CLASSICAL PHARMACOLOGY is broken. Despite having yielded some successful therapies, both clinically and commercially, designing drugs and biologics based on target identification and hit/lead development is failing to systematically produce drugs. It is estimated we understand the mechanism of just 30% of small molecule drugs due to their lack in specificity and, most importantly, our lack in understanding of systems biology. Cells, on the other hand, have been engineered by millions of years of evolution to respond to specific needs while in specific conditions. It is this potential that cell therapies are trying to harness. However, such progress would be almost idle without the possibility to produce and culture mature (functional) cells at scale. A bioinformatics approach to systematically control the transcriptomic network with transcription factors and/or small molecules to culture or convert any cell type opens up the opportunity to develop any autologous, allogeneic cell therapies and a new class of therapies: in vivo reprogramming.
used to replace missing or malfunctioning cells. This is the principle of regenerative medicine. Because of the enormous potential of cells in both of these spheres, the field has seen upwards of $7 billion of investment in 2018 between the US and EU alone. Since the publication of Shinya Yamanaka’s discovery of ‘Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors’ in 2007, the field of cell therapy has seen an exponential rise in investment, with many researchers and new institutes dedicated to advancing cells as therapeutics. This discovery was considered ground-breaking because it was thought that for the first time any cell could be made from pluripotent cells following developmental pathways. Shortly after this, in 2009, the first regulatory approval (EMA) of the cell therapies Holoclar (for corneal burns) and ChondroCelect (for cartilage defects) built further confidence in the fact that cell therapies would soon become a significant player in the treatment of disease. However, since then, despite the incredible amount of investment and research, Holoclar and ChondroCelect have been withdrawn by the EMA (retained by the FDA). Only a handful of other therapies have been approved and none of these are showing any commercial success, at least not compared to the likes of small molecule drugs such as apixaban (anticoagulant used to prevent strokes in patients with atrial fibrillation), or biologics such as Merck’s Keytruda (anti PD-1 cancer immunotherapy).

So why have cell therapies fallen short of their potential?
Unlike small molecules and biologics, introducing entire cells into the body represents completely new challenges. During a full organ transplant, whereby a foreign entity is introduced in the body, the immune system is activated as it would be during a common cold because of the organ’s immune signature, unique to its donor’s DNA. This unique signature consists of the family of proteins human leukocyte antigens, expressed and presented on a cell’s surface in a unique way akin to one’s fingerprint. Individual cells are no different, therefore placing any engrafted cells from a foreign donor in danger of destruction by the immune system, rendering the treatment redundant. This hurdle was originally never tackled head-on, but rather bypassed by creating autologous
therapies in which cells are extracted from one patient, grown and implanted back into the same patient. This suited Holoclar and ChondroCelect as the treatment aimed to regenerate a small and damaged proportion of tissue using cells from the healthy portions. The recently-approved CAR-T therapies KYMRIAH and YESCARTA still use this principle to attack cancers, with the patient’s own T-cells being modified ex vivo and reinjected. Bypassing the immune system with these therapies, however, comes at the price of one of the key performance indicators: scalability. While the therapies are mostly safe, having to extract and grow cells for individual patients under GMP conditions is extremely expensive, logistically complex and, most importantly, does not scale in the same way as having an off-the-shelf product. As a result, therapies such as KYMRIAH cost $475,000, while therapies that cannot justify such a high price tag to support a GMP facility (e.g. ChondroCelect) are withdrawn because of a lack of commercial interest.

Owing to these factors, the field of cell therapy has, in the past decade, shown a clear trend towards the development of allogeneic therapies, in which cells are extracted from one patient and implanted in another as an off-the-shelf product. For cells to be implanted allogeneically, they need to be modified to remove the HLA complexes on their surface, making them ‘invisible’ to the immune system, and therefore tolerated by the host. This requires an acute knowledge of the immune system and highly specific gene editing technology. Fortunately, leaps and bounds have been made in both of those fields, with many companies now leveraging different technologies in an attempt to create ‘universal donor’ cells, akin to the O-negative blood type which can be perfused into any patient in case of blood loss (a much-forgotten example of cell therapy). Notable examples include Cellixir with its immunomodulatory progenitor cells (iMPS), recently-acquired Juno Therapeutics using its clustered regularly interspaced short palindromic repeats (CRISPR) technology, Cellectis with its transcription activator-like effector nuclease (TALEN) technology, and Sangamo therapeutics using its zinc finger nuclease technology in collaboration with Gilead (Kite Pharma).

However, in the case of Sangamo, Cellectis and Juno, avoiding transplant rejection is not the only hurdle when developing CAR-T therapies. As immune cells, the T-cells injected also have the innate ability to recognise foreign cells (such of those of the host in the case of an allogeneic therapy) and destroy them. This is known as grafts-versus-host disease (GvHD), which can cause major adverse effects and, in many cases, death. To avoid this, these innovators also have to modify the T-cell receptors (TCR) or CAR-receptors used to avoid recognition of any healthy human cells while still recognising the cancer. Cancers having initially evolved from the body, this finely tuned level of specificity is very hard to achieve.

It is worth noting that there are some cases in which little-to-no genetic modification is required to create an allogeneic therapy. Organogenesis’s GINTUIT is an FDA-approved cell therapy product, developed for surgically-created vascular wound beds in the mouth using allogeneic human cells (keratinocytes) and bovine collagen. This product has shown satisfactory efficacy in 50% of...
patients in trials but still causes a notable immune reaction with common adverse effects including sinusitis (sinus inflammation) and nasopharyngitis (inflammation of the upper throat and upper respiratory tract). Additionally, in the cartilage (affected by defects and osteoarthritis) and the back of the eye, where little vasculature is found, the hosts immune cells do not come in contact with the implanted cells. This has led to several trials using unmodified chondrocytes and retinal pigment cells to treat cartilage defects and age-related macular degeneration respectively, some of which have shown good success but are not commercially viable as a result of the second major hurdle: manufacturability.

Even if an allogeneic therapy is possible – either by gene editing the cells or by the immunoprivileged nature of the host tissue – the cells need to be manufactured at scale in order to provide sufficient material for all patients that require an off-the-shelf product. Scientifically, this manufacturing hurdle is two pronged. Firstly, we need to discover the ability to make cells and, secondly, we need the ability to culture those cells. Unfortunately, many differentiated cells in the body do not have the innate ability to divide. Chondrocytes, for example, create an extracellular matrix which makes up the cartilage but directly inhibits their growth, and terminally differentiated neurons do not divide because they lack centrioles. Yamanaka’s discovery of the OKSM factors to make iPSCs was thought to open up the possibility of producing any cell type by following the developmental pathways (described by Waddington as small balls rolling down a hilly landscape). Following the expansion of iPSCs this would allow the production of large quantities of any cell. However, to do so the discovery of the combination of factors required to convert iPSCs into a specific cell type remains to be discovered, for which the number of combinations are astronomical (~10^62). Moreover, even if a combination is discovered, identifying suitable culture conditions for the cells to be maintained in their transcriptomic state remains a huge challenge. Many cells are known to be very hard to culture such as megakaryocytes, zombie and foam cells, all of which have therapeutic potential which remains to be unlocked.

This hurdle of cell conversion is being approached in many ways. OxStem, an Oxford University spin-out, carries out phenotypic screening using small molecules to create the desired cell type \textit{in vivo}. The Cambridge-based company Mogrify has leveraged large amounts of transcriptomic (FANTOM5) and regulatory data (MARA & STRING) to develop a systematic algorithm which predicts the combination of transcription factors required to convert any human cell type into any other human cell type without going through a pluripotent stem cell state (ie transdifferentiation). This technology represents the first systematic control of the transcriptomic network and therefore is to transcriptomics what gene editing technologies such as ZFNs/CRISPRs are to genomics. The technology has been validated in more than a dozen cell types in quick succession, which shows great promise for the future of scalable cell manufacturability. Similarly, this technology can be extended to identify the culture conditions systematically by stabilising the cell type in its epigenetic state by sustaining the transcriptomic state.

Looking further into the future, such technologies have the potential to create the next generation of cell therapies. Instead of autologous or allogeneic
implantation of cells, these technologies can be used to convert cells already in the body by *in vivo* reprogramming using small molecules or transcription factors to create the desired cells from others in the body that are either too abundant or grow quickly. Similarly to gene therapies, however in most cases this will require the development of much finer control of the delivery to avoid adverse effects. Chondrogenix, Mogrify’s wholly-owned subsidiary, is already developing a small molecule cocktail to reverse the de-differentiation that occurs in the chondrocytes of an osteoarthritic knee, which would represent the first disease-modifying approach to this condition which affects over a third of our elderly population. Other fields in which cell therapy could expand in the future are infectious diseases. CAR-T therapies have mainly been focused on cancers, however T-cells are naturally also very effective at fighting infections and, unlike antibiotics, can adapt over time in the arms race of bug versus host. Could CAR-Ts be quickly tailored to fight future epidemics?

Overall, despite some of the scepticism that has arisen around cell therapy from slow development and clinical trial failures, it seems the field is making enormous progress on all the hurdles found with the development of cell therapies that provide the best possible patient outcome at a commercial scale. Ultimately, like any other complex problem, a combination of disruptive technologies will be required for cell therapies to succeed. Once achieved, cells will be able to reach their full therapeutic potential in endless applications, including in diseases which have long suffered a lack of any treatment and many clinical set-backs, such as neurodegeneration.

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