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Advanced Therapies – Opportunities and Challenges

A EUROPEAN PERSPECTIVE TO ACCELERATE ADVANCED THERAPIES

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ADVANCED THERAPIES - OPPORTUNITIES AND CHALLENGES

A European Perspective To Accelerate Advanced Therapies

A report of the meeting held at the British Medical Association, London, 14 November 2017

Discussion and Conclusions

Advanced Therapies (Advanced Therapy Medicinal Products (ATMPs), also referred to as regenerative medicines) are at a tipping point, where the means are at hand to move on from being a cottage industry based on academic research programmes, to forming a mature, integrated and sustainable sector.

This is best illustrated by the US Food and Drug Administration's (FDA) recent approval of three Advanced Therapies: Novartis' Kymriah, Kite's Yescarta and Spark's Luxturna.

Underlining that Advanced Therapies are now ready for the big time, Gilead Sciences' $11.9 billion acquisition of Kite in August 2017 demonstrates that big pharma is ready to take these products seriously.

Of course, there have been Advanced Therapies approvals before, in the US, Japan and Europe. While these have represented scientific breakthroughs, commercial success has been limited so far and patient access restricted.

Now, however, governments in the US, Japan, Europe and elsewhere have implemented policies to foster development of the Advanced Therapies sector, providing incentives, regulations and the infrastructure it needs to grow.

Those involved in the sector recognise they must seize the opportunity that such advances present. Experience to date indicates that collaborations are needed, stretching from academia to clinicians, SMEs, regulators, payers, bioprocessing specialists and big pharma, to bring about the transition from handcrafted cell preparations to industrialised products.

The collaborative networks that have developed so far are also highlighting the areas where barriers remain, and where further research, finance or policy change is required. Notably, difficulties remain in designing trials and generating the evidence needed to convince regulators and payers, and also in developing processes that are robust and that would allow Advanced Therapies to be manufactured at an acceptable cost.

The conference assessed the state of play in the Advanced Therapies sector from the perspective of all stakeholders in Europe and particularly the UK, and discussed possible changes and ways to clear the route for the sector to reach maturity, and for Advanced Therapies to reach patients.

Recommendations

1. The higher valuations on offer and ease of access to capital have seen many European companies transfer advanced therapy commercialisation activities to the US. The first FDA approvals of gene therapies and moves by the FDA to smooth the regulatory pathway will likely increase this pressure. There therefore needs to be renewed effort to make available in Europe the patient, long-term capital that European companies need to get ATMPs to market, thereby enabling them to develop Advanced Therapies for European patients.

2. The relocation of the European Medicines Agency (EMA) from London to Amsterdam must be sensitively managed to ensure a smooth transition, to retain the Agency's highly specialised staff and to maintain the current workload of appraisals, approvals and pharmacovigilance activities.

3. EU-27/UK collaboration should be maintained in Advanced Therapies, as in all other areas of science, post-Brexit. Those involved in the sector should take the message to EU-27 governments and institutions that continued collaboration is in the interests of the sector, and, in consequence, of patients in Europe.

4. Advanced Therapies cannot be mapped onto existing pharmaceutical supply chains. In order for the sector to scale and grow in Europe, new infrastructure, including manufacturing facilities, supply chain management and specialist treatment centres, are required.

5. Europe should promote standardisation in Advanced Therapies. The field is now reaching the stage of maturity where it is possible to set international standards for starting materials, such as stem cell lines, and for components, such as viral vectors.

6. Partnering is key to advance ATMPs from academic labs to clinical development in SMEs, and in the formation of marketing and manufacturing partnerships with big pharma and bioprocessing specialists to bring products to patients as soon as possible.

7. Europe needs to develop its skills base to support ATMP manufacturing. Specialists should be trained in an ATMP environment and should have the ability to design more efficient processes, especially for patient-specific products.

8. While Europe has a centralised approval process, it remains necessary to take on national systems, each with different requirements, when it comes to reimbursement and market access. Health Technology Assessment (HTA) bodies need to be involved from the early stages of ATMP development to ensure clinical development programmes will generate the evidence HTAs require for cost-effectiveness assessments. In addition, HTA bodies should make greater efforts to harmonise their requirements.

9. There should be a push to build international consensus around safety and quality standards for induced pluripotent stem cells (iPSCs). Cell therapies derived from iPSCs will be cheap to

manufacture, but currently barriers exist, including genome stability, stability of the phenotypes and tumorigenicity, that should be addressed at an international level to give clarity to the industry.

10. A number of regulatory hurdles also exist, including quality control and quality assurance in manufacturing, how to control trials in rare diseases and how to decide endpoints. To deal with these, companies should be encouraged to engage with regulators early and often – and should remember that regulators cannot and do not put conditions in place that are impossible to meet.

11. ATMPs will raise new ethical issues. It is therefore essential that those working in the sector communicate with the public to ensure the public understand the benefits of Advanced Therapies.

12. Advanced Therapies have made significant progress over the past 20 years, but there remains a need for further fundamental research to increase understanding of their precise mechanisms of action and the routes of administration and for harmonisation of the regulatory requirements if products are to be developed for global markets.

Opening Keynote Session. The Future of Advanced Therapies

Regenerating the future, again

The concepts that form the basis for Advanced Therapy Medicinal Products are not new, but the means are now at hand to move from 'black box' approaches to precisely engineered products.

"We have got the tools to make biology a predictive science, and by understanding biology we can make therapies", said **Peter Goodfellow, Scientific Advisor at the venture capital firm Abingworth**, setting the scene.

The power of these tools is evident in products such as Uniqure's Glybera, Spark Therapeutics' Luxterna and Novartis' Kymriah. In the next three years, these will be joined by a slew of other Advanced Therapies. "Efficacy that will drive access and pricing", Goodfellow told the meeting.

His interest in developing tools for genetically modifying cells dates back more than 30 years. These manipulations are now "facile" and no longer a barrier to developing products to "replace, repair and regenerate", Goodfellow said.

1. Replace. Current replacement technologies are often non-biological; for example artificial joints and heart pacemakers. Now however, there is a marriage of artificial with biological, such as in Medtronic's wearable 'artificial pancreas'. This continuously monitors blood glucose levels and administers a variable dose of insulin 24 hours per day, based on the individual's needs, to minimise both high and low glucose levels.

"In the future, we will see further such miniaturisation, remotely controlled devices, applications of artificial intelligence and continual monitoring", said Goodfellow.

Replacement can also be entirely biological, beginning with the 100 million-plus blood transfusions that take place each year, or solid organ transplants.

The far greater need for transplants than the available supply of human donor organs has led to a search for alternatives. As long ago as 1995, Imutran, based in Cambridge, claimed it had genetically modified pigs to overcome the problem of hyper-acute rejection and was ready to conduct the first pig-to-human heart transplant.

However, not many months later, emerging evidence of the risk of transferring porcine retroviruses from transplanted pig hearts into the genome of human cells led the US Food and Drug Administration (FDA) to put clinical trials of porcine donor organs, tissues and cells on hold.

Fast-forward to August 2017 and scientists at Egenesis Bio announced they had used multiplexed CRISPR genome editing to remove endogenous retroviruses from pigs. “Getting rid of porcine retroviruses will lead to another push in xenotransplantation”, Goodfellow predicted. He also expects replacement technologies to reach a new level of sophistication in mixing biology with devices.

2. **Repair.** Throughout the life cycle, the body continually draws on stem cells to repair itself, but currently there is not enough understanding of these natural processes to be able to control and direct them. “If we understood the niche stem cells sat in, we would be in a better position to repair organs, such as the heart”, said Goodfellow.

One approach involves replacing all the essential genes in yeast cells with their human counterparts, providing a powerful screening tool.

Another approach is aiming to create a computer model of the origin of every cell in the human body, providing a route map back to the stem cell niche of each cell type. As an example of the potential power of this model, Goodfellow referenced the inherited muscle-wasting disease muscular dystrophy, in which patients “run out of the stem cells for producing muscle, but we don’t know what the stem cell is”, he said. “We think this model will help.”

A third approach aims to overcome the barriers to using induced pluripotent stem cells as the starting point for cell replacement therapies. The tools now exist for routinely reprogramming adult cells to stem cells and then differentiating them to the desired cell types, including neurons and cardiomyocytes. “But”, Goodfellow said, “we have not fully solved the problem of epigenetic imprinting, which means we don’t get to the exact cell type. It needs more thought”.

A second hurdle lies in a lack of understanding how and where cells should be administered. In the case of bone marrow transplants, the niche that needs to be available for transplanted cells is understood. In most other cases, “you introduce cells and nothing happens – the cells just disappear,” said Goodfellow. More work is needed to understand the niche requirements and find the correct locations for administration of cells.

3. **Regeneration.** Increased understanding of stem cell function will lead onto the ability to control the regeneration of organs, including the heart and the liver, predicts Goodfellow. “It’s a multifactorial problem of getting a series of stem cells to work together”, he said.

The generation of organoids – 3D miniaturised and simplified versions of organs with a realistic microanatomy – is paving the way to full organ regeneration. “I believe we will be able to replace all parts of the human body in 20–30 years”, Goodfellow told the meeting. “There will be missteps but we will get there.”

However, he warned, this will raise ethical issues; particularly, once it becomes possible to replace parts of the brain. The banning of first-generation genetically modified crop plants in Europe highlights the importance of ensuring the public understands the potential benefits of these kinds of technological advances.

The key factor in getting public acceptance and securing reimbursement lies in delivering products that offer a high therapeutic value. “Efficacy will probably trump everything”, Goodfellow concluded.

The political context

Lord James O’Shaughnessy, Parliamentary Under Secretary of State for Health, outlined the British government’s intention to maintain its relationship with the European Medicines Agency (EMA) after the UK leaves the EU in March 2019.

The discussions the government is having with the EU-27 to secure this objective are based on three principles:

- Patients in the EU-27/UK should not be disadvantaged in any way;
- The UK will fully maintain its current contribution to public health;
- Companies will continue to be able to market products across the EU-27/UK and the EU/UK will remain at the forefront of medical innovation.

“We start from a position of regulatory alignment and partnership”, Lord O’Shaughnessy said. That position will be protected – though on new terms – to avoid harm to patients and to protect public health.

It is recognised in negotiating new terms that health is in a different category from consumer products. These differences will be respected and the integrity of the pan-European health system will be protected, O’Shaughnessy said.

The UK’s withdrawal from the EU means that after more than 30 years, the EMA is to relocate from London. During its time in London, the Agency has been “highly effective”, not least because of the contribution of the UK Medicines and Healthcare products Agency (MHRA), which reviews 20 per cent of all new drug applications and conducts 33 per cent of pan-European pharmacovigilance activities.

The MHRA and the UK government will work to ensure a smooth transition for EMA when it leaves London for Amsterdam. “There are no benefits in tearing up existing arrangements”, Lord O’Shaughnessy said. “Continued collaboration is in the interests of public health and safety.”

Lord O'Shaughnessy also reiterated the UK government's position that it wants to remain in the EU's Horizon 2020 R&D programme, and to take part in its successor Framework Programme 9. It has committed to underwriting any Horizon 2020 projects that run beyond March 2019 when the UK leaves the EU, and Lord O'Shaughnessy said the UK will continue to be open to scientific talent and to welcome "the best and the brightest" scientists and their families.

In terms of ATMPs, Lord O'Shaughnessy said he "hoped to provide some reassurance" that the UK intends to remain at the forefront of their development. The sector in the UK has made notable progress, expanding from 24 to 64 companies and the number of clinical trials growing from 21 to 59, between 2013 and 2016.

This progress is underpinned by work undertaken by the Cell and Gene Therapy Catapult to support translation and commercialisation, and by the strategic roadmap drawn up by the Advanced Therapy Taskforce.

The potential exists to deliver huge leaps forward for significant patient benefit, and in some cases cures. "Advanced Therapies is one of the most exciting areas of medicine", said Lord O'Shaughnessy. The opportunities and challenges can best be tackled through continued and deepened collaboration.

To ensure that products can get to patients, the National Health Service (NHS) is in the process of setting up three Advanced Therapies Treatment Centres with the specialised skills and equipment required for the administration of ATMPs.

Advanced Therapies represent one of the most exciting areas in medicine, but they need continuing and deepened collaboration to achieve their potential. "We want to continue to collaborate", said Lord O'Shaughnessy, calling on the audience to relay this to EU-27 member state governments and institutions. "I ask you to take the message out that continued collaboration is in the interest of patients and is something we should strive for", he said.

Supporting research, development and manufacturing

Over the past ten years, the UK innovation agency Innovate UK (formerly the Technology Strategy Board) has provided a broad base of support for research, development and manufacturing in Advanced Therapies. Initiatives for which it is responsible include the Cell and Gene Therapy Catapult, the Small Business Research Initiative and the Biomedical Catalyst Fund, as **Ian Campbell, Director for Health and Life Sciences at Innovate UK**, described.

In addition, Innovate UK works with government departments across the UK to promote business-led innovation.

The Regenerative Medicines Programme, set up in 2009 to grow the sector, has to date received £75 million of public funding, leveraging in a further £36 million from industry. “In total, 147 R&D projects have been funded”, Campbell said. “In the last five years, progress has accelerated and there is a need for later stage investment.”

In 2012, Innovate UK established the Cell and Gene Therapy Catapult to support companies to get products into the clinic, to de-risk projects, to develop the skills base and to work on creating the right environment for the adoption of Advanced Therapies.

This included the construction of a £55 million Advanced Therapies manufacturing facility in Stevenage, where companies will be able to move products out of academic labs, optimise bioprocesses and conduct manufacturing for pivotal trials and the early stages of commercialisation.

Currently, three specialised NHS treatment centres are being set up to ensure Advanced Therapies “will get to patients”, Campbell said.

Innovate UK grants and other forms of support have been instrumental in helping Advanced Therapies companies to develop and commercialise products. For example, Cell Medica has grown from just four employees to 70 and raised £110 million in two funding rounds since 2009; while Oxford BioMedica received support for its lentivector manufacturing facility from where it will supply vectors for Novartis’ Kymriah – the first CAR-T therapy to be approved by the FDA; and ReNeuron received backing to scale-up manufacturing for its neuronal cell therapy for treating the after-effects of a stroke, at its new manufacturing facility in Wales.

In addition, Innovate UK has also promoted development of the supporting services needed for Advanced Therapies. One case in point is its support for TrakCel, a company that provides a comprehensive ATMP supply chain management system, providing visibility for cell therapy products from the initial collection of material to delivery to the patient. “We recognise the benefits of partnership to help companies scale and grow”, Campbell said.

Advanced Therapies – regulatory challenges

Since 2009 when the regulatory framework was put in place, ATMPs have gained increasing momentum in Europe. More than 135 products have now been granted ATMP status, and 18 marketing authorisation applications have been submitted, which have resulted in nine approved ATMPs, with four applications withdrawn and four still under review.

However, noted **Christian K Schneider, Director of the UK's National Institute for Biological Standards and Control (NIBSC)**, there have been setbacks, with the licences for Glybera and ChondroCelect withdrawn at the request of their owners due to their lack of commercial success.

It is important to recognise the complexity of ATMPs and the issues this poses for regulators, Schneider said. One example is the complexity of NF-kB signalling (Nuclear Factor-kappa-beta, a transcription factor that influences a broad range of biological processes) within the T-cell receptor-signalling pathway.

Another example is in gene therapies, where regulators must distinguish the safety and efficacy of gene vectors from the clinical effects of the gene that is expressed, address the challenges of how to administer the gene therapies to achieve the desired distribution, how to control clinical trials and blind trials and how to measure the clinical outcome.

"As regulators, we have to learn how to deal with this complexity without overcomplicating things", Schneider said.

As the first EMA-approved gene therapy, Glybera exemplified such challenges. The product was for lipoprotein lipase deficiency, an ultra-rare disease with a fluctuating clinical course, in which, apart from dealing with episodes of acute pancreatitis, the only existing treatment is to maintain a fat-free diet.

The small number of patients and the nature of the disorder make it impossible to conduct a randomised controlled trial. Although the EMA has previously approved treatments for ultra-rare conditions, in those cases there was either a continuous course of deterioration or a very active disease course, making it easier to measure the benefits of the drugs. This is not the case in lipoprotein lipase deficiency, where pancreatitis is intermittent and patients are otherwise healthy, Schneider noted. "It is important to work together to find measures of efficacy", he said.

A further complication for regulators arises where advances in technology are leading to the development of constructs that do not fit neatly into the ATMP classification, which covers products based on genes, cells or tissues. These include the use of bacteria, bacteriophages and exosomes as the vehicles for delivering therapeutic genes.

In addition, there are borderline cases, such as bedside preparations containing autologous stem cells, where it is not always clear whether products should be classified and regulated as ATMPs or under the EU Tissues and Cells Directive. Further complicating matters is the Hospital Exemption, under which ATMPs that are not centrally approved can be custom-made for an individual patient.

ATMP developers – which in the main are small companies – must draw on top-level science to develop complex products. The EMA Committee for Advanced Therapies (CAT) was set up to

provide advice on how to do this, from initial discussions, to classification as an ATMP, to certification and scientific advice, to bridging from preclinical development and to submission of a marketing authorisation application.

Taken overall, “ATMPs are special”, Schneider said. As a consequence, their development and commercialisation may be difficult. This raises the question of whether their regulation should start from the nature of the products, rather than trying to shoehorn ATMPs into the existing regulatory framework. “It’s probably both”, Schneider said. Regulators have to adapt to the specificity of the products, but developers also have to adapt to the medicines regulatory framework.

In October, the EMA and the European Commission published an update of the joint ATMP Action Plan, in which they promise to “streamline procedures” and “better address” the specific requirements of ATMP developers. The plan includes 19 actions, which EMA said will improve the regulatory environment for ATMPs.

Schneider suggested that the field is now reaching the stage of maturity where it will be possible to set international standards for component parts.

For example, in February 2017, the UK Stem Cell Bank at NIBSC released what it called its first “regulatory ready” stem cell lines suitable for development into novel cell-based medicines. The stem cell lines are produced and quality controlled under European regulations and are therefore suitable for use as starting materials in manufacturing therapies for clinical trials, thus saving researchers time and effort. Each cell line will be supplied with a certificate of analysis and a starting materials dossier.

Similarly, there are moves to establish World Health Organisation standards for gene therapy vectors.

Amongst other measures, the UK’s Advanced Therapies Manufacturing Action Plan, published in November 2016, sets out a recommendation that the MHRA, NIBSC and the British Pharmacopoeia should lead a series of stakeholder engagement meetings with industry, SMEs and academic innovators to identify current gaps in Advanced Therapies standardisation and to address different aspects of cell, gene and viral vector materials, as well as their manufacturing.

“My vision is to deliver standards for ATMPs”, Schneider said. “I’m looking forward to taking the plan forward.”

Session 2. Building Effective R&D Partnerships to Accelerate ATMPs

The view from pharma

Partnership is at the heart of Takeda's mission of becoming an industry leader in Advanced Therapies, delivering highly effect regenerative medicines to patients with life-threatening diseases.

"No one can do this alone", said **Seigo Izumo, Senior Vice President for Regenerative Medicine at Takeda Pharmaceuticals**. Takeda is strong in small molecules, but it does not have all the required expertise in cell and gene therapies.

To build collective know-how, Takeda has formed a number of collaborations with SMEs in the field, focussing on marrying external expertise with its existing areas of therapeutic specialisation. It has agreements with TiGenix in gastroenterology, K Pharma in central nervous system diseases and GammaDelta Therapeutics and Noile-Immune Biotech in oncology.

In addition, Takeda has established two large-scale academic collaborations: the Takeda–Sanford Innovation Alliance and T-CiRA, a ten-year collaboration with Kyoto University, led by Nobel Prize winner Shinya Yamanaka.

Under the $10 million, five-year Takeda–Sanford Alliance, scientists at member institutions of the Sanford Alliance for Regenerative Medicine can get funding for basic and translational projects in stem cells related to Takeda's areas of therapeutic focus. The institutes involved are:

- La Jolla Institute for Allergy and Immunology
- The Salk Institute for Biological Studies
- The Sanford Burnham Prebys Medical Discovery Institute
- The Scripps Research Institute
- The University of California San Diego.

In 2015, Takeda made its first move into regenerative medicine when it formed a $200 million collaboration with the Center for iPS Cell Research and Application (CiRA) at Kyoto University.

As Izumo noted, the T-CiRA agreement is "unusual" in running for ten years. "This means you can get people to do high risk projects," he said. Over 100 researchers from CiRA and Takeda are involved in the project at Takeda's Health Innovation Park in Shonan near Tokyo, and Izumo said Kyoto University considers the Shonan unit to be a branch of CiRA. The brief is both to develop cell and gene therapies and to generate induced pluripotent stem cell-based disease models for use in preclinical toxicology and drug discovery.

Professor Yamanaka has the final say on what research is conducted, and intellectual property is 50:50 co-owned, with Takeda having preferential rights to licence technology arising from T-CiRA's work.

At present, T-CiRA is advancing regenerative medicine products, including iPSC-derived islet cells for treating type I diabetes, cardiomyocytes for heart failure and T-cell therapies for cancer.

In drug discovery, iPSCs derived from patients exhibit the disease phenotype when they are differentiated into specific cell types. T-CiRA is using iPSC-derived models of:

- Neurons derived from adult cells of patients with amyotrophic lateral sclerosis to find ways of promoting recovery of motor function and suppressing neuronal degeneration;
- Hepatocyte models for preclinical liver toxicity testing and drug screening;
- Skeletal muscle models of muscular dystrophy for drug discovery and as the basis of potential therapies.

Spurred by the progress of T-CiRA, and the evident need for collaboration and partnership in regenerative medicines, Takeda is developing a Health Innovation Park in Shonan, transforming the facility from an in-house R&D centre to an "open innovation hub". The company has spun off start-ups into the hub and also attracted other biotech firms to make it their base, even providing business support and a fund for start-ups.

Izumo said the aim is that "in the next three to four years", multiple products originating in the T-CiRA collaboration will start clinical trials.

R&D partnerships – the perspective of an SME

As part of its strategic move into regenerative medicine, in July 2016, Takeda reached an agreement with TiGenix, whereby it acquired the rights to market TiGenix's Cx601, a treatment for anal fistulas caused by Crohn's disease, in Europe and Japan.

The product, now named Alofisel (darvadstrocel), is poised to become the first allogeneic cell therapy to be approved by the EMA, with the Committee for Human Medicinal Products due to give its opinion on the marketing authorisation application in December. Allogeneic cell therapy has the great advantage of allowing pre-production, making it available off the shelf rather than being specifically produced for an individual patient on the basis of their own cells.

Alofisel, produced from adipose-derived stem cells, is undergoing a phase III study in the US for anal fistulas caused by Crohn's disease, and has also advanced to phase II as a treatment for severe sepsis. In parallel, TiGenix is developing an allogeneic cardiac stem product, Allo-CSC01, for acute myocardial infarction.

As **Eduardo Bravo, CEO of TiGenix**, described, based on its experience with ChondroCelect, the company is acutely aware of the need to convince payers of the value of Alofisel. “Small clinical trials and hints of efficacy are not enough”, Bravo said.

Despite having an Orphan Drug designation, TiGenix was able to recruit 204 patients to the phase III trial. Following consultation with the EMA, it was also possible to design a randomised and controlled trial, in which Alofisel was compared to the standard of care.

In the phase III trial, 56.3 per cent of Alofisel-treated patients achieved remission at 24 weeks, and the fistulas healed sooner, at a median of 6.7 weeks versus 14.6 weeks for the 34 per cent of patients in the control arm who responded to the standard of care and achieved remission ($p = 0.024$). Of the Alofisel-treated patients who responded by week 24, 75 per cent continued to be in remission one year after a single course of treatment, compared to 55.9 per cent of the control patients who responded at 24 weeks. “We have got pretty convincing evidence”, said Bravo.

TiGenix engaged with EMA on five occasions to seek advice on the design and conduct of the trial. These inputs had been “very helpful”, Bravo told the meeting. “My advice is to go quickly, go early, go as many times as you can.”

Pending European Commission approval, expected in February 2018, Takeda will take on commercialisation in Europe. “The deal with Takeda is great for us”, Bravo said. The €25 million upfront payment has provided working capital and there is a further €15 million due on approval, followed by 18 per cent royalties on sales. In addition, Takeda invested €10 million in TiGenix equity.

TiGenix retained the rights to the US market and to all future indications. “We kept the upside”, Bravo said. “And we got access to Takeda’s marketing expertise.”

SMEs are good vehicles to transfer academic programmes to the clinics, but as a small company with fewer than 100 staff, TiGenix “cannot do it all”, said Bravo. “We hope we can partner to accelerate other indications and make Cx601 a very successful product.”

The role of academia in building effective R&D partnerships to accelerate ATMPs

Publicly funded academic research forms the bedrock of ATMPs, but beyond initial discovery and translation, there is now a need to bring together biology and manufacturing to develop production processes and to expedite therapies to patients.

The Department of Biochemical Engineering (DBE) at University College London (UCL), set up to develop bioprocessing methods and build the skills base for monoclonal antibodies, is now aiming to do the same for ATMPs, as **Qasim Rafiq, Senior Lecturer (Associate Professor) at DBE**, described.

The global reach of DBE's industrial collaborations enables it to ensure its academic research is aligned to clinical and commercial requirements. To date, DBE has collaborated in process design with more than 100 companies. In regard to ATMPs, it has formed two centres of excellence – with GlaxoSmithKline and MedImmune, respectively – for the development of specific processes for each company. "We want to establish more partnerships around [ATMPs]", Rafiq said.

As one example of how DBE has contributed to process design, Rafiq described a £250,000 Innovate UK-funded project carried out with the equipment supplier Sartorius AG. The project identified a need for models and tools that would enable ATMP processes to be tested at a small scale. That led onto the development of a 'micro carrier' vessel, which Sartorius has now commercialised.

Rafiq has also contributed to the Autostem Consortium, a €6 million, three-year Horizon 2020 project aiming to develop an automated production line for stem cells. The process starts with a bone marrow donation, which is processed in a closed system without the need for manual intervention, to produce cells for use in human therapies.

A related UK-funded project 'Future Targeted Manufacturing Healthcare Hub' led by DBE, is engaging with academics at five other universities and a user group of more than 50 companies and industry organisations to address manufacturing and regulatory challenges to ensure that patient-specific ATMPs can be delivered quickly and manufactured at a low cost.

DBE is also involved in a number of translational research projects, including the development of ultra-scaled down cell culture platforms, optimising the cell culture environment and the closed-loop point-of-care processing of cells.

"The focus is on the cost of goods; [ATMPs] can't just be science- or clinically-driven. They have to deliver a profit", Rafiq said.

R&D partnerships to fill the ATMP gaps

The Cell and Gene Therapy Catapult (CGTC) was set up in 2012 by the UK government to promote the growing ATMP sector by filling the gaps between academia and industry, to deliver therapies to patients and to help drive economic growth. It is not a grant-funding body, but rather exists to provide capabilities, tools and assets that can help companies developing ATMPs to overcome the

barriers to scaling, process development, meeting regulatory requirements, conducting clinical trials and commercialisation.

The CGTC, based at Guy's and St Thomas' NHS Foundation Trust in London, is completely focussed on industrialising processes and "moving cell and gene therapy on from the handicraft stage it was in", said **Keith Thompson, CEO of the UK Cell and Gene Therapy Catapult**. "We are ecstatic with the progress, it has gone really well."

The purpose-built process optimisation centre at Guy's Hospital is complemented by a large-scale manufacturing facility in Stevenage, which is about to come on stream. The facility has 12 separate modules, where products can be manufactured at scale for pivotal trials and for the early stages of commercialisation.

"We have been able to build assets in people, buildings and equipment", Thompson said. In turn, these skills and resources have made CGTC a nexus for partnerships.

By providing the means to validate products, CGTC is unlocking private funding for ATMPs. "Venture capitalists don't want to spend £25 million on manufacturing development. We've taken that off the table", said Thompson. "It's not just the reduction in capital risk – long-term success depends on the ability to manufacture."

To date, CGTC has carried out or committed to projects worth £107 million with partners from across the UK, Europe, Asia and North America, working with them to accelerate nascent technologies into investible products. Typical projects include manufacturing automation and upscaling, developing potency assays and equipment design.

Hand-in-hand with this technical work, CGTC is helping to shape the environment; for example, by addressing regulatory bottlenecks and paving the way for patients to get access to ATMPs in the NHS.

The success of CGTC is reflected in the growth of the sector in the UK, Thompson said. While there were 22 ATMP companies in the UK in 2012, there are now 64; employment has risen from 540 to more than 1,000 jobs and the number of GMP manufacturing facilities has gone from 21 to 59.

"It's all illustrative of the differences you can make in a sector by doing the right things", Thompson concluded.

Session Three. ATMPs as Cures: The Opportunities and Challenges for Europe

Pioneering gene therapies for central nervous system disorders

Nine years on from its formation in 2009, Lysogene is poised to start a pivotal phase II/III trial of its lead product LYS-SAF302 in the treatment of Sanfilippo A (also known as mucopolysaccharidosis III), a rare, inherited lysosomal storage disorder.

The cause of the disorder is the loss of the gene encoding N-sulphoglucosamine sulphohydrolase (SGSH), leading to an absence of an enzyme involved in metabolising heparan sulphate.

The disorder causes severe neurodegeneration. There is no treatment and fewer than 15 per cent of affected children survive beyond adolescence.

Although the missing enzyme can be manufactured and administered intravenously, it cannot pass the blood brain barrier to address the neurological symptoms. “We aim to overcome that hurdle by injecting [LYS-SAF302] directly into the brain, so that the missing enzyme is sustainably produced where it is most needed”, said **Michaël Hocquemiller, Scientific Director of Lysogene**.

Lysogene previously completed a phase I/II safety study with a first-generation construct, LYS-SAF301, in which the product was injected into the white matter of the brain. That study demonstrated its safety, showed there were no neutralising antibodies to either the gene vector or the expressed protein and also allowed the company to explore potential future efficacy endpoints.

Hocquemiller described how, since the phase I/II study, Lysogene has been working to optimise the product. Amongst other modifications, LYS-SAF302 now has a different promoter, which has the effect of increasing the expression of SGSH. The company also moved manufacturing from an academic group in the US to a contract manufacturing organisation: Novasep in Belgium. In addition, it changed to an FDA-approved device for administering the drug, making it possible to inject a higher volume into the brain and get a better distribution of the product in the brain.

In mouse models that replicate the features of the disease, the improved construct increased enzyme activity in the brain and corrected the disorder, so that treated mice showed a normal phenotype. But the trial was only performed in mice, said Hocquemiller. “How do you move from mice to children?”

As a first stage, Lysogene conducted biodistribution studies in larger animals (that were not disease models), showing it was possible to get good coverage in the white matter of the brains of dogs.

Mapping these results onto the larger brain of a six-year-old child, Lysogene believes it will get good distribution in children with three injections of LYS-SAF302 per hemisphere.

The phase II/III trial in 20 children has approval from the FDA and EMA. However, it is not possible to have a control arm, and so Lysogene has undertaken an observational trial of patients who are not receiving any treatment, in order to define the endpoints. “There is no control arm; we will compare treated patients with the natural history of the disease to see if our treatment is effective”, Hocquemiller said.

The work Lysogene has done in Sanfilippo A can be read across to similar lysosomal storage disorders that also have a serious effect on the central nervous system. The company is preparing for a phase I/II study in GM1 gangliosidosis, which, said Hocquemiller, “has a huge CNS involvement”.

In collaboration with two US academic groups, Lysogene has shown that direct brain injections of LYS-GM101 in cats as a model of the disease arrests motor impairment. The cat is still alive and fit at five years post-treatment.

The choice of gene vector and route of administration are crucial, Hocquemiller said. “The choices need to be supported by an animal model of the targeted disease and by biodistribution studies in larger animals. Concerted efforts are required for gene therapy development. To accelerate research, you need to work with lots of partners.”

Overcoming the complex challenges associated with the development of *ex vivo* gene therapies for rare diseases

Orchard Therapeutics was spun out of University College London (UCL) in September 2015 to specialise in translating gene therapy studies carried out by academic groups into programmes that can get regulatory approval.

To date, the company has accumulated ten *ex vivo* gene therapy constructs generated in UCL, the University of California Los Angeles and Boston Children’s Hospital, all of which have leading expertise in *ex vivo* gene therapy, but were finding it challenging to navigate regulatory requirements to take products to later stage trials. “We want to be a leading global, fully integrated company, from discovery to commercialisation in rare diseases”, said **Adrien Lemoine, Vice President of Business Development & Operations at Orchard Therapeutics**. “We want to make a profound change in severe disease.”

Orchard raised a hefty £21 million in its first funding round, to which it added a $19 million grant from the California Institute for Regenerative Medicine. This is being applied to generate the files for the company to make its first application to the FDA and to regulators in Europe in 2018 to conduct a pivotal trial of OTL-101 in the treatment of ADA-SCID, an inherited immune system deficiency. Further back in the pipeline, Orchard has two other programmes in primary immune deficiencies that are being shaped for the clinic.

Orchard is also advancing a programme in Sanfilippo A, though unlike Lysogene, it is taking an *ex vivo* approach. Lemoine said reference studies have shown that it is possible to get modified cells into the brain, and consequently he expects this programme to enter clinical development next year. If successful, Orchard will pursue other lysosomal storage disorders that have a CNS component.

Although there is now an EMA-approved gene therapy for ADA-SCID – GlaxoSmithKline's Strimvelis – Orchard says it has developed second-generation vectors that are more efficient in inserting the functional genes in to patients' stem cells. In addition, the product is cryopreserved, meaning that, unlike Strimvelis, for which patients from around Europe must travel to the one centre that can prepare the product in Milan, it will be possible to ship the product and treat patients in local specialised hospitals.

Lemoine pointed to three challenges in transforming OTL-101 and other *ex vivo* autologous gene therapies into commercially available medicines. The first is the long and complicated patient journey from diagnosis to the removal of stem cells, to processing and transducing the stem cells, to re-administering them to the patient and then to initial follow-up. Cryopreservation is an important element in simplifying things, Lemoine said.

The second challenge is putting in place a commercial supply chain for manufacturing a personalised GMP-grade cell product that previously was prepared on site in a GLP-grade hospital lab. Once the bone marrow is harvested, it must be shipped to a central facility where haematopoietic stem cells are extracted. These stem cells are then transduced with a disease-specific lentiviral vector made by Oxford BioMedica, before being cryopreserved and shipped back to the bedside.

All of Orchard's products originate in academic labs. In order to commercialise them, it is necessary to transfer manufacturing to a commercial facility and to show that the products are equivalent, in order that the academic data can be read across to their commercial development.

A key factor is controlling the cost of goods. "It's good to be starting with ADA-SCID, because you only need small amounts", said Lemoine. "We are working with Oxford BioMedica on expanding production. The field needs to work together because it will benefit [us] all – we can go after bigger indications."

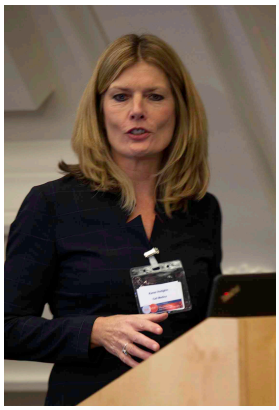
The third challenge will be to manage the long-term safety follow-up that regulators have to date required for gene therapies. As Lemoine noted, there has not been any evidence of oncogenesis with lentiviral vectors.

As of the end of June 2017, 48 patients have been treated with hospital-produced versions of OTL-101, of whom 37 were treated in an academic-led clinical study and 11 were treated under compassionate use. All are still alive and the safety profile continues to be favourable. “Patients are leading normal lives, with normal stem cell counts”, Lemoine said.

Based on the 100 per cent survival, the fact that 98 per cent of those treated have stopped receiving enzyme replacement therapy and that the safety profile of OTL-101 continues to be favourable, Lemoine believes post-approval obligations should be relaxed. “There is an accruing body of data; I hope there will be less-demanding follow-up requirements.”

Cell Medica: novel approaches for the treatment of solid tumours

Cell Medica was spun out of UCL in 2007 to commercialise a cell therapy for treating cytomegalovirus infections in immuno-compromised bone marrow transplant patients, and launched a 110-patient phase III trial in 2008. That was intended to demonstrate that it was possible to set up a commercially viable national cell therapy service, serving 11 specialist centres around the UK from a single lab in London.



The trial required Cell Medica to master the economics of scaling up the manufacturing of patient-specific therapies – expertise it is now applying to the development of both autologous- and allogeneic-engineered, chimeric antigen receptor expressing, natural killer T-cells (CAR-NKT) for treating solid tumours. The lead programme, CMD-501, for treating neuroblastoma, is due to enter phase I/II trials in the second quarter of 2018.

Cell Medica also has a second platform technology, based on targeting engineered T-cell receptors at solid tumours, which also originated at UCL.

As **Karen Hodgkin, Chief Operating Officer of Cell Medica**, noted, CAR-T therapies, led by Kymriah and Yescarta, are poised to transform the treatment of haematological cancers. The challenge now is to move on from this, “relatively easy, low-hanging fruit” to the “peaks of solid tumours”, she said. Haematological malignancies are easier to research and treat, as a specimen of malignant cells can more easily be obtained from the peripheral blood of patients than from samples of solid tumours. In addition, it is often more difficult to completely penetrate a solid tumour, which is not the case for haematological malignancies.

In an animal model of neuroblastoma, autologous CAR-NKTs were shown to home in on and penetrate tumours. Cell Medica also has autologous programmes in liver cancer and glioblastoma.

The lead allogeneic CAR-NKT, CMD-502, being developed with Baylor College of Medicine, Houston, Texas, is engineered so that it will not activate a patient's immune system. As with TiGenix's Alofisel, the technology opens the way for a mass-produced therapy that would be available off the shelf. "That would completely transform the logistics, etc., to get closer to the conventional industry model", Hodgkin said. Cell Medica expects to file an Investigational New Drug (IND) application for CMD-502 with the FDA by the end of 2018 and to start a phase I/II trial in 2019.

The lead programme from the engineered T-cell receptor platform, CMD-601, for treating ovarian and pancreatic cancer, is also due to start a clinical trial in 2019, with CMD-602 for multiple solid tumours following close behind.

Cell Medica has been working with the UK Cell and Gene Therapy Catapult to de-risk the T-cell receptor technology, and plans to carry out manufacturing at the Catapult's new manufacturing facility in Stevenage. In March 2017, the company raised £60 million in a third round of private funding, enabling it to fund the simultaneous development of four immuno-oncology products targeted at solid tumours.

Partnering well together

The presentations at the conference demonstrate that stakeholders are partnering well together to create a global ecosystem for ATMPs, said **James McBlane, Committee for Advanced Therapies (CAT), Alternate Member for the UK and Preclinical Assessor at MHRA**. "What we have heard today is a tremendous demonstration of the expertise that is available", he said.

However, McBlane said, this begs three questions:

- Why has not a single UK patient been treated with an ATMP on a commercial basis?
- Are the regulators being unreasonable in licensing decisions?
- What can be done to ensure Advanced Therapies get to patients?

Centralised approvals require ATMPs to pass the scrutiny of CAT and CHMP, thus demanding a more substantial evidence base than products used under the Hospital Exemption, or schemes such as the Specials scheme in the UK. However, the central approval of ATMPs adds significant value, allowing products to be sold, in principle, in all EU Member States.

To overcome the greater regulatory hurdles of getting EMA approval for an ATMP, companies need to engage with regulators, McBlane advised. However, he stressed, "Engage is not partnering: regulators are not your partners in development, but if you don't engage them, you will fail".

Companies should seek scientific advice through national and EMA channels, with sufficient preparation beforehand to be able to present data that enable regulators to agree a product is safe enough for the intended use, is efficacious and is made consistently to an acceptable standard.

The data should include proposals for demonstrating comparability following any post-marketing changes; the design of (or justification if not necessary) an *in vivo* tumorigenicity study; the design of a phase III trial that reflects the fact that it is difficult to conduct randomised, double-blind studies and that outlines what the primary and secondary endpoints will be. “Come and talk to us”, McBlane said. “It all comes down to engaging the regulators early.”

In answer to his own questions, McBlane suggested that UK patients are not yet getting treated with ATMPs because the early products were not particularly effective; the small number of patients and high cost of manufacture make it difficult to get a return on investment; and because of the challenges posed by the short shelf life of cell therapies.

As to whether regulators are being unreasonable, McBlane pointed to all the drugs CHMP has approved in the ten years since the advent of the ATMP regulations and that are available in the UK. “It is possible to get through that Committee and to get products used – so why not ATMPs?”, he said.

However, as the subsequent (see page 27) presentation by Deborah Morrison of the UK National Institute for Health and Care Excellence demonstrates, passing CHMP scrutiny does not open the door to market access; ATMPs then face the subsequent challenges of satisfying health technology assessment bodies, and of securing reimbursement.

Session 4. R&D Commercialisation 2020: Maximising the Value of European Innovation

The global cell and gene therapy market is forecast to be worth £9 billion–£14 billion by 2025 and to grow to £21 billion–£32 billion by 2030.

However, to reach these heights, it will be necessary to turn a cottage industry of academics and clinicians with lab-capacity constraints, into a robust, growing and sustainable sector, said **Magda Papadaki, Head of Product and Process Innovation at the Association of the British Pharmaceutical Industry (ABPI)**. "There is a lot of clinical promise – we need to put our heads together to see how to commercially manufacture them", she said.

Issues to be weighed in the mix include target product profiles, how to manufacture at a reasonable cost and where to manufacture products that have a short shelf life.

ATMP manufacturing is challenging for industry, both because the requirements are very different from small molecules and other biologicals, and because ATMP is a catch-all term for a wide range of different types of products with different manufacturing requirements.

The example of autologous CAR-T cells illustrates the process constraints. T-cells extracted from a patient must then be transported for processing to a manufacturing facility, going through a complicated chain of selection, activation, transduction and expansion – all of which require the oversight of an expert workforce – before being transported back to the clinic for administration back to the patient. "It's not a door-to-door linear supply chain, but vein-to-vein", Papadaki said.

These constraints are reflected in supply shortages. For example, it has been reported that Novartis is not yet able to meet all the demand for its Kymriah CAR-T cell treatment for acute lymphoblastic leukaemia, while the difficulties of transporting and processing autologous stem cells mean all the EU ADA-SCID patients eligible for treatment with GlaxoSmithKline's Strimvelis must travel to the San Raffaele Hospital in Milan, Papadaki noted.

The UK has taken a lead in ATMP science and process development and is now at a tipping point in terms of the resources available to industrialise these processes. In November 2016, the UK Advanced Therapies Manufacturing Task Force, co-chaired by the then Minister for Life Sciences, George Freeman, and Ian McCubbin, Senior Vice President at GlaxoSmithKline, set out six recommendations to make the UK a global hub for manufacturing these therapies.

Now, there needs to be a "cognitive shift" in approach to product development, manufacturing, clinical assessment, market access, adoption and in-market supply. "The process is the product", said Papadaki. "It is not a sequence of doors; it has got to be a continuous process."

A number of issues remain to be resolved in order to make the processes so robust that they are independent of the starting material from the patient and the type of ATMP. “The aim”, said Papadaki, “must be to predict demand and meet it cost-effectively. Early and continued engagement between scientists, manufacturers and regulators is needed to achieve this”.

While in future, ATMPs are likely to be developed for larger markets, for now, ATMP developers are addressing rare conditions and as a result, have to deal with uncertain prospects. The small patient cohorts mean it is not easy to get a return on investment, gathering sufficient evidence of efficacy to satisfy regulators and payers is hard and the promise of long-term efficacy raises affordability concerns under the existing payment/pricing structures.

Papadaki suggested the way to address these uncertainties is to take an integrated approach to clinical production, the conducting of trials and portfolio planning. Companies should be looking at the cost of goods from the start and should be aiming to take advantage of accelerated/adaptive assessment pathways and engage in reimbursement considerations/discussions early in development.

Rather than the traditional licensing, companies should adopt a life-cycle management approach. This would mean, for example, rather than focussing on getting a licence, patient access should be the objective; instead of randomised control trials, biomarkers, registries and surrogates should be the source of evidence; regulatory/reimbursement strategies should be based not on benefit/risk predictions but benefit/risk monitoring; and products should be designed for a targeted population and access should be controlled.

To promote access, the UK is setting up three Advanced Therapies Treatment Centres. These centres will establish best practice for safe and effective delivery and near-patient GMP manufacturing, be the focus of robust supply chains, implement traceability and tracking systems and devise best practice for patient follow-up.

“The aim”, said Papadaki, “is to make the UK the global destination not just for research, but [also] in the use and clinical adoption of ATMPs”.

After the audience had heard how five companies are dealing with the challenges of R&D and commercialisation, and what is being done on a national level in the UK, **Barbara Freischem, Executive Director of European Biopharmaceutical Enterprises (EBE)**, described the work that her organisation is doing at a European level to maximise the value of innovation in ATMPs.

EBE has a specific focus on SMEs and providing an expert voice for emerging bioscience, while being a specialised group of the European Federation of Pharmaceutical Industries and Associations, which represents mainly large pharma companies.

Europe is the world leader in the fundamental research and early clinical development of Advanced Therapies, and is home to some of the most innovative companies in the field. “But”, said

Freischem, “who reaps the benefits?”. European innovation frequently ends up in the US, either as a result of products or companies being acquired, or because companies need to establish bases in the US to access the deeper capital pools in venture capital or a listing on Nasdaq.

“We hope to change that a bit”, Freischem said. In collaboration with other stakeholders, including the European Investment Bank (EIB), the European Investment Fund, the European Commission and the European Parliament, EBE is working to improve the financial environment.

Meanwhile, on the regulatory front, EBE is collaborating with the EMA, the European Commission, the European Directorate for the Quality of Medicines and Healthcare, the European Parliament and other interested bodies to address the hurdles in clinical development and licensing.

During 2017, EBE provided feedback to EIB on its draft report *Financing the EU Life Sciences Sector*. “The aim is that companies in Europe find the money in Europe, to bring ATMPs to patients”, said Freischem. EIB’s conclusions are expected soon.

To generate political pressure, EBE supported the organisation of a workshop by the European Parliament’s Science and Technology Options Assessment (STOA) office called ‘Therapies of the Future’ to help make members of the European Parliament more aware of the potential – and the constraints – that are facing ATMPs. Other outreach activities included impressing on the European Commission, the European Parliament and the EMA the value of intellectual property and the need for incentives, especially for SMEs, most of which are formed around publicly funded academic research.

EBE has taken a lead in shaping and publishing industry and joint stakeholder position papers setting out the problems posed by the Hospital Exemption and asking the Commission to set boundaries around it. The concerns are related to patient safety and the ability to track and do long-term follow-up for the benefit of patients, not just on the impact the Hospital Exemption has on the commercial prospects of ATMPs. “In some countries, the Hospital Exemption is an alternative route to market, on a scale beyond individual use. So we need to be clear about the dos and don’ts”, Freischem said.

In October, the EMA and the Commission’s DG Santé published an Action Plan for ATMPs, which acknowledged Hospital Exemption as a concern and stating that they would initiate a reflection process to discuss the matter with Member States.

EBE also supported publication of a joint position paper relating to a second regulatory barrier, namely the environmental risk assessment of genetically modified organisms, which is required to be completed prior to clinical trials with ATMPs that are or that contain genetically modified organisms.

EBE and EFPIA jointly commissioned research on the factors hindering developers of ATMPs, with the results due to become available in December.

In addition to its advocacy work, EBE – as part of EFPIA – is supporting pre-competitive research in ATMP manufacturing through the Innovative Medicines Initiative. Three projects are in development, with further calls expected next year in areas including ATMP testing methods.

On the face of it, the National Institute of Health and Care Excellence's (NICE) objectives of speeding the NHS uptake of treatments that are clinically effective and of encouraging the creation of new and innovative technologies should mean there is a favourable environment for ATMPs. However, said **Deborah Morrison, Senior Technical Advisor, NICE Scientific Advice**, "While we want to speed the uptake of products that make a difference, there is an opportunity cost and that always needs to be considered".

However, changes introduced to NICE Technology Appraisals in 2017 have raised the barriers. All products are now subject to a budget impact test and any that will cost more than £20 million in the first three years may be subject to commercial negotiations with NHS England to better manage their introduction. Also in 2017, a cost per Quality Adjusted Life Year – NICE's chief cost-effectiveness metric – was introduced for highly specialised technologies, a category that includes ATMPs. Whereas previously there was no threshold, now the threshold is from £100,000 to £300,000 per QALY, depending on the nature of the patient benefit.

There has been concern that NICE's stringent appraisal process would automatically exclude Advanced Therapies from coverage because they cost a lot for each treatment and reach the market with a limited evidence base. That concern was allayed by a study carried out by the Centre for Health Economics at York University published in 2016, which found that a – hypothetical – T-cell cancer immuno-therapy would pass NICE's scrutiny and secure reimbursement.

NICE is aware that the barriers to conducting randomised controlled trials, the small sample sizes, the reliance on surrogate endpoints and the limited scope for generalising make it hard for companies developing ATMPs for rare diseases to generate the evidence that health technology assessment bodies need for their appraisals.

In one initiative to address this issue, NICE and its counterparts elsewhere in Europe are trying to work more collaboratively in support of such efforts by providing companies with joint EMA/HTA

advice. HTA bodies recently agreed to get together beforehand to agree their requirements in advance of the joint advice sessions with EMA.

In addition, NICE is encouraging companies to consider creating historical controls. “If you are compiling a registry, start from the beginning and make sure it is relevant,” Morrison advised. To reduce the economic risk, NICE is promoting cost-sharing agreements and managed access agreements, to reduce the budget impact.

As an example, under the five-year managed access agreement for Ataluren, all patients with muscular dystrophy over the age of five who are still able to walk will get access to the exon skipping drug. PTC Therapeutics will create a registry of all those treated to gather evidence of efficacy and a decision will then be made on whether Ataluren will continue to be reimbursed after five years based on the in-market data. NICE estimates that 50–60 children could receive the drug during the five years.

To date, NICE has turned down the ATMPs ChondroCelect, MACI and Provenge as not being cost effective, and said yes to Amgen’s Imlygic oncolytic viral therapy for metastatic melanoma (which the EMA classifies as a gene therapy), the stem cell product Holoclar for treating burns in the eye and Strimvelis for ADA-SCID.

“We have seen 16 ATMPs come through and get advice from NICE while they were in development”, said Morrison.

Advancing from research to an approved ATMP is a very hard thing to do and the difficulties faced by the emerging sector should be reflected in the regulatory system, **said Steve Bates, Chief Executive of the UK BioIndustry Association**. “We have to be careful not to test things to destruction”, he said.

The sector needs to build a stronger voice in Europe to address the policy challenges, Bates said, pointing to the differing requirements of health technology assessment bodies across Europe, which are creating significant hurdles. While it is positive that NICE promotes scientific discussions and engages with companies and patients, its methodology is purely focussed on extracting the maximum clinical benefit from a fixed drugs budget.

What is not factored into NICE is the opportunity cost of missing out on a new industry, and the benefit to society. “NICE only works in health budget terms”, Bates said.

For evidence that NICE’s focus on QALYs could constrain the development of ATMPs, Bates referenced bone marrow transplants, which he suggested would be unlikely to cross NICE’s cost-effectiveness thresholds if they were assessed now.

There are alternative approaches to health economics that could factor in the impact for the UK in terms of the development of the sector. “Don’t let Advanced Therapies be slain on the altar of QALY”, Bates said.

With Brexit poised to throw up additional complications, the fact is that Europe does not have a single set of rules, but rather a cottage industry of Hospital Exemptions with different standards. “That is not the basis on which to build to build global businesses”, said Bates. “I do not want this industry to be a Specials industry – in the US you can get from a university lab to market.” Meanwhile, a focussed government policy and investment in the sector has pushed Japan ahead of Europe in Advanced Therapies.

From this perspective, Brexit could represent an opportunity for the UK. “We would like to [develop the sector] with Europe”, said Bates. “But if we are outside, we will build Advanced Therapies value elsewhere.”

A wish list for disruptive innovators

To date most attempts to apply stem cells to develop treatments are focussed on whole cells. Oxstem is taking a completely different approach of combining stem cells and medicinal chemistry – ‘stemistry' – to discover small molecules that activate stem cells *in situ*.

The technical advance around which the company was formed is the ability to culture tissue-specific human stem cells in suspension, preventing them from differentiating. Maintaining their ‘stemness’ in this way allows the cells to be used in conventional small molecule drug screening.

“All the information is in the cells”, said **Michael Stein, CEO and Chair of Oxstem**. The brain, heart, eye, cancer are all “big examples” of where the information to activate stem cells to promote repair is available. “But”, said Stein, “can we find the master switches?”.

Oxstem was founded two years ago by the eminent Oxford University chemists Kay Davies, Steve Davies and Angela Russell, raising a substantial £16.9 million in its first round of funding in May 2016. The founders are “medicinal chemists thinking outside the box”, Stein said.

The company also has an innovative, capital-efficient structure, sharing resources across five different departments of Oxford University and having access to clinical trials infrastructure and patients at the John Radcliffe University Hospital, a leading centre for medical research.

Oxstem is using its platform technology to look for small molecule activators of stem cells in cardiovascular disease, ophthalmic disorders, neurodegeneration, immunotherapy and cancer. Each therapeutic area will be handled by a separate daughter company that is fully owned by Oxstem. “It’s quite a radical model for a start-up”, said Stein.

Oxstem has now got proof of scientific principle in an animal model, having shown that it can highly specifically activate one stem cell population in the mouse brain. “We are moving forward quickly”, Stein said, setting out his “wish list” of measures to support Oxstem and fellow disruptive innovators.

Oxstem: a wish list for disruptive innovators

- Government is traditionally bad at picking winners but can create the infrastructure for disruptive innovators to thrive, as for example in Japan where METI, the Ministry of the Economy, rather than the Department of Health, has put in place an integrated set of policies to promote regenerative medicine as a driver of economic competitiveness.

- Provide matched funding specific to regenerative medicine, modelled on the approach used by Finland’s innovation agency Tekes, in which the agency provides a percentage of the funding required and the private sector backers handle the due diligence.

- Designate Oxford University, the largest life sciences campus in Europe, as a centre for regenerative medicine, with much greater backing for the required infrastructure and the means to work in partnership with innovators and established industry.

- Bring international investors, including industry, together with start-ups in regenerative medicine, backed by a specific Regenerative Medicine Fund for supporting meetings.

- The innovation funding model should include support for ‘left-field’ or ‘Black Swan’ ideas that are outside of the norm in regenerative medicine, but from where disruptors are likely to emerge.

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