



Organisational & Regulatory Implications for
the Translation & Valuation of Health Research

**Making ‘good targets’ for translational
research**
Policy Briefing July 2020



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Overview

- This is the first in a series of Policy Briefings from the ESRC Biomodifying technologies project.
- It sets out the main factors that currently shape what makes for a ‘good clinical target’ in each of our case study technologies; gene editing, induced pluripotent stem cells, and 3D bioprinting.
- There is no one determining factor for success. Instead, different combinations of clinical, commercial, regulatory and manufacturing factors combine to make certain applications more attractive than others: as such ‘good clinical targets’ reflect the interplay of these factors
- Indications that can draw on pre-existing procedures, standards and requirements established with previous therapies, such as gene therapy or foetal stem cell therapy, are seen as less risky and so seen as more promising clinical targets.
- The challenges of manufacturing at scale, combined with high anticipated costs, work in concert to make niche indications with high unmet need a preferred route for commercial development., especially where they demonstrate significant Quality of Life gains over the current standard of care.
- While there are aspects that are common to all three fields in determining good clinical targets, any strategic policy approach needs to respond to and support the specific development pathways each has especially when the shift from a niche to a more broadly based application becomes possible.
- Future Briefings will consider accelerating innovation, customisation, and the value chain for biomodifying technologies.

Background

This Policy Brief considers findings from the *Biomodifying technologies* project (2017-2020), which is an interdisciplinary analysis of the social, organisational and legal implications of biomedical innovation in the 21st century.¹ The project focuses on three case studies: gene-editing, induced pluripotent stem cells (iPSC) and 3D bioprinting - technologies that enable the modification of living biological tissue in novel ways. Biomodifying technologies are ‘gateway technologies’; they offer versatile, accessible tools for use in experimental settings, have broad potential application, and offer advances over existing practices, resulting in

simultaneous, rapid and far-reaching adoption in a range of sectors. In this work, we are primarily concerned with their human, clinical applications. In the healthcare context, they may be both ‘transformative technologies’ of the sort recognised by the 2016 Accelerated Access Review, capable of delivering significant benefits in terms of patient outcomes, and ‘disruptive technologies’ in that their development is likely to challenge existing translational and regulatory pathways.²

Biomodifying technologies is a collaboration between researchers at the universities of Oxford, Sussex and York and is funded by the UK Economic and Social Research Council. The aims of the project are:

1. To characterise the ‘experimental space’ where clinical applications of gene editing, iPSC and bioprinting are developed, focusing on the UK within a global context.
2. To understand what makes a promising application and how this is shaped over the course of the translational pathway from bench to bedside.
3. To identify the particular challenges and risks posed by these technologies for existing organisational, regulatory and governance regimes and how these in turn affect the development of our case study technologies.
4. To interrogate how the benefit or value of biomodifying technologies is defined by different stakeholders, how benefit and value are assessed, and explore which constituencies benefit or are seen to benefit.
5. To consider the role of patients and patient groups in engaging with or helping to define risks, possible governance options (e.g. patient registries), and the role of patient-centred care in assessing value.
6. To deliver an informed and constructively critical social science approach to make recommendations supporting responsible research and innovation in this field.

Multiple research methods were used, including interviews with diverse stakeholders, review of scientific articles, mapping of patents and publications, and updates of research and clinical developments.

The Experimental Space

The term ‘biomodifying technologies’ describes tools and techniques that allow researchers to modify

living biological material at the fundamental level of molecules, cells and tissues:

1. Induced pluripotent stem cells (iPSC) are made by ‘reprogramming’ ordinary cells of the adult body, such as skin or hair cells, back to a ‘pluripotent’ state. This means that, like the cells of an early embryo, they can become any type of cell in the human body –eye, liver, heart and so on. Unlike embryonic stem cells, cells and tissues made from iPSC have the same genetic material as the original adult donor.
2. Gene editing describes the alteration of DNA using molecular tools such as CRISPR/cas9, TALENS, and Zinc fingers. Each of these tools contains a programmable ‘targeting’ domain (such as the ‘CRISPR’ part of CRISPR/cas9) that can be designed to find and attach itself to a particular sequence of genetic material in a living cell. Once the target sequence is found a ‘molecular scissors’ part of the tool (e.g. the cas9 enzyme) can cut out a particular piece of the DNA, replace it, or change its content. Gene editing can be considered an upgrade on older genetic modification techniques, in terms of speed and accuracy.
3. 3D printing, also known as ‘additive manufacturing’, involves adding multiple very fine layers of material, one on top of the other, to create a complex three dimensional solid object. 3D bioprinting takes this concept and applies it to living organic material. Instead of creating objects from multiple layers of plastic, concrete or metal, bioprinting uses ‘bioinks’ made from cells and extracellular scaffolding materials.

These technologies are not inherently ‘for’ any particular type of application (e.g. medicine, agriculture). Each represents an advance or improvement on older more established techniques such as recombinant DNA (rDNA) technology or other (stem) cell culture techniques. Some of these (rDNA, cell culture) are themselves examples of prior biomodifying technologies. As a result, gene editing and cellular reprogramming technologies are not especially disruptive to basic research. They align more or less readily with the existing skills of researchers and laboratories. Much of the popularity of CRISPR-Cas9 gene editing is attributed to its reputation for being easier, faster and cheaper to use than other gene editing tools, as well as more accurate than rDNA. Research groups used to working with human embryonic stem cells (hESC)

found that the techniques for culturing hESC, tests for pluripotency, and protocols for differentiating the pluripotent stem cell to make particular tissue types (e.g. dopaminergic neurons) were readily transferable to iPSC. Bioprinting is somewhat more heterogeneous as it brings together the technique of additive manufacturing, originally developed as a way of building rapid prototypes using plastic or metal, with the field of tissue engineering whose primary aim is to replicate functional human organs and other tissues *in vitro*. Nonetheless, each of our case study technologies has taken on some of the expectations and translational goals associated with these existing fields and technologies.

Gene editing is seen as a successor to gene therapy for genetic diseases. iPSC have taken on the promise of hESC to produce differentiated cells for cell therapy and regenerative medicine, while bioprinting is seen as a way of achieving the tissue engineering goal of producing viable whole organs for transplant. The tissues produced by iPSC and 3D bioprinting are also being developed as platforms to screen novel small molecule drugs for toxicology during preclinical development, and as tools for *in vitro* modelling of human diseases, with further applications in pharmacogenomics and diagnosis being considered. Clinical trials of gene editing and iPSC-derived cell therapies have been initiated, while bioprinting is currently in preclinical development.

As with any more or less disruptive, innovative biomedical technology, there is considerable policy interest in where the first beneficial applications are likely to be seen. We outline our findings and suggestions on this below, considering clinical, commercial, and regulatory and governance aspects.

Clinical considerations

Evaluation of ‘good targets’ requires considering both the features of the technology and the features of the therapeutic target(s). Clinical considerations include how well characterised the relevant features of the disease are. For example, in gene editing monogenic diseases are considered more suitable early targets than genetically complex conditions like cancer or asthma. Moreover, clinical sites that have prior experience of and capacity to deliver novel therapies will draw on this understanding and practice in selecting good targets. The accessibility and physiological characteristics of the primary or organ tissue to be targeted are also relevant. Both iPSC and gene editing treatments are being developed for eye diseases like age-related macular degeneration partly because the eye is an enclosed, immune privileged compartment within the body and

is amenable to non-invasive post-treatment monitoring.

The capacity to build on existing clinical skills, treatment pathways, and delivery mechanisms is also important in reducing the uncertainty and risk that come with novel biomodifying technologies. Skin and bone (orthopaedic) implants are considered promising early translational targets for bioprinting because they would build on existing and relatively routine skin grafting and bone replacement or repair (e.g. hip implant) procedures and products. Many of the current clinical trials of gene editing involve modification of white blood cells of one sort or another; for example modified haematopoietic stem cells for β -thalassaemia or sickle cell disease. Both gene editing and iPSC are being tested as ways to make next generation CAR-T therapies for blood borne cancers. These developments all build on the now routine and trusted clinical pathways for accessing and manipulating bone marrow derived stem cells in leukaemia therapy.

Even where previous research has not led to a successful treatment, it can still provide knowledge and experience to build on. The use of iPSC-derived neurons to treat Parkinson's disease (PD) is considered more feasible because developers can build on experience gained from previous attempts to treat PD using neurons derived from foetal stem cells. Although clinical results from foetal cell therapies were equivocal and did not clearly demonstrate efficacy they provided a translational pathway in terms of appropriate animal models and other preclinical studies, surgical delivery mechanisms and protocols for evaluating and measuring clinical outcomes of cell therapy that can all be adapted for iPSC. Similarly, prior unsuccessful attempts to develop gene therapy (using rDNA) have provided a wealth of knowledge about which viral vectors do or do not efficiently modify which tissues. Adeno-virus and adeno-associated viruses are poor vectors for the lungs (relevant for Cystic fibrosis, once thought to be a prime candidate for gene therapy because it is a monogenic disease) because they induce an immune response, while lentiviral vectors are more efficient at transfecting lungs, eye and brain, but less so for muscle or liver.

Manufacturing considerations

Scale up and manufacturing been a challenge for cell and gene therapies since the first wave of tissue engineering companies emerged in the late 1980s and biomodifying technologies are no different. The fit between existing manufacturing capacity and the amount of material needed to treat a particular target tissue plays a role in assessing what makes for a good

target. Smaller tissues like the eye, or targeted parts of complex tissues like the brain or heart typically require fewer cells (for iPSC treatments) or lower titres of vector (for gene editing treatments) which are more consistent with current manufacturing capacity. As one interviewee noted:

“One of the nice things about trying to treat macular degeneration is you only need a few thousand cells. Although they are an absolute nightmare to make, you’re not making that many. If you’re trying to do something where you are making cells for an artificial liver device or something like that you’re looking at... 10^{10} or something [similar]” (Commercial stem cell developer 2#).

Efficiency of production is also important, with low dosage and fast production currently being the preferred goal for getting products into clinical testing. 3D bioprinting is further from the market than the other two case study technologies, remaining at the preclinical stage, in part due to the greater variety of expertise involved including engineers, biologists, materials chemists, computer aided design et cetera. However, part of this complexity is because bioprinting is itself a novel manufacturing technique. Although the field may move slowly through the early stages of translation, once bioprinting reaches clinical applications the major uncertainties in the manufacturing process may already have been addressed, trading off a restricted pace now for a more rapid scale up later on.

Commercial considerations

Commercialisation of biomodifying technologies is largely the province of Small to Medium-sized biotechnology firms, although the involvement of traditional ‘big pharma’ players in bringing CAR-T therapies to market suggests that there may be more opportunities to out-license development and marketing of promising cell and gene therapies that have made it to later stage clinical trials. Although larger patient populations mean a larger market for any potential intervention, there are a number of factors pushing commercial developers to target rarer diseases or well-defined sub-populations within common conditions. Biomodifying therapies are likely to be expensive, so developers must consider what other treatments are currently on the market.⁴

To be viable, the added value of gene editing, iPSC or 3D printed treatment over a conventional one must be assessed in terms of cost-benefit, not just overall performance. For example, an acellular scaffold product may be somewhat less efficacious than a scaffold lined with iPSC-derived cells, but if it is

significantly cheaper than it may still deliver the greatest cost benefit for healthcare payers (whether public or private) and so outcompete the more advanced products.

This means developers are more likely to look for sub-populations of a disease that may have the greatest unmet need or which may have the highest costs to the healthcare system (such as patients whose haemophilia is poorly controlled and have repeated bleeding episodes requiring hospitalisation) as these will show the greatest improvement in quality of life over the current standard of care, and can justify the higher prices associated with advanced therapies. Some narrowly defined indications may also qualify for orphan drug status, which confers longer market exclusivity and can provide an expedited route to marketing authorisation and approval.

These incentives may also align with manufacturing limitations, so that in conditions where demand exceeds current manufacturing capacity such as producing iPSC-derived red blood cells or platelets, it makes more commercial sense to target niche submarkets such as patients who need HLA matched platelets, or blood products for use in treating battlefield trauma. Military applications of the latter kind may also enable access to dedicated funding streams, such as the Ministry of Defence' Defence and Security Accelerator (DASA) programme in the UK or DARPA in the US. Costs of manufacturing also inform the ongoing debate with cell based products (here iPSC and bioprinted constructs) about autologous (using a patient's own cells) versus allogeneic (using a limited pool of donors to create an 'off the shelf' product) therapies. Autologous treatments are potentially more achievable in the medium term, but the allogeneic option could be more commercially viable as it allows greater standardisation and quality control at the level of batches rather than bespoke runs for each patient.

Finally, developers should consider other advanced therapy products on the market or in development for particular diseases. Existing gene and cell therapy products can provide opportunities for follow-on products but also competition. The emphasis on viable mid-term targets means that multiple therapies may be in development for a limited range of conditions. For example, at least four firms are developing gene therapy products for haemophilia A. This raises the potential for markets to be segmented among several developers or for some viable products to fail to find a market, both of which have financial implications for the developers.

Regulatory and governance considerations

Most clinical applications of biomodifying technologies are likely to fall within the scope of the European Medicines Agency 'Advanced Therapy Medicinal Product' (ATMP) classification. Although the UK has left the European Union the regulatory framework for cell and gene based medicines remains aligned with Europe at the present time. The fact that the current Gene Therapy Medicinal Product (GTMP) category is defined in terms of recombinant DNA techniques means that some gene editing applications may technically fall outside its scope.⁵ In practice they are likely to be required to adhere to the GTMP pathway, in a manner not dissimilar to the way gene edited crops in Europe are compelled to follow the existing regulations for GM crops, despite again not involving recombinant DNA.

Some 3D bioprinted constructs are more likely to resemble organs for transplant than ATMPs, although as only the most preliminary trials of bioprinted products have so far occurred, the regulatory classification remains to be clarified. More mobile bioprinters may be used to repair tissue directly during surgery, which would make them more akin to medical devices. Bioprinting also involves Computer Aided Design software, to design the shape and structure of the implant to be printed. This may also require the software itself to be considered a medical device under some interpretations of the new EU Medical Devices Regulation.

Each biomodifying technology raises particular safety concerns above those associated with all cell and gene therapies. As standards are still emerging, 'safety' has been configured in different ways for different products. Genetic stability is a concern for gene editing, in terms of predicting 'off-target' effects of editing and assessing whether their likely effects are serious, negligible or unknown. Similarly, the presence of novel deleterious mutations produced by cellular reprogramming or culturing is a concern iPSC and bioprinting. Some iPSC derived therapies such as blood or platelets may be considered safer as they have no nuclear DNA. There is also a tension between products that must persist in the body for a long time to have the desired effect, such as bioprinted organs, and iPSC-derived neurons for Parkinson's or spinal cord repair, and those that produce a therapeutic effect with a shorter timespan before being eliminated from the body, such as gene edited CAR-T cells or iPSC-derived mesenchymal stem cells used to treat Graft versus Host Disease.

Regulatory considerations also have implications for manufacturing strategies. The requirement for adequate quality assurance and, in Europe, for a

Qualified Person to approve each batch of product makes centralised manufacturing more practical and cost effective. However, near-patient manufacturing may be desirable for some diseases where the need for a rapid turnaround time between collecting the cell sample and applying the intervention is acute. Bioprinting facilitates ‘redistributed’ models of manufacturing, to hospitals or third party commercial providers. Finally, there are ethical considerations, such as the greater social and ethical acceptability of iPSC compared to hESC, and the distinction between somatic and germline gene editing, that make some applications more feasible than others.

In light of the above, ‘good targets’ can be identified according to the following criteria:

CRITERIA FOR ASSESSING GOOD TARGETS
Manageable size of cell population needed to treat
Speed of production and mode of delivery
Well-characterised disease
Vector-selection strategy
Well-defined subpopulation with unmet need
Product has capacity to produce clear benefit as defined by QALY or other relevant HTA measure
Stable product that meets regulatory requirements

Priorities for policy

- It is important to consider how the mix of incentives that are currently shaping translational research with biomodifying technologies aligns with NHS England strategic priorities and the mid-term goals of other devolved health authorities.
- Developers and regulators should consider what evidence requirements might be necessary and appropriate to enable biomodifying therapies, initially approved for tightly defined sub-populations of disease, to be made available on the NHS for patients with other forms of the same condition.
- Policymakers should consider how schemes such as Early Access to Medicines (EAMS), the Accelerated Access Review’s ‘transformative designation’ or the orphan drug designation might best respond to the possibility of several competing high cost biomodifying therapies applying to these schemes in relation to the same, or very similar indications.
- The modelling efforts of Health Technology Assessment, including NICE, should be

encouraged to develop scenarios of these technologies’ clinical applications.

- Horizon scanning and strategic planning activities should also include ancillary technologies that might make currently unfeasible possibilities commercially viable
- It is worth considering whether there needs to be a single ‘winning’ therapeutic modality for any one disease (e.g. AMD) or biomodifying technology (e.g. iPSC ‘cell therapy’ with a transient effect and limited persistence in the body vs iPSC regenerative medicine with long term effects and extensive durability in the body) or whether multiple routes to success can be supported by policy resources.
- The implications of an industrial strategy and funding policy for these technologies should be considered, e.g. in the case of redistributed manufacturing, for bioprinting.
- Early therapeutic successes should be evaluated for their possible biasing and inhibiting effect on other potential development pathways.

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