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Making translational value: Identifying 'good targets' for clinical research on gene editing and induced pluripotent stem cell technologies



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ABSTRACT

Biomedical translational researchers aim to develop knowledge and techniques arising from research in the life sciences into clinical applications. Using the examples of induced pluripotent stem cells (iPSC) and gene editing, this paper examines how translational researchers identify and justify which particular conditions or patient populations make 'good targets' for translational research with particular technologies. Drawing on empirical data from qualitative interviews with academic and commercial researchers working on clinical translation of iPSC and gene editing in the UK, this study illustrates how particular combinations of technology and disease (for example iPSC-derived cells as a therapy for Parkinson's disease or gene editing for Cystic Fibrosis) were evaluated and justified as worth pursuing. The results show that translational researchers anticipate the ways in which their therapies-in-the-making will be evaluated by other groups including regulators, physicians, patients, and bodies charged with health technology assessment. Each of these groups have their own understandings of what is valuable in a novel health technology and their own criteria for evaluation. As a result, translational researchers must supplement justifications that draw on scientific and industrial logics, with accounts that recognise other forms of worth, including market and civic registers of justification. These findings give an insight into the factors shaping contemporary biomedical translational research. The current regulatory and health technology adoption frameworks exert a strong influence, with elements such as 'safety' or 'unmet need' being common to most justification. However there was also sufficient flexibility to allow different competing definitions of what safety or unmet need might look like.

1. Introduction

'Translational research' describes research in the biological and life sciences that is explicitly intended to lead to the development of new biomedical technologies such as therapies and diagnostics for human diseases. The idea of translational research is both instrumental and future-orientated. Advocates and promoters of translational research justify its importance through a combination of a moral imperative to alleviate human suffering by treating 'unmet medical need', and the conviction that the proper purpose and value of scientific research is to generate practical applications with societal and economic utility (Maienschein et al., 2008; Mary-Jo Delvecchio Good, 2001). This instrumental view of research is in line with wider cultural and organisational changes in academia that embed market-orientation,

competition and (fiscal) efficiency in the management practices and incentive structures of the university sector (Hessels et al., 2009; Kleinmann et al., 2013; Vallas & Kleinmann, 2008). This entails 'hybridisation' and blurring of institutional logics and practices between universities and companies, especially when it comes to translational research. Both academic and industry scientists face competition for funding, whether from grants or internal research budgets within a company and must often justify their proposed research activities to managers, whether department heads or commercial science directors and company executives (Vallas & Kleinmann, 2008). Accordingly, we can understand life scientists in both the public and private sectors as subject to a 'translational imperative' (Harrington & Hauskeller, 2014) to deliver new medical products and services. However, while this accounts for the general impetus and ethos behind translational activity, it does

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not by itself explain how *particular* technologies come to be developed for *particular* medical conditions, nor how these more specific aims of clinical translation are justified and evaluated.

In this paper, we address this question of how researchers identify 'good targets' for translational life sciences research by aligning particular technologies with specific medical conditions. To do this we will focus on two contemporary examples of novel biotechnologies: gene editing and induced pluripotent stem cells (iPSC). These technologies can be viewed as foundational or 'gateway' technologies similar to recombinant DNA technology, the Polymerase Chain Reaction, or cell culture (Morrison et al., 2019). They allow scientists to intervene in and modify fundamental aspects of the biology of living organisms. Accordingly, they could potentially be developed for a vast range of applications. However, out of all these *possible* areas of clinical application, translational researchers must make the case why they ought to work on developing any given technology as a treatment for *this* disease or *that* condition and not another.

Induced pluripotent stem cells, as the name suggests, are a type of stem cell. They are produced 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 have the capacity to become any type of cell in the body; eye, liver, heart, etc. Gene editing tools, of which CRISPR/cas9² is currently the most prominent example, contain a programmable 'targeting' domain that can be designed by scientists to find and attach itself to a particular sequence of genetic material in a living cell, and an enzyme that can cut out that particular piece of DNA, replace it, or change its content (for example, changing an 'A' to a 'T' in the genetic code).

Developing a technology like gene editing or iPSC as a treatment for a particular disease requires framing a problem (the medical condition) and the solution (the proposed therapeutic intervention) and justifying the claimed alignment between problem and solution. Making a 'good target' involves justifying and evaluating not simply 'gene editing' or 'iPSC' but something like 'gene editing as a therapy for Cystic Fibrosis' or 'induced pluripotent stem cell derived dopaminergic neurons as a treatment for Parkinson's disease'. This task is made easier by the dominance of mechanistic models of biology and medicine, where diseases are understood as 'malfunctions' of particular biological components within the organic machine of the human body (C.f. McLeod & Nerlich, 2017) that can be treated by replacing 'broken' cells or genes with 'functional' copies. Moreover, considerable prior work in the fields of gene therapy and stem cell science has gone into the framing of particular diseases as 'genetic' (Addison, 2017a) or as the result of tissue damage and degeneration and amenable to cell or tissue based interventions (Wainwright et al., 2006; Moreira & Palladino, 2005). The importance of this prior work is evident in the number of 'good targets' for gene editing or iPSC that had previously been targets for gene therapy (e.g. Cystic Fibrosis [CF], Severe Combined Immunodeficiency [SCID]) or older cell therapies (e.g. Parkinson's Disease [PD], diabetes).

In this paper, we report on one particular, situated empirical investigation of the justification of 'good targets' by researchers working on clinical translation of gene editing, gene therapy (see section 2.0) and iPSC in the UK.

1.1. Translational research as the e/valuation of good targets

The justifications offered by scientists working on biomedical translational research with gene editing or iPSC offers an important window on the factors shaping the processes through which new therapies come into being. As noted above, science, especially the life sciences, is subject to strategic, goal-orientated management (Borup et al., 2006). The incentive and reward structures for scientists increasingly foster

entrepreneurial activity and competition (Hessels et al., 2009; Vallas & Kleinmann, 2008). This suggests that scientists must consider scientific and medical logics, but also take into account the priorities and modes of evaluation of managers and funders. Translational research, with its explicit orientation towards new medical products and services, further extends the remit of concerns and priorities that must be taken into account. As Addison notes in relation to gene therapy "[r]esearcher-clinician relationships are certainly important for gene therapy [however,] interactions between academic and private actors as equally if not more salient to translational research in this maturing field" (2017b, p24). Translational projects connect narrow, near-term future goals, such as conducting a specific piece of research with broader longer-term expectations such as 'curing diabetes through cell therapy' or 'the UK being recognised as a world leader in stem cell science' (Michael et al., 2005). This involves a further set of audiences who are likely to have an interest in evaluating translational projects- or at least their outcomes- and whose interests must also be taken into account in scientists' justifications of their choice of alignment between technology and disease. It is this narrowing down of the possible to the justifiable that is of primary interest here.

The field of valuation studies provides a relevant set of conceptual tools to interrogate the justifications offered for such 'good targets' (Helgesson & Muniesa, 2013; Lamont, 2012). The connecting thread is the idea that value, in the sense of 'worth', goes beyond the use or exchange of commodities, and encompasses a set of ways of accounting for - or justifying-what is worth doing, having, being, or knowing. In particular, the first English translation, in 2006, of Boltanski and Thévenot's *On Justification: Economies of worth* ([1991] 2006) provided a detailed theoretical and conceptual foundation for this approach. Boltanski and Thévenot identified six distinct orders, or registers, of worth; the civic, the domestic, the inspired, fame, the industrial, and the market. Importantly this formulation breaks down the traditional distinction between 'value'; often considered quantitative, singular, and usually related to economics, and 'values', usually regarded as plural, social or cultural, and qualitative (Dussage et al., 2015). Instead, each order of worth comprises a distinct social world, with a particular conception of what is good, desirable and worthwhile, and where the legitimacy of justifications depends on their alignment with the norms of that social world. For example, in the 'industrial' order of worth, productivity, performance and efficiency are key values, while in the civic world solidarity, the collective good, public duty and representation are considered exemplary (Boltanski & Thévenot, 2006). Moreira (2012) has built on the work of Boltanski and Thévenot to identify different 'modes of co-ordination' prevalent in Western healthcare systems which are underpinned by "diverse orders of worth or systematic principles of evaluation" (Geampana & Perotta, 2022, p. 7). These modes of co-ordination are; 'efficiency' reflecting the values of the market, choice, competition, and financial benefit, 'effectiveness' which evoking the ideals of the laboratory, standardisation, evidence based decision making, and knowledge production, and 'patient involvement' which entails both the ideal of a medical duty of care and the more recent turn towards 'patient centred care' and joint decision-making by physicians and patients (Geampana & Perotta, 2022).

Of course, 'orders of worth', or 'modes of coordination' are abstractions, academic constructions derived from the history of social and political philosophy in the case of the former and theorisation from empirical analysis for the latter. Real world situations are typically messy and heterogeneous. They are unlikely to fit neatly into any one order of worth. Valuation studies allows that different orders or logics of worth can be in conflict with one another but are also (potentially) commensurable and capable of being weighed, balanced, and traded-off against one another. Boltanski and Thévenot recognised this propensity, nothing that 'the workings of an industrial enterprise cannot be understood on the basis of resources stemming from the aims of this world alone, even if the aim of efficient production based on functional investments finds its justification in the industrial order' (2006; p203). Instead, the

² CRISPR stands for 'Clustered Regularly Interspaced Short Palindromic Repeats' in reference to the characteristic sequence of the RNA 'targeting domain'.

development of a new product or service could incorporate aspects of the register of fame, as in the case of advertising, the domestic register if a well-known brand name was used to establish trust in the product, and the market order of worth if the product outcompetes rival offerings and becomes profitable for its developers. Similarly, [Geampana and Perotta \(2022\)](#) observed both tensions and alignments between different modes of coordination in healthcare professionals' accounts of novel 'add-on' IVF treatments.

Valuation Studies also takes a strong pragmatist emphasis on processes and practices of valuation ([Dussage et al., 2015.](#)). The worth of things - and the plausibility and power of justifications - is something that is achieved rather than being an inherent property. Claims of worth and justification must be *tested*. Tests and regimes of testing play an important role in the development and evaluation of technologies ([Mackenzie, 1990; Pinch, 1993](#)). Tests ascribe value by measuring some property or behaviour of a technology (or a component) and using the reported outcomes of this measurement as the basis for assessing the performance of the tested entity in a 'real world' situation. Testing therefore involves an act of projection from one set of outcomes in the present (the test conditions) to another set of outcomes in the future (the 'real world' use) ([Pinch, 1993](#)). This connects very clearly to the idea of an extended horizon of assessment for particular translational projects. The value of a particular alignment of technology and disease category (e.g. gene editing for cystic fibrosis) involves anticipation (i.e. projection) about its performance if and when it might become available for clinical applications. In this case we would expect tests to assess different claims about the merits of gene editing and iPSC as therapeutic interventions for different diseases such as Cystic Fibrosis or Parkinson's' Disease. Our empirical data derives from qualitative interviews with translational scientists and close readings of the biomedical and commercial literature on gene editing, gene therapy (see below) and iPSC meaning we did not witness any tests ourselves. However, we look for accounts of tests and testing in the interview data and literature to identify how justifications for particular diseases as good translational targets were assessed in practice, and what criteria (that is what registers of worth) these tests utilise.

Analytically, this directs our attention to both the practical and discursive strategies through which particular 'good targets' for translational research were evaluated and how the translational researchers we interviewed balanced and weighted the different criteria to construct justifications for their particular chosen 'good targets'. Bearing in mind the institutional embedding of evaluative mechanisms for academic translational research ([Hessels et al., 2009](#)), we also pay attention to the impact of similarly institutionalised and obligatory regimes of evaluation that exist for medicinal products.

2. Methods

This analysis draws on empirical research conducted by the authors as part of the project 'Biomodifying technologies and experimental space: organisational and regulatory implications for the translation and valuation of health research' ran from 2017 to 2020. The project was conducted by researchers at the universities of Oxford, York, and Sussex and funded by the UK Economic and Social Research Council (ESRC). The analysis here draws on findings from a sub-set of 33 semi-structured qualitative interviews with academic scientists, biotech company employees, and clinical researchers conducted in the period 2018–9.

These interviewees were all based in the UK and were working on translational research for human clinical application. As there were a limited number of UK-based researchers working exclusively in clinical gene editing, we also contacted and interviewed translational researchers working on clinical gene therapy. This also allowed us to ask whether gene editing had, or was anticipated to, replace gene therapy research. How our case study biomodifying technologies were viewed compared to antecedent technologies such as rDNA and human embryonic stem cells (hESC) was an important secondary research question for this project. In

practice, almost all the gene editing researchers also had experience working with rDNA and almost all the scientists working with iPSC had experience working with hESC, and in many cases continued to conduct experiments with both technologies. AB led on conducting the gene editing/gene therapy interviews and MM led on the iPSC interviews (See [Table 1](#)).

We approached clinical researchers, laboratory-based academic researchers and representatives of UK-based companies working with gene editing, gene therapy or iPSC technology. Almost all research we encountered was multi-disciplinary where biologists were aware of the clinical aspects and clinicians were aware of the biological properties of the technologies. The 'clash of cultures' between laboratory and clinic detected by [Wainwright et al. \(2006\)](#) seems to have been somewhat ameliorated by the continuing integration of clinical and biological expertise in dedicated translational research groups (see also [Addison, 2017b](#)) for a similar finding in an ethnographic study of a UK translational gene therapy laboratory). This paper focuses on discussions of the relative merits of different clinical conditions as 'good targets' for translational research. While interviewees working for commercial companies were also asked about business models and commercial valuation of different biomodifying technologies much of that material lies outside the scope of this paper and will be reported elsewhere.

Research ethics approval for the study was obtained from the University of Oxford Social Sciences and Humanities InterDivisional Research Ethics Committee (SSH IDREC approval no R55654/RE001) and the University of York ELMPS Ethics Committee prior to any contact being made with potential interviewees. Written informed consent was obtained from all participants prior to the commencement of interviews. The majority of interviews were conducted in person (prior to the advent of widespread Covid-19 in the UK) and were audio recorded. A smaller number of interviews were carried out using online platforms such as Skype, when face-to-face meetings could not be arranged. These interviews were also audio recorded. In all cases, the audio recordings were transcribed using a professional transcription service. One interviewee refused permission to record and in one instance the digital recording function failed, meaning two interviews produced only notes made during and immediately after the interview.

Interview transcripts were uploaded to NVIVO for analysis. Analysis was partly deductive, as the interview questions were designed to elicit discussion of specific topics and themes, for example relating to the translational projects the interviewees were working on and their justifications (e.g. in terms of anticipated outcomes) for the choice of those projects. The main part of the data analysis was inductive. One project member took a lead on reading the transcripts for each of gene editing and iPSC. They then selected a limited number of transcripts (3–4) and performed a preliminary coding exercise. This subset of coded transcripts was then shared with the wider team (including the authors) for review. The different potential codes were discussed by email and digital video calls among the group, and assessed in light of the project aims, the background literature, and the information presented in the transcripts themselves. Following this collective evaluation, a revised set of codes was devised and applied to the full set of interview transcripts, with further collective discussion of any new issues taking place as needed.

All interviews analysed in this paper were conducted in the UK, with interviewees who were working in UK institutions and firms (although exclusivity of affiliation was not required so some interviewees also held posts in non-UK institutions). The data and analysis therefore capture translational research on gene editing, gene therapy and iPSC only in the context of the UK and for a particular 'snapshot' in time.

Table 1
Number of interviews conducted for each case study technology.

	Academic respondents	Commercial respondents
Gene editing/gene therapy	9	8
Induced pluripotent stem cells	9	7

3. Results

3.1. Existing knowledge as a justification for translational projects

As noted above, many of the disease areas presented as ‘good targets’ have been the subject of prior attempts at gene or cell therapy with older technologies such as rDNA or hESC. These histories were employed to justify these disease areas as ‘scientifically plausible’ (c.f. Selin, 2011) targets for intervention, as in the following quotes:

[A] lot of the knowledge they’ve got from doing bone marrow transplants translates to the gene therapy ex vivo, and potentially CAR-T and CRISPR type technologies (Company gene therapy interview 2).

You’ve actually got a very good method which is bone marrow transplant and gene therapy is just an extension of that (Academic gene therapy interview 5).

Here the method and site of genetic modification, by extracting bone marrow stem cells and genetically modifying them in laboratory before re-administering the modified cells to the patient, is presented as viable because it builds on the existing, and by now uncontroversial, technique of bone marrow transplantation. This positioning acts to make a novel and therefore potentially risky and uncertain innovation appear more commonplace and reliable, and is a well-established rhetorical trope. As (Addison, 2017a, p. 274) notes “[a] key part of defining a workable field is positioning it in relation to neighbouring practices”. Indeed, the very first human gene therapy trial in 1981 involved modification of cells in extracted bone marrow and utilised similar justifications (Addison, 2017a).

Past failures, as well as past achievements can also be used to justify particular alignments of therapy and disease, as in the following quote from a scientist working on pluripotent cell therapies:

[B]asically what you’re doing is you’re piggybacking off a history of cell therapy. So, in the liver space for example we’ve done almost 150 patients who’ve had cell therapy already and there’s enough of a readout to suggest that there is reason to pursue that as an interventional strategy. And therefore to overcome the deficiencies of the previous cell therapies which was based on [...] insufficient numbers of high quality cells. You can basically address that challenge through iPS (Academic stem cell scientist 7).

Here the prior history of *unsuccessful* cell therapies for liver disease is repositioned to support iPS cell-derived therapy as a viable future prospect for liver disease.³ Similar discourses of ‘lessons learned’ were evoked in relation to early unsuccessful attempts to treat Cystic Fibrosis through gene therapy of the lungs, as a way to increase the plausibility of CF as a good target for contemporary gene editing techniques.

All of these accounts ground their justifications in term of established knowledge and practices. The important connection between these accounts is that each presents a knowledge claim about the functioning of different components-bone marrow transplants, a ‘readout’ from cell therapy et cetera. Proper functioning of things (and people) is an essential basis for rational calculation and control over events in the industrial world:

The proper functioning of beings extends the present into a future, opening up the possibility of prediction. The industrial form of co-ordination thus supports an equivalence between present situations and situations to come, and constitutes a temporality (Boltanski & Thévenot, 2006; p205).

This use of existing knowledge and experience reflects Moreira’s ‘effectiveness’ mode of co-ordination and the ‘industrial’ order of worth, in which what is measurable, quantified and supported by evidence is granted importance as the basis for planning. This is not surprising as ‘the industrial world is the one in which technological and scientific objects have their place’ (Boltanski & Thévenot, 2006, p. 203). However, it also reflects a pragmatic stance in which scientists understand that resources are often constrained, and budgets limited. Building on existing knowledge and experience can also be presented as a more efficient, finically prudent, and ‘plausible’ (Selin, 2011) course of action to research managers whether in the public or private sector. Here researchers also appeal to the more ‘market’ or ‘efficiency’ orientated orders of worth favoured by middle management in universities and companies, as well as by research funders (Kleinmann et al., 2013; Vallas & Kleinmann, 2008). An important part of the justifying a good target is presenting it as a worthwhile investment to these managers (among which we include formal science funding agencies such as UKRI). ‘Progress’ as Boltanski and Thévenot observe ‘is the investment formula in the industrial world. It is associated with the operation of investment (in the classical sense of the term) that weights the “price of efforts” [...] and the “middle term profitability” that they ensure’ (2006; p208).

Justifications of ‘good targets’ also require consideration of projected futures in which the selected technology has been successfully developed as a treatment for the particular disease. The futures constructed in the scientific literature and in interview data on gene editing and iPSC are largely instrumental and means-orientated. They assume the continuation of existing societal conditions, structures and values into the future, limiting change to the realm of the technical (Michael, 2000). Consider the manufacturing options for cell therapies evaluated in the following comment:

If you want to be realistic you have to look at the tissues that can be generated in a reasonably short space of time and in an economically viable way [...] you would think that, for example making Parkinson’s cells for the treatment of Parkinson’s disease is a very well defined disease, the treatments are not good enough and you don’t need that many cells. So, that’s an ideal. If you then look at the more complex things like three-dimensional structures like liver and heart, these are clearly the ones that would have a much higher impact in terms of the number of people who need them but, actually, making those tissues is still at least a decade away (Academic stem cell scientist 4).

This account, valorising Parkinson’s Disease (PD) as a good target for iPSC-derived cell therapy combines appeals to existing knowledge with claims to efficiency and capacity to address unmet medical need. The area of tissue damage in PD is relatively small, meaning that it does not require a large volume of cells to effect a treatment. Manufacturing this volume of clinical grade cells is compatible with existing manufacturing techniques. As with previous examples in this section, this part of the claim appeals to what is already known and evidenced-the industrial or effectiveness register of worth.

However, the appeal to ‘realism’ also represents an acknowledgement that the wider institutional structures through which science, and indeed medical technology, are evaluated are durable and must be given consideration both in the present (in which the justification is being offered) and the anticipated future (in which the developed technology will be evaluated). PD is also valorised as a good target because production can be achieved economically and in a near-term timeframe, and because the existing treatments for PD are seen as “not good enough”. The emphasis on near-term success aligns with that we see in other

³ This rhetorical strategy seems to be a recurring feature of debates on the promise of biomedical therapies, especially stem cells (Kitzinger, 2008; Moreira & Palladino, 2005). It operates to restore, or ‘rescue’ (c.f. Kitzinger, 2008) hope in cell therapy for liver disease by positioning the prior attempts at cell therapy as the medically and scientifically valid idea, let down by inadequate technical performance (the inability to produce enough ‘high quality’ cells) at the time. By acknowledging what did not work before, iPSC can be positioned as a new way of overcoming the limitations of the past and restoring the technology of cell therapy as a plausible approach to treating liver disease.

studies of prospective scientific and technological futures, where legitimacy is commonly associated with ‘near term’ futures, while futures that are further away in time are devalued as more speculative and uncertain (Michael, 2000; Selin, 2011). In this context we can go further and posit that this combination of justifications reflects Academic stem cell scientist 4’s awareness that any successful medicinal product must be economically viable, outperform existing treatments and that ‘near term’ goals suit the preferences of managers for readily calculable cost/benefit analyses, which in turn inform their assessments of which activities are worth supporting and which are not. In other words part of making a ‘good target’ for iPSC or gene editing involves considering the scientific, medical, managerial and economic registers in which such a therapy is likely to be evaluated over the course of its translational journey. This requires an act of projection, but equally requires assuming that the criteria and mechanisms of evaluation that are in place in the present will persist and remain relevant in that projected future. Contiguity with the present allows advocates of instrumental futures, as in the quotes above, to portray themselves as realists “dealing with the way the world really is and will continue to be” (Michael, 2000, p. 29), which strongly aligns with the desire for an ordered, calculable universe manifested in both scientific and market logics.

This quote also highlights the frequent use of comparison, which as Lamont (2012) has argued, is an important sub-process of valuation. PD was positioned as a near term (i.e. more achievable) goal, *compared* to cell therapy to repair more complex organs such as the heart or liver that were viewed as “at least a decade away”. This in turn was partly based on a comparative assessment of manufacturing capacities. PD requires a lower volume of cells, which was seen as more compatible with existing manufacturing techniques, compared to cell therapy for the heart or liver, which would require further work to scale-up the volume of cells that can be reliably manufactured to a clinical grade.

3.2. Anticipating future evaluations

The mechanisms and criteria for evaluating medicinal products are particularly strongly institutionally embedded and stable. The most obvious, and entrenched, evaluation that any therapeutic medicinal product must encounter is that conducted by national medicines regulators. In the UK, this means the Medicines and Healthcare products Regulatory Agency (MHRA). In line with other national regulatory agencies, MHRA assessment of the safety and efficacy of a product constitutes a mandatory passage point for entry to the UK market for healthcare products. In line with this, most respondents incorporated claims about safety in their justifications for the merit of their particular ‘good targets’. Safety was framed in a multitude of ways, often specific to the modality of a particular therapy. iPSC-derived blood cells were valorised as especially safe because mature red blood cells contain no nucleus and so have no DNA that might contain potentially dangerous genetic mutations. Cell and gene therapies that have a transient effect (such as most immunotherapies) and are then eliminated from the body were presented as safer than therapies that require long-term persistence of altered cellular or genetic material in the body, again because any deleterious genetic or other elements would have less time to have a damaging effect on the patient’s health. One recurring theme implicated the size (especially configured in terms of the number of cells) of a target organ or tissue in calculations of safety:

This is where [targeting the liver] gets quite tough in terms of safety [...] In that five billion cells [...] you could say you can’t allow one stem cell to be in there because stem cells can replicate in uncontrolled manners (IPS company interview 4).

So, when you have this kind of isolated tissue, it serves you well if you’re going to have an intervention, let’s say me delivering a genetically engineered virus that aims to correct a mutation, *in terms*

of safety it would be better if that particular vector is isolated to your area of interest (Academic gene therapy interview 4, emphasis added).

Larger tissues require more cells or a larger titre of viral vector containing a gene-modifying agent, meaning there is more material to test for safety (or more likelihood of a contaminant making it through the checking process). Conversely, smaller tissues like the eye are seen as lower risk. Enclosed sites like the eye also allow the body’s internal barriers to be presented as ‘containment’ measures, restricting the potential for therapeutic agents to spread to unintended locations in the body where they could yield uncertain and likely undesirable effects. The eye was presented as an especially good target for both cell and gene therapies for this reason.

Safety was not only evoked in terms of properties of the therapy or the tissue to be targeted, but also, in keeping with results above, in terms of existing clinical settings, expertise, and facilities that might be mobilised to manage any unexpected side effects of new treatments:

Then also haematology sites or bone marrow transplant sites are very used to dealing with a lot of safety issues. Graph versus host disease, infections, cytokine storms (Gene therapy company interview 1).

Here the respondent again evokes the similarities between ex-vivo gene therapy and bone marrow transplants, to suggest that the established skills and infrastructure to manage side effects and complications of haematopoietic stem cell transplants can also be deployed to manage the potential safety issues of genetically modified stem cell transplants. The discussions of how safety could be assessed very much fitted with the predominance of the ‘effectiveness’ mode of co-ordination, where evidence and standards are linked to the idea of predictable and controllable futures, which lie at the heart of the idea of safety. Nonetheless, the wider function of the MHRA and similar agencies in protecting the public, and in acting as a mandatory passage point between developers and the market, draws its justification from the civic order of worth, which is concerned with the public good, the proper functioning of the state and the rule of law.

‘Safety’ and ‘Efficacy’ are not the only ways in which this civic or public good can be framed, and there are other regulatory agencies and other registers of evaluation that must be considered, as the following quote illustrates:

[i]t’s a non-inferiority question, whether what we generate here is affordable, is easier, is something which gives us better benefit for the surgeons, whether it’s easier than doing competitive, synthetic grafts [whether we get a good] share of the market [...] The question is that our idea is good enough and whether we can prove it, at least in the large animal model, that this is at least as good as the other models. So, our project will be a comparative study, comparing synthetic grafts, acellular grafts and acellular grafts with our home-made cells together. Then, if it looks promising, obviously, then it will progress further (Academic stem cell scientist 1).

This quote clearly shows the speaker anticipating the ways in which the use of iPSC-derived grafts might be evaluated by different groups in the future. Surgeons comprise the most obvious end users of an arterial graft and thus the likely ‘market’ for future adoption and use. The success (value) of iPSC-derived arterial grafts as a therapy for arteriosclerosis will in part depend on how well it meets the needs of this important professional user group (market). Again, comparison is a paramount mode of evaluation. Academic stem cell scientist 1 recognised that a successful product must also out-perform rival (i.e. competing) offerings such as synthetic or acellular grafts, by giving better clinical outcomes and/or being easier to apply. In Boltanski and Thévenot’s (2006) schema, the market order of worth is less about economic exchange *per se* and more about providing goods and services to meet a need, and about using competition between rival goods to achieve this. Here we see that competition also extends to the testing process itself, with rival products being compared in small, and then large animal models before being

evaluated to see which (if any) might be taken forward to early-stage human trials. The trial and testing stage of technology development thus combines evidence-based and market logics by placing potential products into competition on the basis of functional performance. This makes sense in the translational environment where scientific and commercial logics often combine in hybrid institutional forms (Vallas & Kleinmann, 2008).

Another important market for medicinal products is, of course, the populations of patients with the various conditions for which gene editing or iPSC are being developed as therapies. This has the potential to evoke a more civic or patient-centred (Moreira, 2012) approach:

[S]o for most of our product development we will talk to patient groups, charities, as a source of funding, but more importantly as a source of information about what the patients need, how they view clinical trials and so on. There's a push to have the patients be more involved in clinical trials, have patient groups review consent letters or other things (Gene therapy company interview 6).

I hate the word, but there's a market there still for CF gene-based medicines. It's a market which is supported by charities, the CF Foundation in the States, CF Trust in the UK, CF Ireland, there's CF groups all across Europe and the rest of the world. They all have the same goal. It's a treatment for everybody (Academic gene therapy interview 7).

The patient voice in both these accounts is primarily represented by organised patient charities and advocacy groups. Patients do not appear to actively get a say in determining what makes a 'good target' for translational research, but organised patient support can help make a particular condition a more feasible prospect. This is especially the case for conditions such as Cystic Fibrosis or Parkinson's disease where there is a long history of trying to develop a cell or gene therapy for the condition and there has been time to build up strong patient involvement and support for this approach, as in the second quote above. In practice only some respondents discussed close contact with patients and patient groups, while other accounts of 'unmet medical need' evoked clinical and epidemiological framings of need rather than patients' perspectives. The idea of 'unmet medical need' comes from a clinical logic of disease or illness that is not adequately addressed by current methods and techniques. The concept has considerable flexibility and was utilised by respondents in different ways to support intervention in different conditions:

"we deal with diseases in children, so that kind of makes it a priority. We deal with diseases, so in SCID, which are rapidly fatal. You really do need to do something" (Academic gene therapy interview 5).

"There is a major need because there are over 600,000 cases of arteriosclerosis per year" (Academic stem cell scientist 1).

These two examples illustrate different formulations of unmet need. In the first, the disease in question, Severe Combined Immunodeficiency (SCID), is both paediatric, and fatal, evoking the common cultural evaluation of childhood death as especially tragic and undesirable. This evokes the domestic order of worth in which the welfare of children, as vulnerable dependents are the responsibility of the more senior and accomplished members of the polity (in this case physicians and scientists). By contrast, the account of *Academic stem cell scientist 1* draws more on the civic order of worth, appealing to the accumulated weight of collective, if not necessarily fatal, adult suffering and the implied economic 'burden' on the NHS (a public service) of untreated or poorly treated illness on the health service. This account refers to the number of 'cases', evoking the regime of 'effectiveness' with its focus on evidence-based decision making to add weight to the justification, while Academic gene therapy interview 5 referred to 'children'. The latter draws more on the 'patient involvement' mode of co-ordination through the urgency and emotional appeal of fatal childhood illness and the

accompanying medical duty of care (Moreira, 2012). As all these accounts show, the patient voice is always somewhat instrumentalised, whether as a 'market' for new therapies, a source of funding and information, a weight of cases for the health service to deal with, or a serious and urgent clinical need that justifies investment in new therapies. The civic and domestic orders of worth are supplemented and intertwined with a market logic, in that a need not adequately addressed by currently available goods is also a potential market opportunity for a therapy developer.

Novel healthcare products are also often evaluated by comparison (again) with the existing 'standard of care' treatment in terms of both effectiveness and cost (often framed as 'value for money'). This kind of calculation matters to National Health Service (NHS) Trusts and hospital managers concerned with annual budgets and is also part of the formal evaluation conducted by health technology assessment bodies such as the National Institute for Health and Care Excellence (NICE)⁴ - another obligatory passage point for novel medicinal products wishing to access the UK market. Part of constructing need as 'unmet', entails presenting existing treatments as in some way lacking by comparison. For conditions with few viable therapies, such as Parkinson's Disease this is taken as self-evident. In other cases, a more sophisticated division of the potential market constituting a good target for translational research must be effected:

[W]ith CF now there's Ivacaftor, the drug I've mentioned, which works for maybe about 10% people. There's another licensed medication which works for under 50% ... [if clinical trials of other new therapies are successful] then it will be drugs for 90% of people with CF. That still then leaves 10% who have got nothing and you've got very severe forms of CF and gene editing or gene therapy may be their only hope (Academic gene therapy interview 7).

In this example, the respondent breaks down the broad population (or market) of patients with Cystic Fibrosis (CF) into sub-populations of patients depending on how well they respond to a variety of extant and emerging conventional pharmacological treatments. Given the risk and uncertainty associated with gene therapy or gene editing and the high probable cost compared to conventional pharmaceutical treatments, this respondent identified only one putative sub-group, the "10% who have got nothing" (i.e. do not respond well to any other treatments), as the initial 'good target' population for gene therapy or gene editing. Here the civic, or compassionate element of unmet medical need is tempered by the utilitarian calculations of health technology assessment (HTA) and the criteria of 'value for money' for medicinal products. HTA comprises another set of future tests and another regime of worth to be anticipated and accounted for in the construction of a good target for translational research.

4. Discussion and conclusions

The goal-orientated nature of translational research means that translational researchers trying to develop clinical applications for gene editing or iPSC-derived cell therapy must necessarily anticipate how their efforts will be evaluated by a range of different groups using a variety of criteria. Most immediately, scientists must provide scientific justification for the validity of their approach to their colleagues, including referees if applying for a grant or submitting a publication for review. They must also justify their planned activities in light of the institutional logics of

⁴ NICE operates by calculating the impact of a therapy in Quality Adjusted Life Years (QALY) and comparing it to the existing standard of care, set against a pre-defined threshold of cost-per QALY. Although a higher threshold of cost-per-QALY exists for rare diseases, this methodology has been seen as challenging to RM, where large data sets from randomised control trials are rare, patient populations are often small, and manufacturing costs are high (Faulkner & Mahalatchimy, 2018).

their organisation, whether a university or a small-to-medium sized biotechnology firm. Typically, this means meeting criteria of efficiency, financial prudence, and near-term goal orientation. In keeping with the idea that the “codes and practices from academic and industry have grown more intertwined” (Vallas & Kleinmann, 2008; p302), scientific evidence from previous experiments and attempts at translation is often marshalled to meet these more market-orientated institutional criteria of evaluation. As noted, translation has a dual temporality. Beyond meeting these proximate criteria of evaluation, scientists must also look ahead to anticipate further ways in which their translational activity might be assessed in future.

The pathway for bringing a medicinal product to market is well established with a number of obligatory passage points. Some of these have legal as well as institutional force; notably, in the UK, regulatory evaluation for safety and efficacy by the MHRA and cost-benefit assessment by NICE or NHS England (which can conduct its own assessments where NICE guidance is absent) (Faulkner & Mahalatchimy, 2018). If a medicinal product successfully navigates these hurdles it then enters what Ulucanlar et al. (2013) call the ‘adoption space’. Here approved medicinal technologies are further assessed in terms of whether the product functionality aligns with the needs, capacities, skills, budgets, and ways of working of physicians, patients (or at least physicians' views of patients), hospital managers and trusts. These evaluations may in some cases be less formal, but are nonetheless important.

The different organisations or groups in this space utilise different types of tests, and the types of testing regimes they employ are based in different orders of worth corresponding to their (distinct) social worlds. For example, the MHRA employ tests that value evidence-based functional assessments of new products, but the agency derives its ultimate rationale-the mission to protect the public from harmful medicinal products-from the civic world. The comparison of products with an existing standard of care, cost-benefit analyses, and the competition with rival offerings to meet professional and patient need all evoke the market order of worth. The diverse framings of ‘unmet medical need’ can also frame appeals in the civic and domestic orders of worth. As a result translational researchers must construct justifications of ‘good targets’ that combine and balance multiple orders of worth, in anticipation of the way their efforts will appeal to, and be subject to assessment by, multiple constituencies.

The translational research process is therefore one of ongoing evaluation and assessment of particular technology-disease dyads. Every experiment, animal test, and clinical trial affects both the immediate short-term worth of a particular approach and its anticipated future as a successful therapy. If we were to repeat this research in five years' time, we would expect that at least some accounts of what constitutes a good target for each of these biomodifying technologies would have changed, as a result of the experimental testing of translational claims conducted in the interim period. At the same time, a ‘failed’ test does not automatically invalidate a particular good target or a programme of translational research. Indeed, as past research has shown biomedicine in particular seems to retain an almost limitless scope for rescue and rehabilitation of the translational hopes of various technologies despite poor results (Kitzinger, 2008; Moreira & Palladino, 2005). Moreover, even within the limited dataset reported here, we find a plethora of different ways of justifying particular conditions as ‘good targets’ for cell or gene therapy. There was no one set of criteria that was used to support all disease-treatment dyads.

This shows that existing institutional methods and criteria for assessment and evaluation have a strong structuring effect on what translational researchers identify as ‘good targets’ for new technologies such as gene editing and iPSC, but not to the extent of being deterministic. In theory, the result of almost any test can be disputed, but in practice, some tests are more socially embedded and durable than others (Mackenzie, 1990). In translational research, laboratory experiments can be redesigned and redone at relatively little cost of time and resources. A disappointing experimental result can readily be revisited with a slightly

(or drastically) altered methodology. The tests applied by the MHRA or NICE are harder to dispute, have greater institutional authority and typically are much more costly in terms of time, labour, resources and money to retake. There are currently no gene editing or iPSC therapies on the market, and even the number of approved cell and gene therapies using other biomodifying technologies is limited (Eder & Wild, 2019). This means that although there are established regulatory frameworks for cell and gene therapies there is no ‘blockbuster’ product to create an exemplar pathway to market or to generate path dependency. Even the successful and much publicised Chimeric Antigen Receptor T-cell therapies (CAR-T) for cancer remain limited to a subset of blood cell cancers and have not yet demonstrated that they work on solid tumours, which are by far the more common type of cancer. This uncertainty means there is still some flexibility in determining what is or is not worth pursuing –‘what works’. Although the established socio-technical system for medicinal products, as well as the prior history of cell and gene technologies, clearly exerts a structuring effect that is both material and discursive, multiple different ways to justify a particular disease as a good target for iPSC-derived cell therapy or gene editing remain open. However, if a major national or international regulatory agency does approve a number of iPSC or gene editing based therapies in future this will potentially entrench a narrower set of criteria on which the value of clinical applications of these technologies are assessed, or at least set a new benchmark against which subsequent efforts will be compared. Equally, future policy initiatives (such as novel regulatory pathways) could potentially open up a different, or wider, range of ‘good targets’ as new justifications become available.

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Ethics review

Research ethics approval for the study was obtained from the University of Oxford Social Sciences and Humanities InterDivisional Research Ethics Committee (SSH IDREC approval no R55654/RE001) and the University of York ELMPs Ethics Committee.

Ethics statement

This study reports the results of in depth qualitative interviews with scientists, clinicians and employees of biotechnology companies. Research ethics approval for the study was obtained from the University of Oxford Social Sciences and Humanities InterDivisional Research Ethics Committee (SSH IDREC approval no R55654/RE001) and the University of York ELMPs Ethics Committee prior to any contact being made with potential interviewees. Additional research ethics approval was not required from the University of Sussex. Written informed consent was obtained from all participants prior to the commencement of all interview, whether in person or online. All consent forms, participant information sheets, interview questions, and supplementary material was reviewed and approved prior to use by the Oxford and York RECs. All clinical staff interviewed were affiliated with a teaching hospital or other academic institution and were interviewed in their capacity as academics, not as NHS staff and were not interviewed on NHS premises or asked to discuss any information about specific patients. As such IRAS approval was not required for this research.

The collection of personal data was minimized but unavoidable. All personal data collected was treated in a manner compliant with both the EU General Data Protection Regulation and the institutional data protection policies of the Universities of Oxford, Sussex and York. More information on the project's publicly facing privacy statement can be found here: <https://www.biomodtech.com/privacy>.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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