implies reducing the number of experimental animals, refining experimental protocols and replacing animals, whenever possible, by in vitro tests and cell cultures. Fortunately, we have a growing list of alternatives to the use of experimental animals (Moore, 2001).

In considering these options, it could be argued that the other living organisms of this world have been created for human service. That can certainly be granted:

The Night Journey: 70

وَلَقَدْ كَرَّمْنَا بَنِي آدَمَ وَحَمَلْنَاهُمْ فِي الْبَرِّ وَالْبَحْرِ وَرَزَقْنَاهُمْ مِنَ الطَّيِّبَاتِ وَفَضَّلْنَاهُمْ عَلَىٰ كَثِيرٍ مِمَّنْ خَلَقْنَا تَفْضِيلًا (70)

70. WE HAVE HONORED THE SONS OF ADAM; PROVIDED THEM WITH TRANSPORT ON LAND AND SEA; GIVEN THEM FOR SUSTENANCE THINGS GOOD AND PURE; AND CONFERRED ON THEM SPECIAL FAVORS, ABOVE A GREAT PART OF OUR CREATION.

However, being superior over other organisms does not justify degrading and spoiling on Earth. Human beings should behave in full respect for themselves through respect to God's creatures, which are communities like us.

Livestock: 38

وَمَا مِنْ دَابَّةٍ فِي الْأَرْضِ وَلَا طَائِرٍ يَطِيرُ بِجَنَاحَيْهِ إِلَّا أُمَمٌ أَمْثَالُكُمْ ۚ مَا فَرَّطْنَا فِي الْكِتَابِ مِنْ شَيْءٍ ۚ ثُمَّ إِلَىٰ رَبِّهِمْ يُحْشَرُونَ (٣٨)

38. THERE IS NOT AN ANIMAL (THAT LIVES) ON THE EARTH, NOR A BEING THAT FLIES ON ITS WINGS, BUT (FORMS PART OF) COMMUNITIES LIKE YOU. NOTHING HAVE WE OMITTED FROM THE BOOK, AND THEY (ALL) SHALL BE GATHERED TO THEIR LORD IN THE END.

Trying to respond to these (at least apparently) contradictory injunctions is difficult. Living organisms including humans cannot survive without consuming other organisms. Resolving the dilemma therefore entails answering the simple but challenging question: Do you want to stay alive at the expense of another "community". If the answer is yes, then we would seem to have an unsolvable dilemma. However, we find a reconciliation of these perspectives in the Koranic principle that human beings are responsible for the stewardship of this Earth. We can, therefore, benefit from the other creatures as long as we do not

seek to exercise an absolute domination. This can be understood from the following Prophetic Saying in which "Allah instructs us to behave in complete beneficence and kindness in everything. If you kill, kill with kindness, if you slaughter, slaughter with kindness. One should sharpen his knife and the animal should be positioned restfully":

The borders are not evident and not easy to trace. Biologists, religion scholars, ethicists and ecologists should refine the ethical rules that make our lives durable and sustainable. This implies that "our" includes humans and non humans!

Meanwhile transgenic plants can be both an efficient and at the same time an ethically accepted alternative food source that would reduce the sum of animal suffering. Transgenic plants possess a fragment of DNA, a gene, or more that have been transferred artificially from a different species using recombinant DNA technology. Transformation is usually achieved using gold particle bombardment or through the process of horizontal gene transfer using a soil bacterium, Agrobacterium tumefaciens, carrying an engineered plasmid vector mainly Ti plasmid, or carrier of selected extra genes. Many transgenic plants have already been designed to possess useful traits such as salinity and drought resistance (Lea et al., 2004) and pest and herbicide resistance (Hattori et al., 1995). Genetic engineering has also a great potential for improving the nutritional value of plants. One example is the creation of yellow rice which contains β-carotene that the human body uses to make vitamin A (Ye et al., 2000). The use of transgenic plants as sensors of environmental pollution and mutagenecity is another illuminating example (Kovalchuk and Kovalchuk, 2008)

Conclusions:

Let us advance with courage in the efficient bio-techniques: genetic engineering and transgenesis, but with sufficient precautionary measures and in full respect to both the ecological equilibrium installed over millions of years and in full respect to the religious, ethical and moral considerations. Suggested solutions to assess risks are given such as metabolic footprinting (Henriques *et al.*, 2007) and the "substantial equivalence concept" (Novak and Haslberger, 2000). It is, after all, of utmost importance for us to achieve a stewardship role of man on Earth rather than a dominating role. The full respect of our stewardship on Earth through a series of ethical precautionary measures might hopefully make us far from those who "slit the ears of cattle, and to deface the (fair) nature created by Allah"

النساء:The Women: ١١٦-١٢١

إِنَّ اللَّهَ لَا يَغْفِرُ أَنْ يُشْرَكَ بِهِ وَيَغْفِرُ مَا دُونَ ذَٰلِكَ لِمَنْ يَشَاءُ ۚ وَمَنْ يُشْرِكْ بِاللَّهِ فَقَدْ ضَلَّ ضَلَالًا بَعِيدًا (١١٦) إِنْ يَدْعُونَ مِنْ دُونِهِ إِلَّا إِنَاثًا وَإِنْ يَدْعُونَ إِلَّا شَيْطَانًا مَرِيدًا (١١٧) لَعَنَهُ اللَّهُ ۘ وَقَالَ لَأَتَّخِذَنَّ مِنْ عِبَادِكَ نَصِيبًا مَفْرُوضًا (١١٨) وَلَأُضِلَّنَّهُمْ وَلَأُمَنِّيَنَّهُمْ وَلَآمُرَنَّهُمْ فَلَيُبَتِّكُنَّ آذَانَ الْأَنْعَامِ وَلَآمُرَنَّهُمْ فَلَيُغَيِّرُنَّ خَلْقَ اللَّهِ ۚ وَمَنْ يَتَّخِذِ الشَّيْطَانَ وَلِيًّا مِنْ دُونِ اللَّهِ فَقَدْ خَسِرَ خُسْرَانًا مُبِينًا (١١٩) يَعِدُهُمْ وَيُمَنِّيهِمْ ۖ وَمَا يَعِدُهُمُ الشَّيْطَانُ إِلَّا غُرُورًا (١٢٠) أُولَٰئِكَ مَأْوَاهُمْ جَهَنَّمُ وَلَا يَجِدُونَ عَنْهَا مَحِيصًا (١٢١)

116. Surely Allah does not forgive that anything should be associated with Him, and He forgives what is besides this to whom He pleases; and whoever associates anything with Allah, he indeed strays off into a remote error.

117. (The Pagans), leaving Him, call but upon female deities: They call but upon Satan the persistent rebel!

118. Allah did curse him, but he said: "I will take of Thy servants a portion marked off;

119. "I will mislead them, and I will create in them false desires; I will order them to slit the ears of cattle, and to deface the (fair) nature created by Allah." Whoever, forsaking Allah, takes Satan for a friend, hath of a surety suffered a loss that is manifest.

120. Satan makes them promises, and creates in them false desires; but Satan's promises are nothing but deception.

121. They (his dupes) will have their dwelling in Hell, and from it they will find no way of escape.

Acknowledgments:

Many thanks are addressed to my colleagues at the Arab American University mainly Dr. Gerham Stott for his kind linguistic revision of the English manuscript, Dr. Mohammad Dawabsheh for his kind Arabic revision, Prof Bashar Sa'ad and Mr. Saeed Khaseeb for their kind reviewing of the manuscript.

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39. *The remarks of the reviewers are taken into consideration as following in green (taken point by point in order). In the beginning of the following lines, you find the number of pages in the old version of the manuscript, while at the end of each line, you find the new number of pages (in the new version)*

40. Reviewer 1:

- *Page 1 and 2: The title is changed in English and Arabic (in green)*
- *Page 2: The definitions of Transgenesis and Genetic Engineering are modified in Arabic and English (in green).*
- *Pages 3: The definitions are corrected as above (in green).*
- *Page 3 line 10: The statement was cancelled after the reviewer*
- *Page 4 (old version): The methods of genetic engineering and transgenesis are mentioned on page 5 (new version) in green in "Methodology"*
- *Page 4: (A) Basic Research Based on Transgenesis is in a separate line*
- *Page 5, middle of the page: The language problem is corrected in green: page 6 (new version)*
- *Page 5: the many details on examples of using animals models for human diseases are much shortened in green: page 6 (new version) as "Many other examples can be cited in the explosive domain of creation of a transgenic animal models for research on human diseases as the human papilloma virus (Souders et al., 2007), prion diseases (Moore and Melton, 1997), atherosclerosis (Iritani et al., reviewed by Houdebine, 2003), oncogenes and cancer (Bartek and Lukas, 2001), mammary tumors (Geng and Sicinski, 2001; Schwertfeger et al., 2001), Alzheimer's disease (Chapman et al., 2001),...etc."*
- *Page 5 (the end of page) and not page 6!: The misconception is corrected (in green) on page 6 (new version)*
- *Page 6: a reference for production of antibodies in animal cells was added in the bottom of the page (in green)*
- *Page 6 (toward the middle of the page): gene therapy was defined on page 5 in the new version (in green)*
- *Page 7 (toward the middle of the page): genetically modified organisms preceded the abbreviation GMO*
- *Page 7: the spaces problems are settled.*
- *Page 8 (toward the top of the page): correction of language as following:*

Is it designing new organisms just to make them suffer?

- *Page 8 (toward the middle of the page): the apparent contradiction is discussed in order to settle it (page 9 in the new version in green).*
- *Pages 9 (bottom) and 10 (top): Transgenic plants are defined with explaining the ways to make them and their advantages with some convincing examples and appropriate references page 10 in the new version in green*
- *Page 10 (Conclusions): Suggested solutions are given such as*
- *Page 10 (Conclusions) a paragraph on epigenetic inheritance was added on page 4 in the new version at the end of "Introduction".*

Reviewer 2:

- *Page 2: the remarks (in the text) are taken into consideration (in green)*
- *Page 2: The new sections suggested by the reviewer are taken into consideration (Schools of Thinking, Hypothesis and Objectives). They are written in page 3 (in green)*
- *Page 3: Creation is characteristic of God was added to link the text with the verses as recommended by the reviewer*
- *Page 3: the remarks (in the text) are taken into consideration (in green)*
- *Page 3: In bottom: The verse number of the English translation precedes the text of the translation, in contrary to the Arabic where the verse number comes after. Therefore, the verse number is 73 and not 72.*
- *Page 4: Writing down the aims (objectives) of this study (in green)*
- *Page 4: Explaining the two opposing schools (opponents and proponents) concerning these new technologies of genetic engineering and transgenesis on page 3 in the new version (in green)*
- *Page 4: Remarks are taken into consideration on page 5 in the new version (in green)*
- *Page 5: The remarks including the rearrangement of two definition*

paragraphs are taken into consideration. Transgenesis definition was moved to the beginning of "Introduction" page 3 in the new version. The definition of animal models was moved to the very beginning part of the same section page 6 in the new version "Study of Human Diseases". However, the lower part of the page was shortened as recommended by the other reviewer (in green)

- *Page 6: The upper part was rearranged as recommended by both reviewers and shortened also.*
- *Page 6: 7 references are added as recommended by the reviewer (in green)*
- *Page 7: The paragraph in the middle of the page (In addition to the nutritional applications, pharmaceutical virtues can be obtained. Human-glucosidase secreted in transgenic rabbit milk, improved the clinical condition of babies suffering from Pompe disease (Van den Hout et al., 2001)) was cancelled and its brief meaning and reference were transferred to amore appropriate place pp 6 in the new version.*
- *Page 7: The suggested remarks and modifications are taken into consideration (pages 7 and 8 in green)*
- *Page 8: The suggested remarks and modifications are taken into consideration (pages 8 and 9 in green)*
- *Page 9: Remarks and modifications are taken into consideration on page 10 in the new version (in green)*
- *Page 9: Koran verses and Prophetic Saying are better linked to the text as recommended by the reviewer.*
- *Page 10: As recommended by the reviewer, several references were added page 8 in the new version (in green)*
- *Pages 11, 12 and 13: As recommended by the reviewer, 6 extra references in the list of references were cancelled from the references list. Now, all the listed references are cited in the text.*