Cell and gene therapies
the emerging fourth pillar of healthcare systems

As the CEO of an organisation that deals exclusively in cell and gene therapies, it is no surprise that I would champion the emergence of these products as the fourth pillar of medicine alongside small molecules, biologics and devices. But it is a statement that has a huge amount of proof building behind it – from the interest of large pharma and investors to the volume of companies spinning out of universities and the creation of supply chains and skills that will be needed to make it a reality.

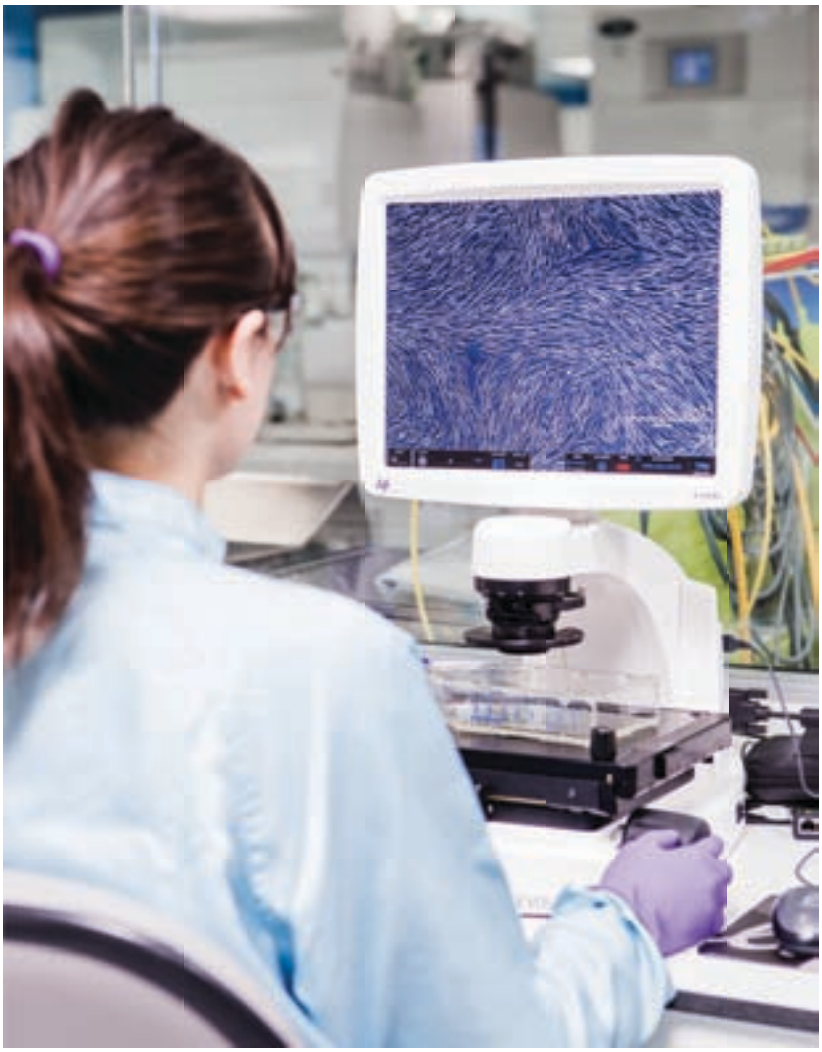
By Keith Thompson

The latest data from the Association for Regenerative Medicine (ARM) showed that there are more than 704 regenerative medicine companies worldwide, including cell and gene therapies and 728 clinical trials under way at the end of the second quarter in 2016[1]. This is a growing global market where companies are spread across different parts of the world, with larger volumes in North America, Europe, Israel and parts of Asia[1].

These types of therapies – cell therapies, gene therapies, tissue engineering and regenerative medicines, usually referred to collectively as ATMPs (Advanced Therapeutic Medicinal Products) – are not a new phenomenon. Blood transfusions, bone marrow transplants and skin grafts, which are well known and well used in modern medicine are all predecessors. In fact the history of cells themselves goes back more than 350 years – something we celebrated with the Royal Society in October 2015 with their discussion meeting on 'Cells: from Robert Hooke to cell therapy – a 350 year journey'[2].

So what turns a cell into a medicine that requires regulation and licensing familiar to readers of *DDW*? It is quite simple really, once you start to alter or manipulate a cell to do new things, you have to prove the product is safe and efficacious and all the usual questions of drug development start to flow; the development, licensing and regulatory machine kicks into gear and the established world of drug development collides with the new world of cell and gene therapies.

I listen to the radio every morning as I am getting up to go to work and there has been a daily diet of stories for the last decade or more about the latest advances in stem cells or gene therapies from eminent researchers, often quoting fantastic results *in vitro* or in animal models, offering tantalising prospects of revolutionary cures. The question is always asked "so professor X, when is it going to be available to patients?" and the answer has always been the same, "lots more research, it is least five years away", and it has been that way for many years. In fact, the whole sector was dogged by the idea that it was too early, too difficult and uncertain, the regulators will never approve it, big pharma won't like it because it doesn't conform to



their model etc, etc. This was the position often taken by big pharma reluctant to invest in hugely risky development programmes. So apart from some plucky pioneering firms the sector was largely an academic endeavour with iterative clinical research being pursued. Despite these doubts, the potential for transformative interventions and cures has always been recognised. Translational funding to try to help industry and treatments emerge has been provided to bodies such as the Cell and Gene Therapy Catapult, the Canadian Centre for Regenerative Medicine and a $3 billion intervention forming the Californian Institute for Regenerative Medicine.

I started my career as a young researcher in monoclonal antibodies in 1979, just as they were emerging from Cesar Milstein's lab in Cambridge and right at the beginning of the Biotec revolution. At the time a handful of recombinant products were emerging, largely recombinant versions of purified proteins such as Insulin or clotting factors like factor VIII. Most pharmaceutical firms viewed monoclonal antibodies much as they view cell and gene therapies now, interesting but quirky novelties, uncertain regulation, doubts over whether they would work, and issues over how you could make and control them. Oh and by the way you'll never be able to make them at a cost that makes them profitable, and yes there was a rocky road to start with. Looking back I was too keen and naive to let mere rational analysis get in the way of all the fun I was having. Here we are 35 years later with monoclonals as the largest class of biologicals achieving more than $50 billion sales, continuing to grow and with manufacturing yields that even an optimist like me would never have dreamt of. And the first biosimilars (that would never happen either by the way) are now coming on to the market.

Today, cell and gene therapies feel just like monoclonal antibodies as they were emerging. The set of questions around these therapies is just as great if not greater but the potential for transformative therapies demands answers rather than obstacles. So what are the barriers? Autologous therapies have long been used in medicine but not in pharma. How does a business model that takes a patient's cells, sends them to a factory for modification, then sends them back as either fresh or frozen, often has a finishing step close to the patient with short shelf life and a very precise mode of delivery actually work? You can hardly send this to the pharmacy to sit on the shelf and then be prescribed. And if you cure a disease how does a health system assess and pay for an expensive technology when you may not have all the data to show lifetime durability?

The familiar language of mode of action, potency, toxicity, side-effects, half-life etc, feels inappropriate but when you peel it back to fundamentals familiar questions are being asked, how does it work? Have you delivered the right number of cells or genes to have an effect? Do the cells persist when the effect is achieved by changing the environment and they disappear leaving newly mobilised cells to exert an action?

So why has all this money been pouring into the sector. Again it is quite simple, outstanding clinical results that demonstrate the potential for cures to many unmet medical needs.

And as a result of that we have seen the science start to translate into what I believe will be a huge global industry. The proof here is in the numbers. Specifically the global financial numbers, which are starting to look really interesting as big pharma and

investors have started to engage, take an interest and a position in the industry. There was a doubling in the amount of upfront investment they were making from 2014 to 2015[3]. Suddenly investments of millions are becoming billions and these large global companies are doing more than just dipping their toe in the water. Total global financings in the first half of this year were $2.5 billion[1].

One of the areas where there has been the biggest amount of interest and investment is in immune oncology, specifically genetically engineered T-cells, in the form of T-cell receptors (or TCRs) and chimeric antigen receptors (CAR-Ts).

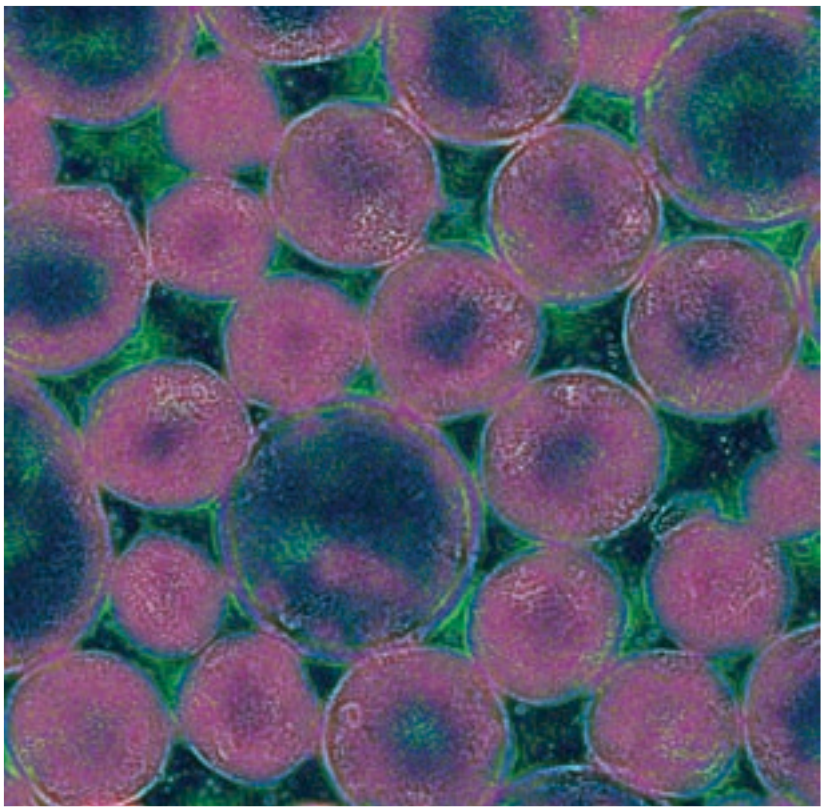
After many years of development in academia we started to see dramatic clinical results in 2012 with Researchers at University of Pennsylvania showing remarkable results with an Autologous CAR-T directed to CD19 and used to treat Chronic Lymphocytic Leukemia (CLL) This aroused the interest of Novartis which quickly signed a deal and pushed forward with the technology although more recently it has mainstreamed the development of the technology and disbanded its specialist cell and gene therapy unit. More recently we saw the surge of global media interest around the first ever use of a gene-edited product in a human patient. The company was Cellectis and the product was TALEN gene-edited allogeneic UCART19 offering the prospect of 'off-the-shelf' CAR-T products. It was successfully used by Great Ormond Street Hospital (GOSH) in a compassionate case to treat a one-year-old child with refractory relapsed Acute Lymphoblastic Leukaemia (ALL)[4].

Before their success in providing treatment at GOSH, Cellectis had received an upfront payment of $80 million from Pfizer in June 2014 to develop CAR-T cell therapies[5], milestones amounting to hundreds of millions will also be due on success. GlaxoSmithKline (GSK) also announced a deal at the same time with Adaptimmune to develop TCR engineered T cells[5]. The race is truly on and other companies have emerged from academia such as Juno, Kite, Bellicum and Bluebird which have, in turn, raised huge amounts of money and some have made deals with big pharma.

As an organisation that exists to help translate promising technologies into commercially viable products, we identified this area before the explosion that has now occurred. We invested in two potential products with academic partners (a TCR to the cancer marker WT-1 and a CAR-T to an angiogenesis marker) partly to develop the products but also to use the products as pathfinders so that we could help lower barriers to commercialisation enabling others to benefit.

Of course it is not a completely smooth path to success. We saw earlier this year that Juno had a setback in its Phase II clinical trial for the JCAR015 product after the death of two patients[6]. However, the trial was soon restarted after agreement with the USA FDA and continues to run. I believe we will start to see these oncology products on the market in the next few years and that they will deliver great results to patients who have no other options. Over time these could also become first line therapies.

And it is not just oncology where advanced therapies are potentially going to offer treatments and where big pharma are investing. In 2010 GSK bought into what is now known as Strimvellis, essentially a gene therapy that modifies the patient's bone marrow. The product has gained approval in Europe for the treatment of ADA-SCID, a rare immune disease in children. One of the firms we work with, ReNeuron, is working on a product for stroke by injecting neuronal stem cells into the brain of stroke patients. It has been successful in attracting funding to the tune of more than £100 million. Our own research into the landscape of the industry this year suggests that, at least in the UK, there were more preclinical studies in ophthalmology and cardiovascular than in oncology and neurology was an area of similar



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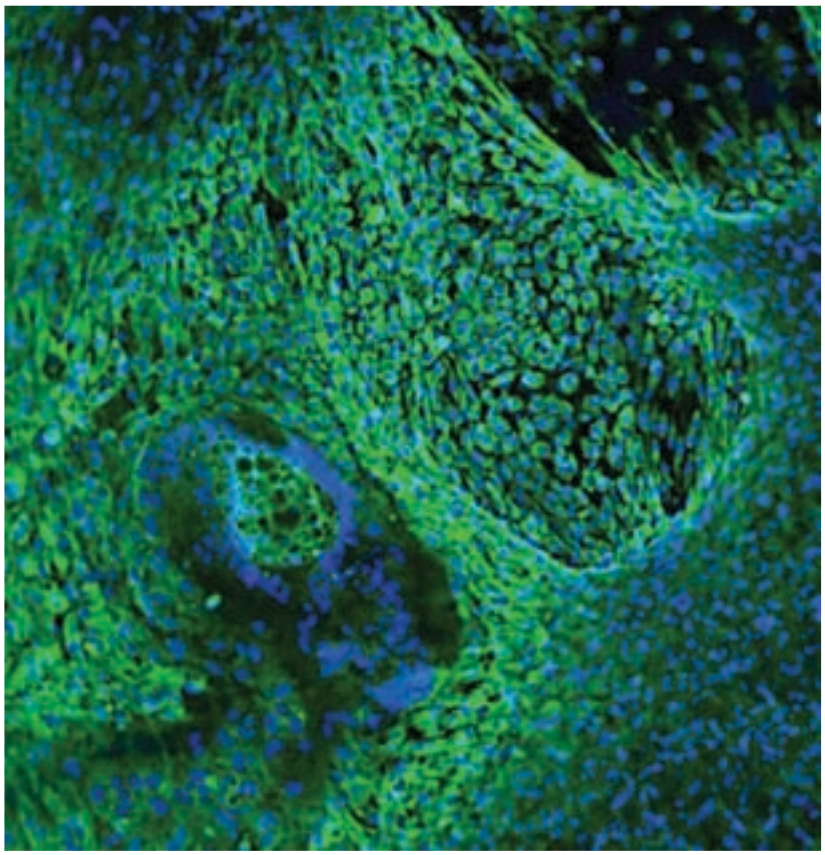


Meso 101115: Random Differentiation of iPSCs

size[7]. In our UK clinical trials database[8], oncology is still the dominant therapeutic area with neurology second.

One of the issues with ATMPs is that the cost of manufacture can still be very high. Of course, just because a therapy is expensive to make it does not mean that a price higher than the health benefit that it delivers can be achieved. We encourage early assessment of what a health system is likely to pay for a new product which can then be used to guide the development of the production process to give a target cost of goods that will allow a suitable margin to be achieved. I am convinced that costs will come down, just as they have done with monoclonals.

GSK's approach to reimbursement for Strimvelis is also interesting – and a great illustration of the sort of problem the industry is now trying to tackle – a money-back guarantee if it does not work[9]. Strimvelis has a price tag of 594,000 Euros ($665,000) but in a trial of 18 children, all but three were cured outright. So GSK has decided that if the drug does not work, the cost will be refunded. This nicely illustrates the combination of business and science and as ADA SCID is an ultra-orphan, it is probably more important that patients get treated and the reimbursement issue does not get in the way of adoption.

It is because ATMPs have their own unique challenges that industry has almost had to start from scratch rather than build incrementally on what we know works for pharmaceuticals or biologics. Take the well-documented case of Provenge, an autologous cellular immunotherapy for the treatment of advanced prostate cancer. The product gained FDA approval in 2010 and was the first time a cancer vaccine had been approved. However Dendreon, the company that was commercialising the product, filed for bankruptcy four years later. The failure of the product was in part down to the prohibitively high manufacturing costs versus other options for treatment and how effective Provenge was in comparison essentially put a price cap on the treatment. If you have a small molecule that works, the manufacturing process is so well known and so established that you do not need to focus on how much it will cost to make, you just assume that the cost of goods will be a small percentage of the selling price. That is simply not true for ATMPs, there are unique challenges to be tackled. We all owe a debt to Dendreon as it pioneered many of the approaches to working out just how an autologous product could be made to work technically but it was definitely behind the curve on cost reduction.

It is not all about direct cost though, analytical platforms are also being developed to characterise products safely along the production line and to form parts of CMC packages. Some of these products can also have much shorter shelf lives meaning that they need to be transported or frozen and thawed in new ways. They can last for as little as three hours compared to a tablet that will not go out of date for years. This also brings us interesting challenges in terms of logistics as well as methods for cryopreservation and all of these things have associated costs.

At CGT Catapult we try to approach these challenges using Quality by Design. In applying this to our own TCR we have already achieved reductions of 60% in the future cost of manufacture for the product in clinical trials. Standardisations that translate into savings can be found and we and the industry are getting better at this all the time.

Gaps in the transportation and cryopreservation chains are also starting to be identified and addressed. One of our projects, for example, has been the development of devices that can thaw materials close to the patients in devices capable of meeting GMP requirements, rather than clinicians using a water bath. The company we worked with

on this, UK-based Asymptote, is now putting the finishing touches to both GMP vial and bag thawing devices.

We are also seeing increased investment into facilities for the manufacture of GMP grade products. Our latest figures for the UK show that there has been a doubling in the amount of GMP floorspace for ATMPs since 2013[10]. We expect that to keep going up and next year we will open our own large scale manufacturing facility for ATMP companies to use.

Another area where there has been great progress made is in the regulation of these products. We have found that by working closely with regulators we have been able to find ways of meeting regulatory requirements rather than just complaining about them. My experience of regulators is that they want the products to succeed as much as industry does.

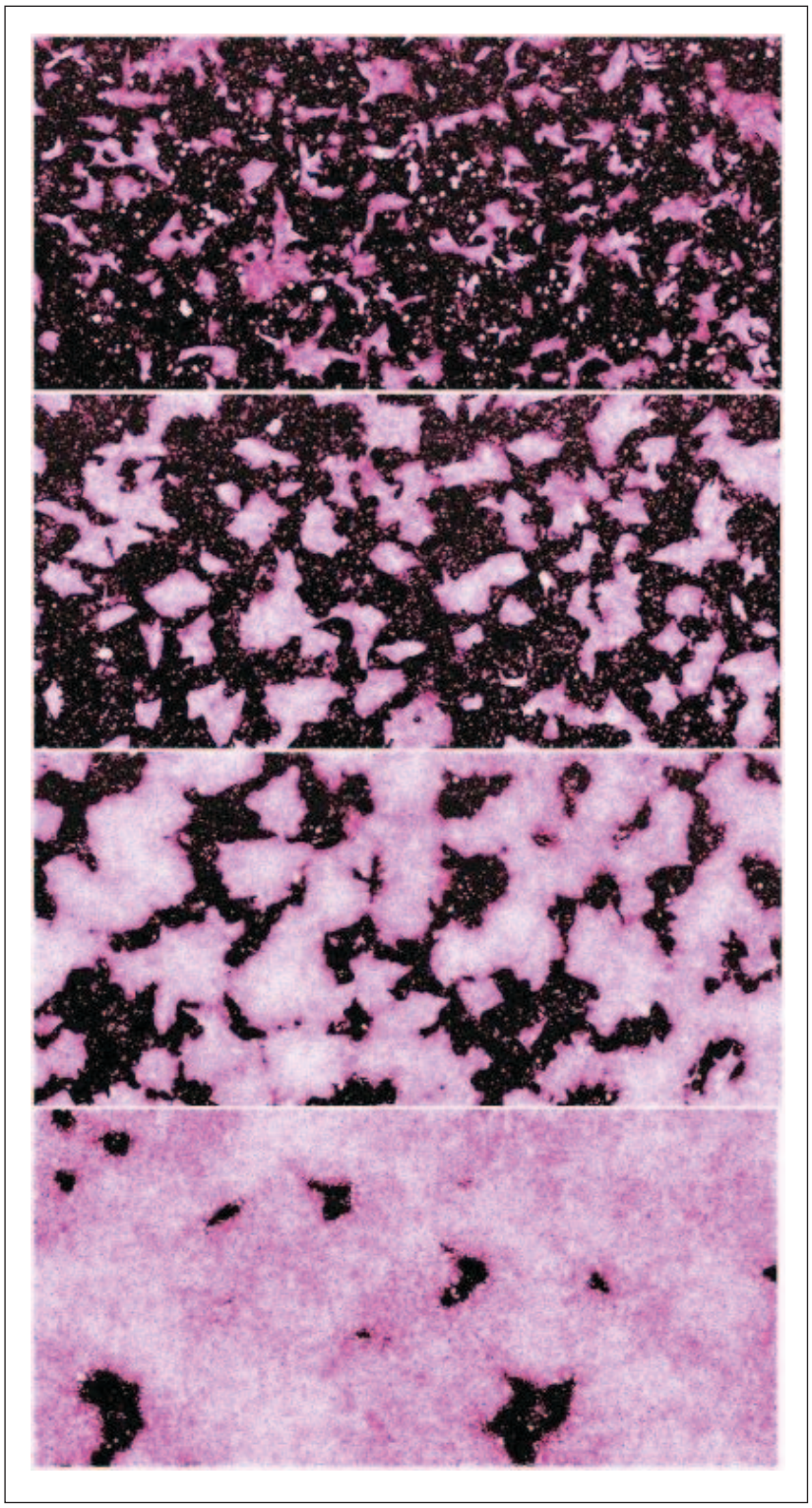
Europe introduced an act to regulate ATMPs in 2008 but there were subsequent calls for clearer regulation due to the fact that most products were being developed by academics or charities who do not have access to the sort of huge regulatory teams that can help untangle the complex requirements[11]. Once again, it has been a case of reinventing because the traditional pharma model does not always fit. For example it is difficult to have multi-site, multi patient trials as current products tend to target rare or orphan diseases – so designing a trial that will pass the regulatory scrutiny required new ways of thinking which requires resources and clarity around what is needed.

The MHRA here in the UK is, I believe, one of the most proactive regulators and is creating the right sort of regulatory environment and with a 'one-stop shop for regulatory advice' has helped companies make much faster progress into clinical trial.

Japan is the home of induced Pluripotent Stem Cells (iPSC) with Shinya Yamanaka wining the Nobel prize. However, despite this in 2012 Japan was lagging behind other leading countries in getting ATMPs to market[12]. To help speed up the ability of ATMP products to get to market, they introduced a new double-track regulation system. This consisted of two new acts that came into force in late 2014 to regulate regenerative medicine and cell therapy. It has certainly attracted global attention as the result can be early reimbursement and along with major investment in continuing in iPSC cells, demonstrates a determination to be a leading nation in this emerging area. Many other governments have taken note of Japan's move and are

References

1 Alliance for Regenerative Medicine Quarterly Data Report, Q2 2016.
2 http://rstb.royalsocietypublishing.org/content/370/1680/20150320.
3 Alliance for Regenerative Medicine State of the Nation Report, January 2016.
4 Cellectis press release 05 November 2015: http://www.cellectis.com/en/content/ucart19-first-man-proof-concept-be-presented-2015-ash-annual-meeting-0.
5 Pfizer and GSK join race for T cell cancer therapies, Biobusiness brief, Alexandra Flemming, August 2014.
6 Juno press release, July 2016: http://ir.junotherapeutics.com/phoenix.zhtml?c=253828&p=irol-newsArticle&ID=2182781.
7 Cell and Gene Therapy Catapult Pre-clincial database update, July 2016.
8 Cell and Gene Therapy Catapult Clinical Trial database update, July 2016.
9 Gene Therapy cure has money back guarantee, Technology Review, Antonio Regalado, 9 August 2016.
10 Cell and Gene Therapy GMP manufacturing in the UK: capability and capacity analysis, CGT Catapult, March 2016.
11 Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive, Maciulatis et al, Molecular Therapy 2012.
12 Japan Pharmaceuticals and Medical Devices Agency presentation: https://www.pmda.go.jp/files/000206920.pdf.



iPS growth time course: iPSC from the same field of view growing over for days (in purple, from top to bottom: day 1, 2, 3 and 4)

looking at how they could respond. Several years ago I could not have imagined that regulatory systems would start to evolve into competitive approaches, yet here it is. Japan saw the first in man clinical application of a sheet of retinal pigment epithelial cells derived from iPSC to treat age-related macular degeneration and MHRA recently approved a trial for GVHD by Cynata, an Australian company, with allogeneic MSCs derived from iPSC cells.

What is encouraging though is that we are truly in the translational phase. The science is there and we are focusing on the next hurdles and imagining what needs to happen when ATMPs are a standard treatment option. Delivering these innovative therapies in hospitals will require skills and infrastructure not readily accessible at the moment outside of specialist clinical research centres. Many of these products are unlikely to be prescribed from Pharmacy in the traditional fashion as there will be a need for controlled acquisition of patient samples to act as the start material, controlled shipping to manufacturing centres (whether local, regional or global), manufacture of patient specific therapies, return to hospitals and then thawing or manipulation of these living therapies to be given to the right patient at the right time. All of this will require specialist cell handling equipment, new IT and data systems and, of course, specialist and skilled staff.

It is all a constant work in progress and as soon as one new method for manufacturing is found or a more suitable regulation comes in the next issue emerges. But that is what makes it so exciting, coupled with the interest that the big players are now taking. I believe that these products have the potential to be as big as biologics in terms of creating wealth. And perhaps most importantly, I believe in the science behind them that can deliver long-term health to patients. DDW

Keith Thompson *joined the Cell and Gene Therapy Catapult from the Scottish Blood Transfusion Service where he was National Director. Prior to this he held various senior positions in biotechnology companies. He is a Board member of the UK BioIndustry Association and Executive Committee member of the Alliance for Regenerative Medicine. Keith holds first and second degrees in Biological Sciences and Applied Genetics from Birmingham University and an MBA from Edinburgh University.*