

Gene therapies and the NHS

Getting new advanced medicines to UK patients



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Gene therapies explained

A new class of advanced treatments has emerged that allows doctors to repair, replace or add new genes into patients' DNA, preventing or treating diseases at a cellular level.



The aim of gene therapy is to repair, replace or add new genes into a body system in order to prevent, treat or cure a disease.



Gene addition utilises viruses, which reproduce by inserting their own genes into other cells. By giving a virus a therapeutic gene to insert, the "viral vector" can thus be used to introduce beneficial genes into the patient's cells.



Genes can be delivered *in vivo* (in the body) by introducing the viral vector directly into the body and using the properties of the virus to target certain cells...



...or *ex vivo* (outside the body) by introducing the viral vector to cells taken from the patient and then reintroducing the cells once their genes have been modified, in a process similar to a blood transfusion.



As the genetically modified cells mature and multiply, they produce a new protein to correct a particular disease, or stop producing a protein which has been causing a disease.



Gene therapy is an emerging technology, but it may be developed to treat inherited disorders, cancers and many other diseases.

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Delivering the next generation of UK medicine

John Bell, Regius Professor of Medicine at the University of Oxford and author of the Life Sciences Industrial Strategy, outlines the need to embrace advanced gene therapies



One of the main aims of the Life Sciences Industrial Strategy was to think about how we can make the United Kingdom an attractive place for innovative companies in this sector to build new things. We thought about where this field was going over the next ten to 20 years, and the things we can do to make the UK good for companies to grow into that space, where there will be large global markets, but also a need for local capabilities too.

The UK has missed the chance to be at the forefront of delivering advanced therapies before. It was the UK, for the most part, that invented monoclonal antibody drugs – the last major platform shift in clinical therapies. All the fundamental work was done here, in Cambridge, and in a number of small startup companies. But the NHS was slow to adopt the new therapies, and because big pharmaceutical companies had no real affinity to biological research at the time, it was left for other countries to develop the commercial opportunities. As a result the UK, where it was all invented, was last to arrive at the party. That's not sensible for economic growth, and it's certainly not good for patients.

The Life Sciences Industrial Strategy was determined, then, to never miss another opportunity like that, and we identified cell and gene therapies as a new territory where there is real potential. Cell therapies of varying kinds, including stem cells, T-cells, and a range of cellular interventions, alongside viral gene therapy and nucleic acid-based therapies, are new therapeutic areas that

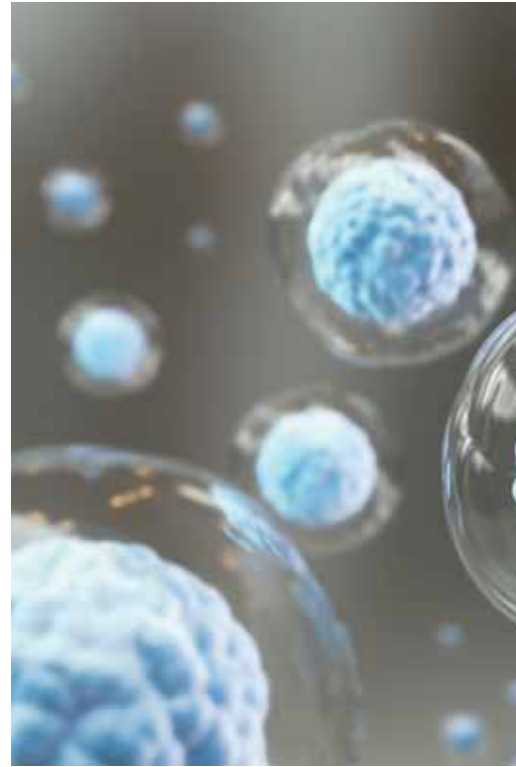
will change the face of medicine without a shadow of a doubt. The question is: how long will it take to get there?

To make the UK an attractive place to build and grow companies that would focus on these activities, we need four things. First, we need a strong science base, with a real focus on delivery – which is not always straightforward. We do already have some outstanding groups, particularly in gene therapy and the siRNA space, and the presence of the Cell and Gene Therapy Catapult gave us an opportunity to test and evaluate manufacturing capabilities. Secondly, we need to enable the NHS to cope with novel therapies. It's for this reason that we recommended the creation of Advanced Therapies Treatment Centres. It gave us a front door, as it were, into the NHS system to be able to start deploying these sorts of therapies. Thirdly, we need to develop the means to manufacture and deploy these technologies, and we've just opened the first accelerator that will develop delivery mechanisms and look at how we manufacture these things efficiently. Finally, something that we don't control in the Life Sciences Industrial Strategy, but with which we are very engaged, is trying to get the NHS to be a good adopter of these therapies. We recommended the creation of the Accelerated Access Collaboration, which is now in place, to pull innovation into the NHS – but issues such as pricing and commissioning remain.

These new technologies will need new pricing models, because for some conditions – haemophilia, for example – the condition could be cured, or something close to cured, but the treatment could be a lifelong therapy. How do you pay for a treatment like that? If you have to pay it all up front, that's going to be a problem. But I think NHS England has a real enthusiasm to explore this new ground, because it realises that there is a change coming, and we need to be nimble enough to overcome the challenges that will come with it.

bluebird bio's chief scientific officer answers the biggest questions on gene therapies in the UK

Q&A: Philip Gregory



Philip Gregory has served as the chief scientific officer at gene therapy company bluebird bio since June 2015. Philip holds a D. Phil in biochemistry from Keble College, University of Oxford and a BSc in microbiology from the University of Sheffield, and was a postdoctoral fellow at Ludwig-Maximilians-Universität München. He has held various research and leadership roles during his career.

What is gene therapy and can you explain how it works?

The goal of gene therapy is to address a disease at its genetic level. Many different approaches are being studied, such as turning off genes that are causing problems or replacing a defective gene by adding a functional version to help do the work of a defective gene.

bluebird bio is working on an approach to gene therapy that adds functional copies of a faulty gene to a patient's own blood stem cells – called gene addition. First, stem cells are taken from the patient's body. Then the functional copies

of the gene are delivered into the patient's blood stem cells outside of the patient's body, at our manufacturing site – a process known as “ex-vivo” as it takes place outside the patient's body, in a laboratory. This is gene therapy.

The gene therapy is then given to the patient via a stem cell (or bone marrow) transplant. In hospital, the patient first receives chemotherapy to make room in their bone marrow for the gene therapy. After the gene therapy has been infused, the patient's cells will need time to multiply and produce enough new stem cells with the functional gene. This process is called engraftment.

From their home in the bone marrow these gene-modified stem cells can give rise to all the different cell types found in the blood. The patient remains in the hospital until their immune system cells have recovered and their doctor determines that it is safe for the patient to be discharged. The corrected gene-modified cells restore the defective function of the patient's cells and hopefully will eliminate the signs and

symptoms of their underlying disease.

What attracted you to join a company like bluebird bio?

I have been working in cell and gene therapy for 20 years and was aware of bluebird bio well before the opportunity to join them came up. There are several things that make bluebird bio special. First is that we make use of different technologies to make the best therapies possible. We do not necessarily focus on just one technology such as gene addition and gene editing. Instead the emphasis is on making the best possible therapies for patients, regardless of the technology.

Next is bluebird bio's ability to translate innovative science from the bench into the clinic where patients can potentially benefit from it. These cutting-edge techniques are hugely complex to put into practice on a large scale, but bluebird bio is dedicated to making that happen.

Importantly, what made bluebird bio stand out to me was that underpinning the incredible drive and commitment to innovative science is the company's focus



on patients. This is led by the management team and it was this absolute dedication to patient-centricity that made me realise this was somewhere I really wanted to work.

What excites you about gene therapy?

I'm excited by the potential of gene therapy to both change the conventional symptomatic approach to disease treatment as well as provide options for diseases that cannot be treated in any other way. We are at an immensely exciting moment in time with CAR-T treatments and treatments for ADA-SCID (an inherited disorder that damages the immune system and causes severe combined immunodeficiency) and LCA (an inherited retinal disease) already approved. Many more are in the pipeline. Most importantly, we are on the cusp of gene therapy becoming more available to patients.

Healthcare providers may have the ability to treat a host of rare diseases which until now have had limited, if any, viable treatment options, and really change the lives of patients, their families and carers, for the better. In the UK, one in 17 people, or almost six per cent of the population, will be affected by a rare disease at some point in their lives – around 3.5 million people in the UK.

Gene therapy is fundamentally a different prospect for many patients. The goal is to address the underlying cause of disease through a one-time treatment.

What do you consider to be some of the challenges around the task of commercialising gene therapy?

Clearly the regulatory environment is a critical factor, but the FDA and EMA have both been incredibly supportive of gene therapies. The key has been their openness to talk with companies like bluebird bio – something that we have tried to do as often and as early as possible in the development process.

Another potential challenge is the inherent difficulty of manufacturing gene therapies and doing so at scale. This is

why we are investing in cutting-edge process which combines working with specialist hospitals and our manufacturing network, supported by a comprehensive training programme for clinical staff who are involved in the process of extracting the patients' cells at the beginning of the treatment and then administering the gene therapy at the final stage. There are also significant logistical and scheduling challenges in getting the therapy from A to B. We are learning a great deal from the established CAR-T treatments, but this is a complex supply chain and our goal is to ensure the process works as efficiently and effectively as possible.

How will UK patients gain access to gene therapy?

The long-term aspiration of gene therapy is that, ideally, after a single treatment, a patient will have reduced ongoing interventions. Given that the UK has a single-payer system, the NHS, the value of that single therapy can potentially be understood more easily because it is able to take a more holistic view of the benefit derived by the patient and the value this represents.

Payers are already showing willingness to discuss an instalment-based reimbursement model based on the treatment's value and we believe this is really important. For example, bluebird bio has publicly stated its willingness to put agreements in place that enable commissioners to pay over a maximum five-year horizon – not the rest of a patient's life even if we expect a lifetime of benefit for patients. These payments would be to specific outcomes which equate to clinical benefits to patients. This also means underwriting some of the uncertainty by sharing the financial risk.

This would mean that the NHS would only have to pay instalments for treatment that has been successful in which patients continue to achieve pre-agreed outcomes. This is an ongoing conversation and one we are actively participating in.



Cutting-edge technologies deserve upscale

SHUTTERSTOCK/ANUSORN NAKDEE

In an event in association with the Cell and Gene Therapy Catapult and sponsored by bluebird bio, the *New Statesman* brought together a group of experts to discuss the evolving challenges in access to gene therapy

Making gene therapy a reality



Thanks to incredible developments in medical science, treatments once considered theoretical could now become reality. But progress can be slow, and access to these potentially game-changing therapies depends on effective trials, as well as a responsive regulatory and access landscape. Earlier this year, the *New Statesman*, the Cell and Gene Therapy Catapult, and bluebird bio gathered a group of industry experts and policymakers to take part in a round table discussion, examining the pathways that new gene therapies and cellular interventions take from production through to adoption.

Sir John Bell, Regius Professor of Medicine at the University of Oxford and the author of the government’s Life Sciences Industrial Strategy, said in his opening address that the United

Kingdom should put “infrastructure” in place to ensure that “the National Health Service became a good adopter of new products”. He noted that the Life Sciences Industrial Strategy mentioned cell and gene therapies as an area of excitement. However, he also flagged that in the past the UK had “not made the most” of its leading role in the development of technologies, such as monoclonal antibodies. Therefore, Bell called for more to be done to realise the commercial opportunities attached to innovation in genetic and cellular medicine. He described the Accelerated Access Collaborative (AAC) initiative – additional government support specifically for “breakthrough technologies” – as a means of encouraging “rapid uptake” of innovative new products by the NHS. But the

incentive for uptake depended, he said, on whether the NHS could assess “value” in its decision to commission a certain therapy or treatment.

Innovation, the group heard, is often accompanied by scepticism. This isn’t to say, clarified Matthew Durdy, chief business officer of the Cell and Gene Therapy Catapult, a private sector research and innovation organisation specialising in the advanced therapeutic industry, that healthcare professionals and decision-makers are negatively pre-disposed. Yet, “qualifying and quantifying value” is a “crucial consideration” for the health service. Durdy said he appreciated that “the NHS only has so much money... so of course it has to be rigorous when it comes to what it invests in”.

But Durdy added that while “new



The UK can be a world leader in technology

THE PHOTO TEAM

technologies could be seen as a risk compared to pre-existing ones”, the life sciences industry needs to get better at articulating the potential “return” at an earlier stage. Durdy asked: “What is the value of 20 or 30 years of extra life? What does a patient stand to gain from a gene or cell treatment, if it is a cure for the condition they have? That could save the NHS millions in treatment costs over time.” According to Durdy, a lot of discussion about value is stalled by the inability of UK system to adapt to multi-year budgeting in health and social care.

Anne Marie Morris MP, chair of the all-party parliamentary group on access to medicines and medical devices, called for “co-ordinated communication [about gene and cell therapies]” with UK business. Morris stated that political will drives political action and politicians

are often moved by their constituents. “Patient stories are powerful, but we have to think about this more broadly. What does that mean for the UK internationally?” She said that while “most members of the general public” would likely be enthusiastic about the UK being a “world leader in science and technology”, it is important to build further on that and argue the case for health economics. “If we can get better at communicating how gene therapies will affect everybody, not just rare and ultra-rare disease patients, then people may be more likely to be enthusiastic about more [taxpayers’] money being spent on new gene therapies and treatments,” Morris concluded.

Any chance at effective collaboration between academia, industry and politics, said Dr Jacqueline Barry, the chief clinical officer at the Cell and Gene Therapy Catapult, would be improved by the further development of Advanced Therapy Treatment Centres (ATTCs), joint government-funded ventures, bringing together industrial, NHS and academic partners to blend experience, expertise and insight. “These dedicated specialist centres are something really unique. This is very much an open collaboration with all parties working together to develop systems to accelerate patients’ access to advanced therapies through the establishment of best practices for manufacturing, supply and safe and effective delivery [of therapies]. The idea is to have an integrated supply chain and data capturing mechanisms which will ensure good patient follow up and data capture.” The power of data collection and collation, Barry said, should not be underestimated in informing better decisions around cell and gene therapy.

Nick Meade, director of policy at Genetic Alliance UK, a national charity working to improve the lives of patients and families affected by all types of genetic conditions, suggested that the “risk” associated with new drugs and technologies should be looked at differently. The current predilection for cautiousness, however well-

Delayed decisions can lead to deaths

↳ meaning, he said, was a risk in itself. “We’re taking so long to decide [on whether a new treatment should be reimbursed] that people are actually dying. That is unacceptable.” Meade lamented the “fragmentation” of commissioning processes, “not least because of devolution”. Meade referred to a compromise recommended by the Scottish Medicines Consortium and suggested that the best way to bring new gene therapies to market more quickly was to test them “within the NHS and monitor them closely”. This would, Meade said, provide “real-world evidence in real time... while patients would have the chance to access life-saving treatments” more quickly. Meade added: “The concept of releasing medicines into the NHS may seem a risky thing to do, and you’d worry about being a hostage to fortune. But we can come up with frameworks, collaboratively, between industry and patients and the NHS.” Meade said that patients should be consulted, and could play an active role in rolling out new treatments.

The theme of uncertainty was further pursued by Marc Turner and Mark Briggs, from the Midlands and Wales Advanced Therapy Treatment Centre, and Scottish National Blood Transfusion service respectively. Turner highlighted small patient populations and time limitations in clinical trials which mean that any long-term benefits of gene therapies are uncertain. Briggs said that uncertainty in cost-benefit assessment is difficult for current HTA methodologies to deal with and collection of real-world evidence is challenging. “It is easier to offer a discount”, Briggs said. Norman Lamb MP, chair of the Science and Technology Select Committee, asked whether there were any other countries that the UK could learn from in this respect. Sir John Bell, in turn, signalled that some gene therapies may not work, and life-long effects are uncertain, therefore “we have to share the risk”.

Meindert Boysen, the director of NICE’s Centre for Health Technology Evaluation, referring to a report on ATMPs (advanced therapy medicinal



products) which focused on CAR-Ts, said that the current methodologies are relevant for assessment of ATMPs. He highlighted, however, the attitude to risk as a key element where NICE takes into account the guidance from NHSE. Blake Dark, the commercial medicines director at NHS England, responded that the recently negotiated Voluntary Pricing and Access Scheme addresses this by allowing the use of commercial flexibility for outcomes-based schemes. According to Dark, outcomes measures in such schemes need to be objective and “obvious”, and also need to be part of care and not to be added on to existing services. Barry added that the development of such outcome measures can be facilitated by ATTCs. Boysen went on to explain that decisions on which medicine and therapies to reimburse should also consider their proportionate impact on the wider NHS.



“You’ve got to take societal benefits into account”

THEPHOTO TEAM

While he agreed that game-changing gene therapy could benefit patients suffering from rare conditions, Boysen warned that investment had to have some accord with rates of incidence. “You’ve got to take the societal benefits into account,” he explained. “It is risky if you start taking money from elsewhere.”

Dark said that while NHS England “truly supports any transformative therapies”, it was important to acknowledge affordability. “We know that cost-effectiveness comes with some caveats that can put huge strains on the overall health budget and create a cost displacement effect.” He also highlighted the importance of transactability: “I’m looking downstream at the service provision... One of the CAR-T services in a hospital required the training or re-training of some 300 staff, so you’ve got to take those things into account.” Dark also highlighted that “pricing needs to be

fair” when it comes to industry pitching products to the NHS. “We do have some ATMPs already in effect and they are being funded.” Dark stressed that if industry was keen to see swift rollout, then companies had to be “responsible” when modelling their prices.

Nicola Redfern, general manager UK at bluebird bio, spoke about the fact that industry very much wanted to partner and work with the NHS and NICE to achieve access for patients, and this was supported by Dr Jacqueline Barry from the Cell and Gene Therapy Catapult. One solution to the access challenges offered by Redfern was to have flexibility in the assessment of gene therapies through STA, to go above the QALY thresholds, where large quality of life gains over time would be possible, as what happens in HST currently.

Ultimately, the round table concluded, for the swifter but no less safe rollout of gene therapies, all stakeholders had to work together. Decision-makers and influencers would need to address the underlying issues of uncertainty in cost-benefit assessment, and develop innovative risk sharing schemes based on clear patient outcomes measures, such as payment for results over time as suggested by Matthew Durdy, or modifiers for severity or rarity, as suggested by Nicola Redfern. Durdy’s vision would see a universal, global and future-proof scheme of patient access to cell and gene therapies. This scheme needs to be feasible and add value, for example by recognising the value of therapies outside the healthcare system, such as industrial value. Durdy stated that failure to develop such schemes would mean that UK patients will be secondary patients on a global scale.

The UK, it was agreed, has the potential to be a leader in gene therapy and export its expertise internationally. It was clear at Portcullis House that the appetite to innovate in gene therapies in the UK is there.

A New Statesman round table event in collaboration with the Cell and Gene Therapy Catapult and sponsored by bluebird bio.

Access is the foundation for a functioning system

The speed and accuracy of medical decision-making is a matter of life and death, writes Nick Meade, director of policy at Genetic Alliance UK



There is a clear link between the availability of effective orphan medicines and outcomes for patients affected by rare conditions. The benefits of effective rare disease treatments are often significant; progressive conditions may be stopped or slowed, and patients may walk and/or see for longer. Orphan medicines can be life-saving and transformative; patients not only live longer but the quality of life they experience may be significantly enhanced.

Failure to provide timely and comprehensive equity of access to medicines in the United Kingdom is a long-standing issue. As increasing numbers of orphan medicinal products have reached the European market we have seen the greatest disparities in access affect rare disease patients. The problem of access is not one that can be laid at the door of any single UK agency; it is systemic. In 2017, the Office of Health Economics published evidence showing that England, Scotland and Wales are behind Germany, France, Italy and Spain both in how many treatments for rare conditions are approved and in how long these decisions take. We are seeing delays within processes, often obscured by poor transparency in NHS England. NICE's processes seem at their slowest when addressing treatments for rare conditions. Where access to an innovative treatment reaches crisis point, it is often dealt with by Parliament rather than by arm's-length bodies of the Department of Health and Social Care.

Without a predictable, consistently high level of access to rare disease

treatments in the UK, the cycle of innovation in the life sciences industry is under threat. Often presented as a matter for the Exchequer, this is an area of health policy which is just as important to patients. When the cycle is healthy, patients, as well as the UK economy, benefit.

Clinical trials are a crucial route to early access for treatments for rare conditions in the UK. With the access environment as it is, this is a route to access a treatment that can deliver three or four years earlier than the "full" commissioned access through the NHS will be available. For a treatment that arrests the progress of a progressive condition, four years can be the difference between life and death. This time period can also be the difference between being able to use the medicine at all, as some market authorisations and some commissioning arrangements specify that the treatment must be delivered in a condition's early stages.

The UK's withdrawal from the European Union is likely to make multinational clinical trials including the UK more challenging to administer. The access environment also affects a sponsor's decision to bring a trial here. If the UK gains a reputation for withholding funding for innovative treatments for rare conditions, companies – who must foot the bill for continuing care after research use – are less likely to want to run trials here. There is also the challenge of running a clinical trial in a sub-optimal care environment. Furthermore, if the latest treatments are not available in the UK, it is more expensive to use them as a comparator in trials for the next generation of patients.

As with any systemic problem, if we are to offer an effective solution it must be system-wide. Genetic Alliance UK has been working with its members and with other key influencers on finding a single approach that improves access to rare disease medicines. We will be delivering our patient-led vision for the future of access to rare disease medicines later in the year.

Gene therapies – where are we now?

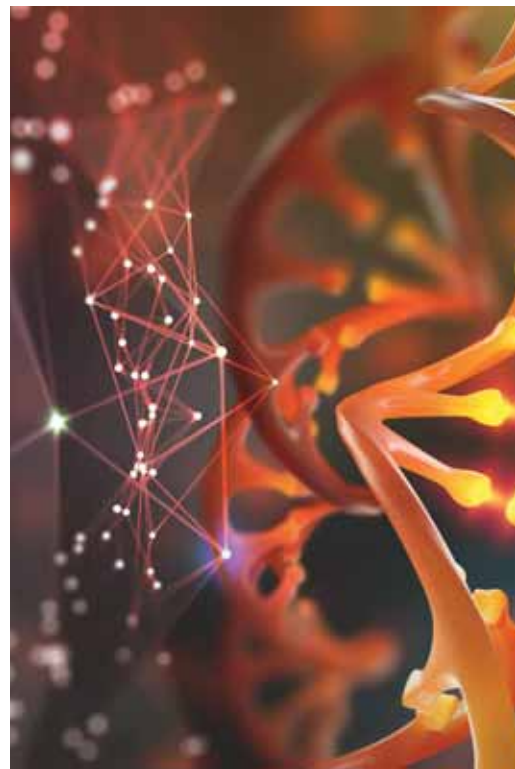
As the rate of clinical trials increases, more products are likely to be licensed in an expanding number of therapy areas



Source: Cell and Gene Therapy Catapult databases 2018

Committing to game-changing treatments can cut costs, create jobs and improve quality of life, writes Matthew Durdy, chief business officer at the Cell and Gene Therapy Catapult

Investment that can save lives



For a parent who has been told that there are no further treatment options and their child is going to die, and then seen that young girl thriving and cancer-free seven years later, the value of the new era of cell and gene therapies is clear.

According to the Alliance for Regenerative Medicine there are nearly 900 companies worldwide conducting over 1,000 clinical trials, two thirds of which are late-stage clinical trials. In 2018, the global industry attracted \$13bn of investment and saw \$19bn worth of mergers and acquisitions. This investment comes with the expectation that the healthcare system will pay a fair price for these life-changing medicines. Many of the first generation of successful advanced therapeutics share a common set of characteristics; they have high efficacy, they are expected to have a long duration of effect resulting from a short period of treatment and they are expensive to manufacture and provide. With healthcare systems increasingly making payment decisions

based upon the value delivered by an intervention, these new drugs can justify a very high price, if they deliver on their promise.

The question of a willingness to pay breaks down into a sub-set. Firstly, should we pay a higher price today to get access to drugs which might become cheaper or better in the future? Secondly, can even the reduced price that they might reach in the future be justified? Thirdly, because we are being asked to pay up front today for many years of healthcare benefit in the future, how do we afford the total cost and what happens if they don't work as expected? There is another, perhaps less valid, but no less real, issue that comes in the same discussion: that we have a government and healthcare system built on the close short-term link between payment for drugs and their benefits.

In order to accommodate paying for long-term benefit over the longer term we would need to make some high-cost and complex changes to the healthcare operating model. As an illustration of this, consider a hypothetical one-off

treatment for haemophilia. Current healthcare costs are in the region of \$150k per annum per patient which would add up to \$6m over 40 years of treatment. A therapeutic which cost half of that \$6m but removed the annual costs could still leave substantial savings for the healthcare provider in the long term. The key issues are: how you would pay the up front costs for the 6,000 patients in the UK (\$18bn), and how do you manage the systems so that you are paying for benefits that are actually received?

At the Cell and Gene Therapy Catapult we are concerned with prompting and facilitating the industry (which includes the NHS) in bringing about this change. The details and blueprint are yet to be determined but from our work to date we can see some clear considerations for how the change should be approached and how its success should be measured.

Clarity of intent

In the centre of the discussion are patients, healthcare providers and



manufacturers. The most basic solution, which will only work with a small number of therapeutics, is an agreed price which reflects good value today compared to today's other healthcare priorities. This would not stimulate new investment, bring on the economies of scale or scope that could lead to lower prices in the future. At the other end of the spectrum we have the interest of society as a whole in the generation of an industry which creates jobs and wealth. We need to be very clear about what we are trying to achieve.

Universal solution

The aspiration should be to engineer a change in the system which is applicable to all novel medicines and advanced therapeutics. It should not be something that just works for cancer such as the Cancer Drugs Fund (CDF) or in rare diseases because, by virtue of being rare, the cost can be easily absorbed.

Future-proofing

If we are to re-engineer the relationship between innovators and payers, let's do it in a way that accommodates future innovation. Advanced therapeutics have their own challenges and we understand them. Patient-specific medicines and the genomic data revolution will bring a whole new set of challenges that we should try to anticipate.

Value addition

Any changes should not be a zero-sum-gain. Simply moving risk from one party to another party, which is more willing to take it, can create economic value. But our aspiration should not stop there. There is value in the NHS that can be released by using it to foster innovation. There is value to society in the jobs and productivity that arise from a growing industry.

Workability

Any solution that looks good on paper but ignores behaviours and borders will not be effective. If there is not self-interest in the solution stakeholders will not engage. Nor should anyone be given tasks and expectations that are beyond their mandate. It is not the role

of the NHS to stimulate economic growth. Economic growth and particularly growth in productivity is important and other key stakeholders (BEIS, HMRC) need to have their role recognised and defined.

Globally facilitative

We shouldn't produce a solution that has no relevance to the rest of the world. It does not need to be a new global standard, but it does need to be understandable, and adoptable.

Step change

The tendency of the system and people to revert to what they are familiar with is a danger here. The change needs to be big enough to breakaway from the gravitational pull of today's bureaucracy. Fortunately, the benefits of these new therapeutics are strong enough to have a pull of their own towards a new way of operating.

As we embark on creating a new relationship between innovators, healthcare providers, payers and patients, continuously calibrating and testing our proposals against these criteria will increase our chances of sustainable success. As we progress we also need to bring people with us. Change of this nature requires political support and for politicians to respond to their constituents, and the voice and support of patients.

We should consider the cost of not redefining this relationship. Firstly, patients may not have access to the life changing medicines, making them second class citizens in global healthcare. Secondly, we fail, again, to harness the power of the NHS to foster and stimulate innovation and thirdly, we miss the opportunity to capitalise upon the world leading expertise of our own researchers, clinicians and companies and build a £10bn industry creating 18,000 new high-value jobs in the UK. The Cell and Gene Therapy Catapult is part of a strong ecosystem of advanced therapy stakeholders who are determined that the benefits of these life-changing medicines reach those who need them.



Genomic data is part of a revolution

bluebird bio asked industry experts, policymakers and influencers to add their insight to the gene therapy conversation

Vox pops: ask the experts



Adrian Thrasher,
professor of
paediatric
immunology
at the UCL GOS
Institute of
Child Health

We've been developing gene therapies for rare diseases for 20 years. Our particular area of interest is inherited immune deficiencies, and we've found that we can use gene therapies as wholly effective treatments for patients with these diseases.

The first patient we treated was in 2001. He had the "bubble boy disease", having been born without any immune system. He could have had a bone marrow transplant, but he didn't have a matched donor, and a mismatched transplant carries significant risks. So we treated him at Great Ormond Street. The treatment itself doesn't look particularly special. We take some bone marrow, in a fairly short procedure, and the bone marrow goes to the lab, and we change that bone marrow by putting the therapeutic gene into it, and then we infuse it back into

the patient, just like a blood transfusion. It takes about 15 minutes. But of course what's happening at a cellular level is much more advanced. It worked, and we still see that first patient today – he's a fit, healthy young man.

We never say "cured" for these patients, because a lot of them still need to receive antibodies, although that can be done on an outpatient basis. But we've had several iterations of these technologies since that first patient was treated, and now we're treating patients so that they don't actually need any further treatment.

At Great Ormond Street, we've now treated over 60 patients with these therapies. Worldwide, that figure is more like 200. There are gene therapies being licensed for other conditions, such as metabolic diseases and haemoglobin diseases, but they are all using the same technology. And while the immune deficiencies that we treat are very rare, the likes of thalassemia and sickle cell anaemia, are not so rare. There are thousands and thousands of patients born each year with those diseases.

So it will be, and almost is, part of mainstream medicine.



Anne Marie
Morris MP,
chair of the
all-party
parliamentary
group on
medicines and
medical devices

Advanced therapies are a revolution in medicine and offer cures for previously untreatable illnesses. They are the future of healthcare and it is right the Government has committed to making the UK a world leader in them. The UK already punches above its weight in the advanced therapy industry and this strength must continue to be nurtured. There is substantial opportunity for the UK to improve patient outcomes while driving future economic growth through developing therapies on a commercial scale. Growing this industry would also help to create large numbers of highly-skilled jobs at specialist centres across the UK.



**Dr Kath Mackay,
director – ageing
society, health
and nutrition at
Innovate UK**

Innovate UK has recognised that there

is the opportunity to drive forward economic growth by building upon gene therapies at commercial scale, and we have made key strategic investments into this field. One of these is the Cell and Gene Therapy Catapult which is an innovation centre tasked with driving the growth of the industry by helping organisations across the world translate early stage research into commercially viable therapies.

UK Research and Innovation – of which Innovate UK is a part – is delivering the Industrial Strategy Challenge Fund (ISCF) a component of government’s modern industrial strategy and a core pillar of its commitment to increase funding in research and development by £4.7bn over four years.

Current challenges include a £181m challenge to develop first-of-a-kind

technologies for the manufacture of medicines to accelerate patient access to new drugs and treatments and £210m to use data for precision medicine applications, including, with industry co-funding, the whole genome sequencing of UK Biobank.

Gene therapies are currently extremely expensive. This could create particular challenges of affordability for the healthcare system if they become widely adopted. The high prices charged for these therapies reflect the intrinsic complexity of manufacture and the fact that many target diseases are relatively rare. Since there’s no early way to reduce the regulatory costs of developing these therapies the emphasis has been on making the manufacturing process as efficient as possible.

Support for gene therapies has included: developing gene therapies for inherited degenerative sight loss and inherited metabolic conditions; supporting and enabling technologies that improve the efficiency of production; the Cell and Gene Therapy Manufacturing Centre in Stevenage – both phases I and II which support manufacturing process development for cell and gene; and the establishment of Advanced Therapy Treatment Centres – a consortia of product developers, clinicians and logistics companies.



**Meindert Boysen,
director of NICE’s
Centre for Health
Technology
Evaluation**

Since NICE started in 1999, we

have been able to produce positive recommendations for a whole variety of medicines. We started with medicines for influenza, we’ve looked at Herceptin and Imatinib, and we’re now looking at new treatments such as immuno-oncology. But while we are very able to cope with the technicalities that surround these difficult decisions, there is a wider question of the appetite that the NHS has to explore uncertainty, and to take risks. Cellular medicine and gene

therapy is one area in which we could do that, but it’s not the only one, and NICE has to be there for all patients, and by extension for their families, the people who care for them and the wider society.

These decisions are only made more difficult when they have to be made on the back foot, when drugs have been developed and prices have been decided. That’s why it’s important that we work with other organisations as early as possible in the development of advanced therapies. The Accelerated Access Collaborative is a step in the right direction for this approach, because it signals early on what we need to do.

NICE is committed to making the AAC a real success by working with partners on aligning horizon-scanning, and by engaging earlier with companies and each other, because we’re not just talking about the advanced therapies that are starting to be made available to patients, but those that are still in the future.

**Thomas Smith,
a patient living with
cystic fibrosis**

Advanced therapies promise to be as powerful as they are expensive and as someone who expects to be a beneficiary and lives in the real world, I cannot acknowledge the former without the latter. Whilst I am fortunate enough to have a work ethic that keeps my condition relatively stable, there will come a time when that is not enough. Thankfully, the commercial argument is not one that I’ll have to make myself but the philosophical argument is plain to see: the chance to be “cured” for a significant amount of time would transform my experience of the world.

As these treatments proliferate (the European Medicines Agency are doing what they can to streamline Advanced Therapy development) there is a chance to reduce human suffering at increasingly lower cost for those currently living with disease and those yet to be born.

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Getting gene therapies to patients

As the number of gene therapy clinical trials rises, more products could receive regulatory approval in an expanding number of therapy areas.

The proportion of gene-modified therapies in clinical trials increased from **47 per cent** in 2017 to **73 per cent** the following year. But patients in the UK still face a number of barriers to access NICE-approved therapies.

What's getting in the way?

At the point of regulatory approval, long-term outcomes can still be uncertain due to limited long-term follow up of patients in clinical studies

The potential lifelong benefit of a one-time treatment for a chronic condition can be hard to factor into health budgets, designed to fund treatments over the longer term

Some multidisciplinary teams and treatment centres require up-skilling

How can these barriers be overcome?

Develop innovative access schemes



Treatment could be paid for over time according to outcomes



Interim conditional reimbursement decisions would allow for real-world evidence generation to supplement the evidence base



Support for patient and product registries would allow for much-needed, real-world data collection

Modify how NICE assesses new gene therapies



An incremental cost-effectiveness ratio (ICER) is used to analyse value for money in healthcare



ICER thresholds could be modified to recognise the value of treatments for severe and rare conditions



Thresholds could move on a sliding scale, dependent upon the QALY gains delivered