The application of Genome Editing in humans

A position paper of FEAM - the Federation of European Academies of Medicine

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Rapid advances have taken place over the last few years in the science and application of genome editing, aided by the development of new techniques such as CRISPR/Cas9. Through its ability to insert, delete or replace DNA in the genome of an organism with much increased specificity, CRISPR/Cas9 has emerged as a revolutionary technology that is relatively easy to use and very cost-effective. It has been adopted in a very short time by researchers worldwide. At the same time, the rapid development of CRISPR/Cas9 technology and its potential to deliberately introduce modifications to the human germline, has also been responsible for driving forwards the current ethical and regulatory debate over the possibility of its future application in the clinic.

In addition to their current usage in biomedical research and their longer-term potential medical applications in the clinic, numerous other potential applications of these genome editing techniques have also been identified in agriculture, plant and animal breeding, biotechnology, bio-processing and in disease vector and, perhaps, invasive species control (gene drive). FEAM welcomes therefore the recent publication of the report[1] ("Genome editing: Scientific opportunities, public interests and policy options in the European Union") by the European Academies Science Advisory Council (EASAC) reviewing these wider aspects of genome editing. FEAM anticipates that the recent publication by the US National Academies of Sciences (NAS) and National Academy of Medicine (NAM) of its new report, *Human Genome Editing: Science, Ethics, and Governance* [2], (and its set of overarching principles that should be used by any nation in governing human genome editing research or applications), will stimulate further discussions globally on the potential use of such techniques in biomedical research and medicine, and on the clinical, ethical, legal, and social implications of their use.

Whilst recognising that the further development of new genome editing techniques will have global significance, FEAM has long considered that it is essential for the European biomedical sciences community to develop its own position, thus helping to support the development of an appropriate regulatory and ethical environment and identify future priorities for the funding of research – for the ultimate benefit of the patient.

FEAM workshop on human genome editing

Recognising the importance of this topic, FEAM, together with the UK Academy of Medical Sciences (AMS) and the French National Academy of Medicine, jointly held a one-day workshop in 2016 titled 'Human genome editing in the EU' at the French Academy of Medicine in Paris, France. The FEAM workshop provided an opportunity to explore the scientific and regulatory landscape for human genome editing across the EU. FEAM was pleased that the workshop also provided an opportunity for European-based experts to contribute to the review carried out by the NAS-NAM Human Gene Editing Initiative. The main aims of the meeting were to:

- Understand current scientific activities in the EU with respect to genome editing – focussing on human applications.
- Understand the current regulatory landscape for human genome editing research and clinical applications across the EU.
- Understand the ongoing debate on genome editing across the EU.
- Identify any areas where there are significant differences, e.g. between countries, and if possible consider the driving forces for these differences (e.g. ethics, public opinion).
- Discuss the need for a European regulatory framework to govern the safe and acceptable use of human genome editing.

[1] http://www.easac.eu/home/reports-and-statements/detail-view/article/genome-editi.html
[2] https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

- Provide information to the public and stakeholders regarding these new scientific and medical possibilities.

The report of the wide-ranging discussions held at this workshop has now been published.[3]
A number of FEAM's Member Academies have carried out their own reviews on the development of human genome editing, including the French Academy of Medicine[4] the UK Academy of Medical Sciences[5], the Leopoldina (the German National Academy of Sciences)[6] and the Royal Netherlands Academy of Arts and Sciences (KNAW).[7]
Arising from the outcome of the Paris Workshop and from the work of its member Academies, FEAM recognises that the EU regulatory context for genome editing is varied across individual countries. FEAM considers it essential however that in any ongoing assessment of the future governance of the new techniques used in this field a distinct separation continues to be made between its use in the basic research context and in clinical applications, and between its use in somatic cells and in germline cells or embryos.

The importance of scientific research using genome editing

FEAM recognises the important potential of scientific research on the genome editing of human cells (including those of the germ line, and early embryos). Such research is able to inform basic research about human development and can be used to increase our understanding of human and animal biology and of the role of specific genes and processes. Ongoing research programmes also include helping to create and study models of human genetic disease *in vitro* and in animals. Research is also needed to improve the efficacy and safety of future clinical applications in somatic cells and in xenotransplantation. Additional fundamental research will be required to understand the germline changes needed to avoid or prevent genetic disease.

European funding for basic biomedical research in genome editing

FEAM welcomes the funding for research into some aspects of genome editing that is already being provided by the European Commission under the EU H2020 programme (and previously by the 7th Framework Programme). Such research includes that into: functional genomics and disease modelling; developmental biology; immunology; rare diseases; and xenotransplantation. FEAM calls for the potential benefits of such continued research funding into genome editing to be fully recognised as preparations to identify content for the 9th Framework Programme take place.
It is acknowledged however that in response to the divergence in regulations and ethical viewpoints across the EU, the EC has determined that that a number of fields of research cannot at present be financed by the EU.[8] These include research activity intended to modify the genetic heritage of human beings, which could make such changes heritable, and research activities "intended to create or use human embryos solely for the purposes of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer."
FEAM would welcome further consideration by the European Commission, at some point in the future, of its restrictions on funding research involving germline cells and early human embryos. This would allow the EC to take advantage of promising research in this field, and considerable relevant expertise that exists across Europe. Whilst FEAM notes that the EC has agreed not to support research that leads to the "destruction" of embryos, it is to be hoped that further consideration is given where such

[3] http://www.feam-site.eu/cms/docs/humangenomeeditingworkshop2016report.pdf
[4] http://www.academie-medecine.fr/wp-content/uploads/2016/05/report-genome-editing-ANM-2.pdf
[5] http://www.acmedsci.ac.uk/policy/policy-projects/genome-editing
[6] www.leopoldina.org/uploads/tx_leopublication/2015_3Akad_Stellungnahme_Genome_Editing.pdf
[7] https://www.knaw.nl/en/news/publications/genome-editing
[8] http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-decl-fp_en.pdf

embryos have been donated under IVF programmes. IVF techniques are in widespread use across the EU, and depend on research to ensure that the safest and most efficient methods are used. Whilst FEAM does consider it desirable for authorisation (and funding) to be made available for basic research, it acknowledges that such research should not lead directly to the birth of a child. Modified cells should not be used to establish a pregnancy.

Human somatic cell applications

Recent advances in the techniques for the genome modification of non-reproductive (somatic) cells are opening up the real possibility of achieving therapeutic genome editing in diseased tissues and cells. A wide range of diseases, including metabolic disorders, cancer, HIV/AIDS, globinopathies such as thalassaemia and sickle-cell disease, and a number of immune-deficiency disorders, are currently being studied in humans at the research and pre-clinical stage. Regulatory approval is anticipated in the not-too-distant future for a number of potential clinical applications. FEAM acknowledges that the risks, safety aspects and potential benefits of each potential somatic cell gene therapy needs to be fully assessed on a case-by-case basis, and in the context of existing, non-genomic based therapeutic approaches.

FEAM considers it essential for the potential benefit and risks of all proposed genome medications in somatic cells to be rigorously evaluated within an appropriate regulatory framework established by the European Medicines Agency and National Agencies. Current laws and guidelines are, in general, reasonably fit for purpose and harmonised across Europe, although not unexpectedly at this early stage in their development, somewhat focussed on vector-based gene therapy applications. FEAM supports the ongoing review of the regulatory guidance in this area and where the methods or the applications being regulated differ from those of conventional gene therapy, further amendments to the regulations should be considered. The preparation of such regulatory guidance will require ongoing effective dialogue between regulators and researchers – not only from the academic sector, but also drawing on the extensive experience of the commercial sector. It is essential for the patient voice also to be included.

FEAM notes that from an ethical perspective European society is generally supportive of the future potential of somatic cell based therapy; although it does appear that some countries may be more advanced than others in the scientific application of such genome editing and are currently taking a more supportive approach to the further development of the technology**.** FEAM considers that through an effective and harmonised, or at least cooperative regulatory environment and through the provision of appropriate levels of funding for collaborative research, there is a real opportunity for the European biomedical community to take the lead in this field, for the benefit of Europe's patients and those from other countries.

Concerns over the potential creation of individuals with enhanced human capabilities

It has been suggested that in the future genome editing could be used in the creation of individuals with enhanced human capabilities, outside the correction of anomalies. This might include for example the enhancement of some aspect of the physiology of healthy individuals, such as muscle function of athletes ("gene-doping"). FEAM acknowledges the possibility that biological enhancements, beyond

prevention and treatment of disease, could exacerbate social inequalities or be used coercively. FEAM does not support the application of genome editing in such non-medical interventions, but anticipates ongoing wide-ranging public discussion on the risks, benefits and acceptability of the potential development of any technological approaches to individual human enhancement.

The potential for future clinical applications using human germline modification

It is possible that genome editing could be used to make genetic alterations in gametes or embryos, which would then be carried by all of the cells of a resulting child and which could then be passed on to subsequent generations and contribute to the human gene pool. Such modifications of human genomes might include the introduction of naturally occurring variants or totally novel genetic changes that were thought to be beneficial.

Possible examples that have been suggested include the avoidance in descendants of severe inherited diseases and the editing of gene defects, in germ cells, responsible for sterility. The application of human germline genome editing could also allow increased reproductive choices. At present EU legislation in general prohibits deliberate changes to the genetic material in the nucleus of human embryos or of germline cells that could be used to lead to a pregnancy, although this prohibition does not apply in some countries to mitochondrial transplantation.

The recent publication of reports of research performed outside of Europe,[9] [10] on the use of CRISPR/Cas9 genome editing in human embryos has added to concerns over the development of germline engineering that could have an impact on the genome of offspring. In particular, FEAM notes the recent work by Tang *et al* [11] and by Mitalipov[12] and his team in the USA that appear to be the first successful attempts to use CRISPR to correct mutations in viable human embryos. A number of organisations and scientists in this field have previously called for a "moratorium" on the modification of the germinal nuclear genome for therapeutic purposes, or at least to adopt a cautious approach, until the uncertainty regarding the biological, societal and ethical risks has been clearly assessed.

Whilst not supportive of any moratorium *per se* FEAM agrees that there are many unresolved questions, particularly ongoing ethical, safety and efficacy issues, that at present remain major barriers to the introduction of clinical applications of genome editing in germline cells and embryos. There is also no broad societal consensus on this matter within Europe. Not enough is known at present about the health risks that may arise from faulty genome editing or identifying adequately in advance what may be the effects of such genetic modifications on an individual's functioning. Concern has also been raised over the consequences for future generations that will carry the genetic modifications that have been introduced. FEAM agrees that much more needs to be known about the potential risks to both the individual and future generations, and the relative advantages and alternative approaches to treatment that are available, before clinical applications of potentially heritable germline genome editing should be initiated.

Other examples of the additional knowledge and safety measures that will need to be considered to minimise uncertainties and uncontrolled risks for future generations, the environment and the biosphere is the potential role of epigenetic and environmental factors during the period around conception. The possible transgenerational consequences of such factors will need to be given further consideration in any future development of genome editing.

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[9] Liang L, et al (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein & Cell 6, 363372.http://link.springer.com/article/10.1007%2Fs13238-015-0153-5

[10]Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. Kang, X., He, W., Huang, Y. et al. J Assist Reprod Genet (2016) 33: 581. doi:10.1007/s10815-016-0710-8

[11] . Tang *et al*: Molecular Genetics and Genomics 1 March (2017). https://link.springer.com/article/10.1007%2Fs00438-017-1299-z

[12] Mitalipov et al. Nature 548 13-14 (03 August 2017).

Assessing the security implications of genome editing

FEAM is aware that some concern has been raised over the possibility that advances in genome editing may pose a threat to national security and that its intentional misuse may be used to develop biological weapons. FEAM considers it critical for Europe's Medical and Scientific Academies to continue to contribute to the ongoing evaluation of the potential misuse of the technology. In this context FEAM welcomes initiatives such as the International Workshop to be held in Hanover (October 2017) which will assess the security implications of genome editing, explore potential concerns relating to intentional misuse and seek to identify possible strategies for preventing and mitigating such risks.[13]

The need for ongoing review of the European regulatory framework

There is a clear need for regulatory oversight across Europe that encompasses current developments in the science of genome editing and is also able to deal with future advances in this rapidly developing field. The current regulatory framework was established to deal with the then emerging techniques for somatic gene therapy, which involved the random integration of gene vectors into the genome, not the precise methods of genome editing that can alter the endogenous gene to make or correct a mutation (e.g. in CCR5, to provide resistance against HIV, or the sickle cell variant of the beta-globin gene). As some of the current regulations across Europe predate the technological advances that have taken place in this field FEAM suggests that they now require further review.

FEAM recognises that the EU regulatory context is varied and that significantly divergent views are held at the national level on the acceptability of some areas of research, particularly concerning the potential genome editing of the germline, and more specifically regarding the use of embryos in research. In this context FEAM acknowledges the constraints imposed by the Oviedo Convention, which has been ratified by several, but not all, European countries. Whilst noting Article 13 of the Convention, which states that: *"An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes, and only if its aim is not to introduce any modification in the genome of any descendants."* FEAM considers that the scope of these restrictions is not as clear as they could be and greater clarity would help to adequately address differences between basic research and potential clinical applications, and between somatic gene therapy and germline genetic alteration. With reference to the statement made in December 2015 by the Council of Europe Bioethics Committee that Article 13 of the Oviedo Convention should act as a starting point for further public discussion and not as the last word, FEAM suggests that it may now be timely for a further review of some of its key elements.

The need for increased public engagement on the development of genome editing

As with all such developments, it is important to balance an environment in which scientists are regulated with the freedom to experiment and innovate. Indeed, it is recognised that changes in public perception across some countries on the wider aspects of genome technology are already leading to amendments to current regulatory controls, as seen in Switzerland, with its vote on pre-implantation genetic diagnosis (PGD).

[13] http://www.easac.eu/home/easac-news/detail-view/article/internationa-3.html

FEAM strongly suggests that there is an important need for the development of an agreed lexicon across Europe (including common definitions; for example, the definition of an "embryo" is somewhat different across Europe), which could help those in different countries better understand the application of the science of genome editing and the different positions and opinions being developed. FEAM recognises the importance of seeking the involvement of European patient organisations during the development of any such potential resource.

This may be something that the EC may wish to support further through its current funding programmes. FEAM considers it essential for a greater distinction to be made, in any further EU-focussed public communications programme, between the application of genome editing techniques in research and in the clinic, and also between potential somatic cell-based therapeutic approaches and those that may involve germline cells and embryos. FEAM calls upon DG Research and Innovation, working with DG SANCO, to establish a new public engagement initiative and in doing so seek to differentiate between the promotion of what could reasonably be achieved in Europe at present and in the near future (e.g. basic research including some research involving embryos, as well as non-heritable somatic cell-based therapy, on which there may be less public concern), and what may be possible in the longer-term (e.g. heritable germline gene editing) once the significant safety, regulatory and public acceptance issues have been addressed.

Regarding the potential for future clinical applications using human germline modification FEAM welcomes the ongoing legal, ethical and moral debates that are taking place on this matter, but strongly believes that there is a need for a step change in public engagement activities in Europe to enable both the research community and society to agree on whether, and if so how, these scientific developments should be taken forward in Europe.

FEAM – the Federation of European Academies of Medicine

FEAM's mission is to promote cooperation between national Academies of Medicine and Medical Sections of Academies of Sciences in Europe; to provide them with a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on these matters. FEAM seeks to underpin European biomedical policy with the best scientific advice drawn from across Europe, through the FEAM network of Academies representing over 5000 high-level scientists from the whole biomedical spectrum. FEAM also seeks to improve the health, safety and wealth of European citizens through research by promoting a nurturing, creative and sustainable environment for medical research and training in Europe. FEAM's strength lies in its member Academies that give it the authority to provide an EU-wide scientific opinion on the European medical science base and evidence to underpin European bio -medical policy. The 18 FEAM Academies represent the following European countries: Austria, French and Flemish speaking Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Portugal, the Netherlands, Romania, Spain, Switzerland and the United Kingdom. Observers include the European Academies Advisory Council (EASAC – the European network of Academies of Sciences) and the Inter Academy Panel for Health (IAP-Health – the global network of Academies of Medicine).

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