

AMRC response to Nuffield Council on Bioethics call for evidence: Genome Editing

ABOUT THE AMRC

The AMRC is the national membership organisation for the health and medical research charity world, influencing the policy and research environment by harnessing the collective strengths of our members, to demonstrate the sector's positive impact on health and wellbeing. Medical research charities exist because the public choose to donate their money to support research to develop new treatments and cures; 7.6 million people donate in a typical month. In 2014, AMRC members invested over £1.3 billion in health research in the UK and funded a third of non-commercial research in the NHS.

- Our members **fund research focussed on the needs of patients** for better treatments, therapies and interventions designed to improve the quality of life and ultimately prevent or cure their condition. This includes funding for rare and neglected diseases, for which other public funding is limited
- We provide **authoritative advice on what matters to patients and the public**. AMRC members represent charities big and small, covering acute and chronic conditions, both rare and common.

Our members have a dual interest in health and care data – both as funders of a significant amount of research using patient data and as champions for the views of patients and the public who support them.

AMRC's key points:

- AMRC, alongside other leading UK research organisations, has co-signed an [initial joint statement](#) in support of the continued use of CRISPR-Cas9 and other genome-editing techniques in preclinical research.
- Research using genome editing tools holds the potential to significantly progress our understanding of many key processes in biology, health and disease and for this reason we believe that responsibly conducted research of this type, which is scientifically and ethically rigorous and in line with current legal and regulatory frameworks, should be allowed to proceed.
- The technique is still at a relatively early stage. However, the science is progressing and it is important that an open debate around these new techniques continues between not just

researchers, but ethicists, healthcare professionals, regulators, patients and their families, and the wider public.

- The concept of genome editing is not new: for many years, scientists have applied a range of tools to manipulate genetic sequences. A number of the ethical questions in this debate can be informed by other research areas, such as mitochondrial donation.
- It is important to clearly delineate the different ways and contexts in which this technology might be used: clearly distinguishing the use of this technology in a research context compared with its potential application in a clinical setting; as well as distinguishing the use of these technologies using somatic (non-reproductive) or germ (reproductive) cells.
- As a basic research tool, genome-editing technologies are already beginning to transform our understanding of genes and processes in health and disease (see Annex 1 for examples).
- We believe that genome editing technologies may hold significant potential for clinical application in the future; and we would be open to supporting the development of new therapeutic approaches should the evidence from research advance sufficiently to justify their use.
- We recognise there may be future potential to apply genome editing in a clinical context using human germ cells or embryos, though this is prohibited by law in the UK and unlikely to be permissible in other European jurisdictions at present. This raises important ethical and regulatory questions, which need to be anticipated and explored in a timely and inclusive manner as the basic research proceeds and prior to any decisions about clinical application. Active early engagement with a wide range of global stakeholders will therefore be needed.
- As with all emerging technologies, robust governance and oversight mechanisms are essential. There are different approaches to achieving this, but in all cases the oversight mechanisms must be flexible, and adaptable to keep pace with fast-moving scientific developments and to ensure that the UK remains a global leader for research.

Annex 1:

Example of CRISPR improving basic research:

Dr Adrian Saurin, a Cancer Research UK-funded expert in cancer cell biology from the University of Dundee

Dr Saurin's group is using CRISPR to target and edit genes in cell lines to understand how the proteins produced by these genes work. They have a particular interest in studying proteins involved in cell division. Before this revolutionising technology, Dr Saurin's research relied on making the cells that artificially produce excess amounts of the protein they were interested in, which isn't representative of the normal biology of the cells. Moreover, if they wanted to switch off the gene, they would have relied on technology that was not very efficient or precise.

Second generation CFTR gene repair

The Cystic Fibrosis Trust is funding a study, led by Dr Patrick Harrison at University College Cork, looking at developing the next generation of genetic therapy for cystic fibrosis. If successful, this study will allow permanent correction of more than 80% of cystic fibrosis mutations in cultured lung cells.

Cystic fibrosis is caused by tiny, yet crucial 'typing' errors in the CFTR gene. The ultimate goal of gene therapy is to stop and reverse the disease in an individual by correcting these 'typos' to restore normal CFTR gene function.

In 2012 Dr Harrison and his colleagues used gene repair to permanently correct the most common F508del mutation in cystic fibrosis cells. The new study is to investigate a 'second generation' approach to gene repair; looking at whether it is possible to repair a much wider range of mutations within the gene by effectively cutting out a stretch of DNA where the six most common CF-causing mutations (and more than 80% of the rarer ones) are located, and replacing this region with the normal sequence.

The advantage of gene repair is that the correction lasts for the lifetime of the cell and the protein is made as and when the cell needs it, meaning that you end up with a cell that looks and behaves exactly the same as a healthy cell.

The main technical challenge with gene repair is finding the section of DNA that needs to be replaced and getting the scissors to the right place. Until recently this has been done with molecules called Zinc Finger Nucleases, which recognise certain 'landmarks' in the DNA. The nearer the landmark is to the stretch of DNA to be replaced, the more successful the gene repair is; unfortunately the nearest landmark for lots of cystic fibrosis mutations is still further than ideal, which makes the process of gene repair quite inefficient.

It is vital to have efficient gene repair because the more individual cells that can have their gene corrected, the more likely it is to lead to a clinical benefit in the lungs. Dr Harrison will therefore use CRISPR/Cas9 to recognise the DNA. This system has the advantage that it can be designed to recognise virtually any region in the DNA, making it possible to direct the scissors very close to the mutations and hopefully increase the efficiency of the gene repair.

While this work aims to confirm the technique works in individual cystic fibrosis cells, there are a number of additional steps before this approach can be tried in CF patients. However, a similar strategy has proved successful in a pre-clinical model of haemophilia, and a first generation gene repair strategy has already entered into early stage clinical trials for another disorder.

More information of this project can be found here: <http://www.cysticfibrosis.org.uk/research-care/research/about-cystic-fibrosis-research/areas-of-research/gene-therapy/second-generation-cftr-gene-repair>

Genome editing to correct mutations in adult cells:

Muscular Dystrophy UK is currently co-funding a research project in Professor George Dickson's laboratory at Royal Holloway, University of London. The team have developed an innovative technique with the potential to repair the genetic mutation that causes Duchenne muscular dystrophy. The ground-breaking technique, described as genome surgery, could be the first therapy that offers permanent correction of the genetic mutation.

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene. The loss of dystrophin in Duchenne muscular dystrophy leads to wasting of the muscle, with the muscle fibres gradually being replaced by fat and scar tissue. Repairing the mutations in the dystrophin gene could restore production of dystrophin to the muscles which could be a viable therapeutic approach to prevent muscle damage and slow the decline in muscle function.

Professor Dickson and his team have been working on a strategy described as genome surgery, which has the potential to permanently correct a gene mutation. This is done by using enzymes called endonucleases that act like molecular scissors to cut the DNA. These scissors are designed to cut out the precise part of the gene containing the mutation. Other molecular tools are used to add in the correct DNA sequence and join the cut ends together. This would correct the genetic mutation and allow production of the full-size dystrophin protein.

In this study the molecular tools required for the gene surgery technique will be generated and then tested in cell culture models of Duchenne muscular dystrophy and in a mouse model of the condition.

If proven to be effective, this therapy has the potential to permanently correct the genetic alteration causing Duchenne muscular dystrophy. The approach is applicable to all the mutations which cause Duchenne muscular dystrophy and Becker muscular dystrophy and could also be adapted for the treatment of other neuromuscular conditions.

More information on this project can be found here:

<http://www.muscular dystrophyuk.org/grants/genome-surgery-for-duchenne-muscular-dystrophy/>

Other genome editing research projects funded by Muscular Dystrophy can be found here:

<http://www.muscular dystrophyuk.org/grants/genome-editing-to-repair-duplications-in-duchenne-muscular-dystrophy/>

<http://www.muscular dystrophyuk.org/grants/developing-genetic-therapies-for-duchenne-muscular-dystrophy/>

Editing specificity and function to enhance T cell therapy of haematological malignancies

Prof Hans Stauss and Prof Emma Morris, UCL Medical School, funded by [Bloodwise](#).

The goal of this programme is to use killer cells of the immune system for the treatment of leukaemia, lymphoma and other types of blood cancer. A major advantage of this type of cell therapy over existing treatment options is that immune cells can recognise specific markers on cancer cells, providing a basis for the selective and enduring attack of cancer while avoiding damage to healthy tissues.

The patient's own immune system is generally impaired owing to inefficient recognition of cancer-specific cellular markers, and because of inappropriate stimulation of the immune cells leading to a state of immune exhaustion and an inability to attack cancer cells.

The genes encoding the proteins responsible for recognition of cancer-specific markers, and for regulating the activation and exhaustion status of immune cells, have recently been identified. Profs Stauss and Morris are taking advantage of this knowledge by inserting the genes involved in cancer-specific recognition into patient immune cells, while using CRISPR-Cas9 gene editing technology to

disrupt the genes involved in immune exhaustion and reactions against healthy cells. They are also testing whether the genetically enhanced immune cells can trigger the patients' own immune system to more effectively fight an aggressive form of blood cancer, known as acute myeloid leukaemia. This form of gene therapy with immune cells has the potential to establish lasting targeted cancer protection, minimising toxic side effects associated with current treatments and without the need for repeated cycles of treatment.

Reduction in the number of animals required for research

Case study from Cancer Research UK:

Ian Rosewell's team at the Genetic Manipulation Service help scientists at the Francis Crick Institute to develop mouse models for their research. CRISPR, being a cheap, quick and easy-to-use method, has already replaced previous technology used for developing knockout mice. Furthermore, the advances in cell culture offered by CRISPR allow for faster results with the use of fewer mice. This is particularly important in relation to the 'replace, reduce and refine' elements of animal research. There is considerable excitement about the potential for performing more complicated experiments that were not possible until offered by CRISPR.

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