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CELL & GENE THERAPY INSIGHTS

SPOTLIGHT ON:
Clinical trial design, supply chain and operations

CELL & GENE THERAPY INSIGHTS

Volume 7, Issue 7

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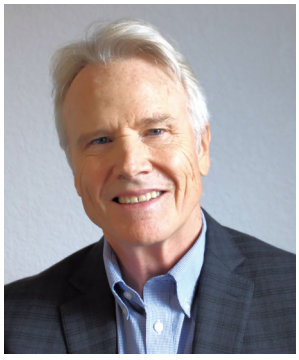
EDITORIAL

CRISPR gene editing for sickle cell disease: one disease, differentiated approaches



"The genetic basis of sickle cell disease is well established, making it an ideal candidate for gene editing therapy."

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CRISPR-Cas-mediated gene editing has had a major impact on biomedical research. The technology was developed in the early 2000s from an elaborate response pathway in bacteria based on the so-called 'clustered regularly interspaced short palindromic repeats' or 'CRISPR' [1]. Reduced to its two essential components — a guide molecule, 'gRNA', and an associated DNA-cutting enzyme, 'Cas' – some current CRISPR-Cas systems

now enable researchers to precisely edit, extend, or delete specific target DNA sequences in the human genome [2].

CRISPR-Cas gene editing is now being studied *in vivo* and *ex vivo* to treat disease with underlying genetic causes. One such condition is sickle cell disease (SCD), an inherited, life-threatening blood disorder with a birth prevalence of approximately 112 per 100 000 [3]. Patients with SCD display anemia and chronic hemolysis due to deformed red blood cells [2].

The genetic basis of SCD is well established, making it an ideal candidate for gene editing therapy. Thus, multiple companies have developed CRISPR-based treatments which aim to correct the sickling phenotype. Although we all share the same goal of relieving the burden of SCD, each of the editing platforms is different, and enables the targeting of different genes or different parts of genes with varying efficiency and specificity.

Herein, we describe some key differentiators between the CRISPR-based SCD therapies which are currently in development.

MECHANISM OF ACTION

SCD is caused by a single point mutation in the gene encoding normal hemoglobin (HbA), the main protein in red blood cells [2,4]. The resulting abnormal hemoglobin is called sickle hemoglobin (HbS). Scientists have tried to directly reverse the point mutation and have either been unsuccessful or had limited efficiency [5,6]. One creative approach being investigated is to induce a different mutation at the same location to create another type of hemoglobin not associated with SCD. However, due to the difficulty of targeting the specific mutation, most other methods aim to induce reactivation of fetal hemoglobin (HbF).

HbF is a natural endogenously produced protein and is the dominant form of hemoglobin present at birth. The protective effect of high levels of HbF are clinically established, as the manifestations of SCD do not appear until after 6 months of age when production of HbF is usually downregulated. Inducing HbF production in the treatment of SCD is the basis for treatments such as hydroxyurea. Similarly, a rare mutation that occurs in the gene responsible for gene switching results in some adults having continuously high HbF levels. This condition, 'hereditary persistence of fetal hemoglobin' (HPFH), is benign. Individuals who co-inherit HPFH and the SCD mutation have few disease manifestations [2,7]. Consequently, reversing the switch that turns off HbF production to mimic HPFH is expected to be safe and a clinically proven therapeutic strategy to address SCD.

TARGET SITE

The switch from fetal-to-adult hemoglobin is mediated in part by transcription factors that suppress *HBG*. Therefore, SCD gene therapy approaches aiming to increase HbF levels could either silence the genes that encode the suppressor molecules, or disrupt their binding sites in the *HBG* promoter [2]. Two such suppressor targets include B-cell lymphoma/leukemia 11A (BCL11A) and leukemia/lymphoma-related factor (LRF) [8]. In HPFH, naturally occurring mutations are in the *HBG* –200 and –115 regions, suggesting that edits in this region would be therapeutically effective and of low risk [9]. EDIT-301, the Editas gene editing product, disrupts the CCAAT box region (–115 region) in the *HBG1/2* promoters. As this site overlaps with the naturally occurring HPFH mutation sites, editing here results in therapeutically meaningful HbF induction without off-target editing [10,11]. Other gene editing techniques target the –200 region [7,12,13], but result in lower levels of HbF induction and have been associated with unintended genetic modifications at other sites (Figure 1) [12].

THE NUCLEASE

Another differentiator between editing approaches is the selection of the modifying

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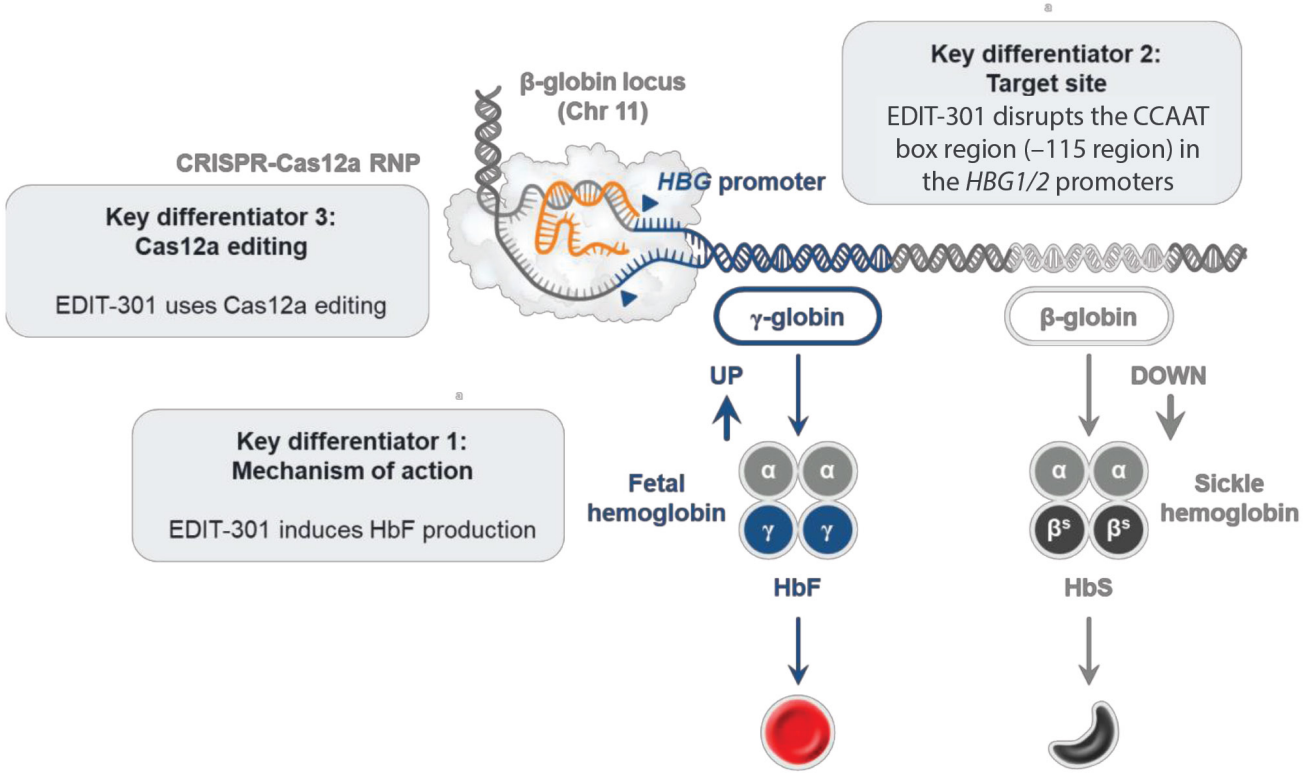
FIGURE 1

EDIT-301 mechanism of action.



enzyme. Several therapies in development use Cas9, the nuclease included in the original precision gene editing system [14–16]. It is well understood that different Cas9 and Cas 12a enzymes possess different abilities to target specific sites in the genome in part determined by their PAM sequence [17]. Our product, EDIT-301, takes advantage of an alternative enzyme: Cas12a. Our data shows that Cas12a can generate a highly efficient editing enzyme with excellent specificity [15]. Moreover, the gRNA used for inclusion in a Cas12a system provides much higher fidelity than those produced for Cas9. This is a feature of the gRNA chemistry and suggests that *in vivo* and stem cell therapies utilizing Cas12a gene editing are likely to have fewer off-target edits and consequently better long-term safety.

CRISPR-Cas disrupts binding sites by introducing insertions and deletions ('indels') in the target region [7]. We found that these indels must be larger than three nucleotides for effective gene induction [11]. While the exact reason for the size relevance is unclear, larger indels may be more efficient at disrupting repressor binding and are thus more effective than small changes. When comparing Cas12a and Cas9, we saw that Cas12a generated larger deletions and was associated with a higher frequency of productive indels than the traditional nuclease, leading to consistent and strong HbF induction [11].

MULTI-NUCLEOTIDE VERSUS SINGLE-BASE EDITING

CRISPR-Cas editing creates indels of various sizes. In contrast, recently developed base editing systems exchange only single nucleotides, while still dependent on the CRISPR-Cas9 system [18]. While, in our experience, indels smaller than four nucleotides have been ineffective, others have recently reported promising single-base editing approaches targeting the *HBG* promoter region

TABLE 1

Summary of CRISPR-Cas technology-based investigative therapies in SCD.

Therapy	MoA	Target site	Enzyme	Phase	Sponsor
EDIT-301	HbF induction	*HBG1* and *HBG2* promoters: BCL11A binding site	Cas12a	Phase 1/2	Editas
CTX001	HbF induction	*HBG1* and *HBG2* promoters: BCL11A binding site	Cas9	Phase 1/2	CRISPR Therapeutics/Vertex
BEAM-101	HbF induction	*HBG1* and *HBG2* promoters: BCL11A binding site	Cas9^{+} base editor	Preclinical	Beam Therapeutics
BEAM-102	Edit of sickle allele (to Hb-G Makassar)	*HBB* gene	Cas9^{+} base editor	Preclinical	Beam Therapeutics
	HbF induction	*HBG1* and *HBG2* promoters: LRF binding site	Cas9	Preclinical	Genethon/ Alia Therapeutics

or changing the disease-causing mutation in *HBB* to a non-pathologic variant [19,20]. It has been asserted that single-base editing approaches could have potential safety advantages and progress has been made on the delivery of the editing machinery to cells, which has been limited by their large size. Current efforts to expand certain base-to-base conversions has also been promising [21].

NON-CRISPR SCD GENE THERAPY APPROACHES

Of note, several non-CRISPR gene therapies are also currently underway, such as editing techniques based on other nucleases (e.g. zinc finger nucleases or TAL-effector nucleases) or gene addition therapy [2,13]. While such treatments differ substantially from those using CRISPR technology, and can be considered distinctly different treatment approaches, there is a zinc finger gene editing technology which also disrupts the BCL11A enhancer currently being investigated for safety, tolerability, and efficacy.

DIFFERENT APPROACHES, DIFFERENT OUTCOMES?

The field of CRISPR-based SCD therapies is wide and varied. While CRISPR-Cas is at the core of all strategies, individual approaches vary with respect to the mechanism of action, target site, and protein/gRNA contained in the nucleases being employed (see Table 1). Thus, it is impossible to draw direct comparisons, as most of these therapies are still in the preclinical or ly clinical development phase. Future research will reveal whether the different approaches summarized above ultimately impact disease sequelae such as organ damage, stroke, cardiovascular and respiratory complications, and ultimately mortality.

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CELL & GENE THERAPY INSIGHTS

CLINICAL TRIAL DESIGN, SUPPLY CHAIN & OPERATIONS

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INTERVIEW

Driving clinical progress of gene therapy in cystic fibrosis

UTA GRIESENBACH is a Professor in Molecular Medicine at Imperial College London, President of the British Society for Gene and Cell Therapy (www.bsgct.org/) and Director (non-excecutive) of the Celll and Gene Therapy Catapult. Uta has over 25 years experience in developing advanced therapeutic medicines. Her reserach interests are related to the development of gene and cell therapy-based treatments for cystic fibrosis and other lung diseases. As part of her translational research, Uta has overseen vector and biomarker development, toxicology studies, as well as GMP vector manufacturing. Uta is Co-Investigator on several gene therapy trials. Uta is a Strategy Group Member of the Respiratory Gene Therapy Consortium (www.cfgenetherapy.org.uk/) and a member of the MRC-DPFS panel. In addition, Uta is interested in teaching and work-force development. She is Deputy-director for post-graduate reserach at the National Heart and Lung Institute, Programme director for the MSc in Genes, Drugs and Stem cells-Novel Therapies at Imperial College and chairs the Pan-UK working group for ATMP workforce training.

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Q What are your working on right now?

UG: We are working on developing gene therapy for a range of respiratory diseases. We have over 25 years' experience in gene therapy for cystic fibrosis (CF) but are also interested in other rare lung diseases.

Our cystic fibrosis program is carried out in partnership with a large pharma, Boehringer Ingelheim, and a virus manufacturing company, Oxford Biomedica. We are currently moving towards a first-in-human clinical trial with a lentiviral vector.

Q Can you frame for us the current status of gene therapy clinical development in cystic fibrosis and the various gene delivery platforms that are being utilized?

UG: In the early days of gene therapy, the early 1990s, everyone thought that developing gene therapy for lung diseases such as cystic fibrosis would be easy. Consequently, CF became one of the initial key target indications for gene therapy development. However, over the past 30 years we have learned that gene transfer to the lungs is actually very challenging and despite over 25 clinical trials having been carried out in CF to date, we still don't have an approved CF gene therapy medicine. That is due to the lung having very active defense mechanisms and barriers that have evolved primarily to keep bacteria and viruses out. Unfortunately, these also act against our gene therapy products.

We have learned that most viral vectors are simply not suitable for CF because they cannot be repeatedly administered. We can give one dose but then patients develop immune responses, and subsequent doses are not efficient. And you do need the ability to repeat dose: cystic fibrosis is a lifelong disease, and it would be naïve to assume a single dose can treat a patient for 60–70 years. So, adenoviral and adeno-associated viral (AAV) vectors have been tried for CF, but they are really not suitable because they cannot be repeatedly administered.

We have worked for many years with non-viral formulations. Indeed, we conducted probably the world's largest CF trial where we gave lipid/DNA complexes to patients 12 times over one year, aiming to demonstrate that a non-viral formulation could ameliorate CF lung disease. Although we showed that gene therapy significantly stabilized CF lung disease, the differences in lung function between the active and the placebo were quite modest, and not high enough to allow us to immediately progress into a Phase 3 clinical trial.

In parallel, we have developed a novel lentiviral vector, which is a vector that integrates into the genome of transduced cells. We have shown that this vector supports very long-lasting and stable gene expression in animal models, and very importantly, that it retains efficacy on repeat administration. This lentiviral vector is specifically designed to transduce lung cells, with proteins on the surface of the virus that we know are suitable for uptake of the vector into airway epithelial cells. This is the vector that is moving into clinical trials in collaboration with Boehringer Ingelheim and Oxford Biomedica.

Q Where do you see recent evolution or innovation in clinical trial design for advanced therapies, particularly in the early phases?

UG: It's difficult to talk about recent evolution because for me, it's a continuous gradient. But I think one thing that has been significant, particularly in the UK, is that

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we have very reasonable regulators. I think the UK's MHRA is world-renowned for its proactive interaction with academics, and for their flexibility with regard to clinical trial design. For example, in terms of rare disease clinical trial designs, small patient numbers are now perfectly acceptable to regulators.

> "...people are now very proactively starting to think about large patient registries, which are going to be important for conducting clinical trials in the UK as efficiently as possible..."

There has been a very important recent development in an area that academics have traditionally always complained about: that vector manufacturing costs are too high to be affordable for small-scale, academic-led clinical trials. The UK Medical Research Council (MRC) and LifeArc, with the contribution of the Biotechnology and Biological Sciences Research Council (BBSRC), have listened to our complaints, and recently made £18 million sterling available to fund three vector manufacturing hubs, which are embedded in academic facilities with the specific purpose of making affordable vectors for early-phase, academic-led clinical trials.

Additionally, I think people are now very proactively starting to think about large patient registries, which are going to be important for conducting clinical trials in the UK as efficiently as possible moving forward. And plans for long-term follow-up of patients treated with advanced therapies are progressing very well, too.

Q Clinical development of novel advanced therapies has clearly suffered significant disruption during the COVID-19 pandemic – but are there valuable lessons that the field can take forward to its future benefit?

UG: Vaccines are not advanced therapies, but some COVID vaccines are very similar to gene therapy vectors, and I think what we have seen through the AstraZeneca vaccine as well as the mRNA-based vaccines is that administration of viral vectors and mRNA into the muscle is safe.

Furthermore, through the extensive media coverage of these types of vaccines over the course of the pandemic, the public's acceptance of using modified viruses or nucleic acid-based molecules such as mRNA has greatly increased. I believe this will help us in future when we talk about using modified viral vectors for gene therapy applications.

Those are a couple of positive points to have come out of this pandemic, and another is that the UK has made very significant investments into large-scale manufacturing. I think the gene therapy field will potentially benefit in future both from these facilities themselves, and from the resultant increase in knowhow on how to manufacture adenoviruses and other viral vectors for gene therapy applications.

Q There are lingering concerns about the longer-term repercussions of the pandemic – for instance, how the regulators will view data from interrupted trials moving forward. What is your take on any potential issues in this regard and how they might be approached by all stakeholders?

UG: I am not sure I can answer this question with any great authority, but I would hope that if the involved stakeholders have a degree of flexibility and use common sense, then these problems can be solved.

Funders, for example, are now applying no-cost extensions for grants that have been given out. This has been a relatively easy adaptation – however, I believe that delays cannot always be covered through no-cost extensions, and so there perhaps needs to be a greater willingness to fund extensions to research programs that have been delayed.

One potential problem that I can see for clinical trials as well as for manufacturing of advanced therapeutics is a consumer goods shortage. We and others experienced problems getting not only reagents but also mundane consumables such as gloves and plasticware, because a lot of these materials are used for vaccine manufacturing at the moment.

Q We are still in the relatively early stages post-Brexit, but do you see any resulting evolution in the clinical development environment within the UK as yet? And what might the future hold in this regard?

UG: The challenge for the UK will be to bring industry into the country, or to retain industry interest in conducting pharma-led clinical trials here. I think our flexible regulators will help with that – as I mentioned earlier, they are world-renowned for being approachable and listening to reason.

However, the UK does have a reputation for very slow recruitment into clinical trials compared to other countries. I don't know what this is due to, I must admit – I don't know if it's the hospital infrastructure that needs to be more tightly connected, for example – but it is a sad fact that we are very slow in recruiting for pharma-led clinical trials, which puts us a little on the back foot. This fact combined with a different regulatory environment in the UK compared to Europe post-Brexit could potentially be a problem as we move forward.

"One potential problem that I can see for clinical trials as well as for manufacturing of advanced therapeutics is a consumer goods shortage."

Q Finally, can you outline the chief goals and priorities for your work over the foreseeable future?

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UG: Our immediate goal is to start the first-in-human lentiviral vector-driven gene therapy trial in cystic fibrosis patients.

We are also very actively trying to spin out a company around our non-CF disease indications using the novel lentiviral vector platform that we have developed.

And the third priority is to continue seeking funding for the research that we would like to do in-house here at Imperial College London, in order to keep our academic development pipeline full.

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CELL & GENE THERAPY INSIGHTS

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INTERVIEW

Learning lessons from the long, troubled history of stem cell therapy for future clinical success

JOHN EJ RASKO is an Australian pioneer in the application of adult stem cells and genetic therapy. Since 1999 he has directed the Department of Cell and Molecular Therapies at Royal Prince Alfred Hospital and the Gene and Stem Cell Therapy Program at the Centenary Institute, University of Sydney. John Rasko is a clinical hematologist, pathologist and scientist with an international reputation in gene and stem cell therapy, experimental hematology and molecular biology. In over 200 publications he has contributed to the understanding of stem cells and blood cell development, gene therapy technologies, cancer causation and treatment, human genetic diseases and molecular biology. He serves on Hospital, state and national bodies including Chair of GTTAC, Office of the Gene Technology Regulator – responsible for regulating all genetically-modified organisms in Australia – and immediate past Chair of the Advisory Committee on Biologicals, Therapeutic Goods Administration. Contributions to scientific organizations include co-founding (2000) and past-President (2003–5) of the Australasian Gene & Cell Therapy Society; President (2018–20), President-Elect (2016–18) and Vice President (2008–12) of the International Society for Cell & Gene Therapy; Scientific Advisory Committees and Board member for philanthropic foundations; and several Human Research Ethics Committees. He is a founding Fellow of the Australian Academy of Health and Medical Sciences. In 2018, the Board of the ABC honored him as the sixtieth Boyer Lecturer. He is the recipient of national (RCPA, RACP, ASBMB) and international awards in recognition of his commitment to excellence in medical research, including appointment as an Officer of the Order of Australia.

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Q Your time as President of the International Society for Cell & Gene Therapy (ISCT) came to an end a year ago now - how do you reflect today upon the challenges and achievements for the society and the global cell therapy community as a whole over this period?

JEJR: There has never been a better time to be in the cell and gene therapy space. There are so many new products being approved and, just as importantly, a vibrant pipeline of products in Phase 1, 2, and indeed 3 clinical trials. These include pivotal studies that will likely lead to further approvals, as has been clearly predicted by many of the regulatory agencies in the world, including the US FDA.

So, for someone who is committed to seeing that the field expands and find its rightful role in the therapeutic armamentarium for diverse genetic and acquired human diseases with unmet needs, this is a wonderfully exciting time.

A year has passed since I stepped down from the role of President of the ISCT. We had to make some very tough calls including a rapid pivot to a fully virtual annual meeting in early 2020, which still ended up being a great success financially and academically. Above all, I wanted communication – both inward and outward – to be a feature of my Presidency. We made great strides in enhancing gender equity and mentorship, strengthening our capacity to lead the sector through strategic liaisons and partnerships, re-energizing the Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies and expanding our membership numbers. Today, I can happily reflect on a period of sustained growth for our sector, and the consolidation of the three main pillars of ISCT – namely, academic research, regulation, and commercial aspects. The field of cell and gene therapy has found its stride. It is here now, and we won't be turning back: there's no possibility of seeing a world where cell and gene therapies don't have some role in fighting diseases with unmet need.

Of course, the potential for further growth is enormous, but what is key now is to ensure – still at this relatively early stage – that our field continues to grow in a methodical way. That we control external threats including lax regulatory environments, as well as a worrying appetite for false claims of efficacy and unproven therapies. These attract public attention and essentially divert funds from individuals and their families who want a better medical outcome. This is something that just breaks my heart. We must remain vigilant against these threats.

Q The new book you've co-authored with Carl Power has a provocative title – what prompted you to write about the 'unnatural history and broken promises of stem cells'?

JEJR: When Carl Power and I first set out to write a book on stem cells (Flesh Made New: The Unnatural History and Broken Promise of Stem Cells) we reflected upon the history of the field with the intention of rejoicing in the promises and success of stem cells – achievements that are not insignificant, given that bone marrow transplantation has been around now for over a half a century and has been

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administered to over 1.5 million individuals. Many BMT recipients would not otherwise have had any possibility of finding a cure. That particular foundational discovery, which occurred even before we really understood what stem cells were, is something that stands as a shining light, a Nobel prize-winning beacon for the field, which should continue to inspire us. Nevertheless, even taking other great successes such as the discovery of induced pluripotency into account, when Carl and I looked critically at the history of stem cell research, we concluded that regenerative medicine as a field is replete with the fraudulent claims of those who prey on unsuspecting individuals, and of the vast proliferation of unproven cell therapies worldwide, which today supports a multibillion-dollar industry.

"...there has never been a better time to publish in the area of science and medicine. The public has an enormous appetite for it because they hear about biomedicine every single day..."

In order to see where we are going, we needed to look back and see where we have been. And over the decade it took us to collate the information, we came to realize that there was a vast number of unproven cell therapy clinics worldwide and that they needed to be called out in a methodical way, so that we could raise broad public awareness about the problems and threats in the stem cell therapy field.

The COVID-19 pandemic has ensured that there has never been a better time to publish in the area of science and medicine. The public has an enormous appetite for it because they hear about biomedicine every single day in their news bulletins, through any type of media they care to access. It is impossible for the general public to avoid gaining a greater understanding and familiarity with issues in medicine, which is hugely positive. But COVID has also highlighted the interplay between politics and medicine and although we might claim that medicine is solely driven by empiricism and 'just the facts', the truth is that it has to interact with the reality of a world that has to pay for ever-increasingly expensive medicines. It needs to deal with the cut and thrust of media, diversity, local politics, state politics, and federal politics.

Flesh Made New really should be a fun read but also a shocking wake-up call about where the broken promises of stem cells have occurred. In particular, I am referring to the simple fact that for well over twenty years now, we have been hearing about the possibility of regenerative medicine. And yet I think it would be fair to say that possibility remains a long way off. The prospect of innovations such as growing replacement organs or other body parts, either inside or outside the body, seems as far away today as it was two decades ago.

Q What for you will be the key next steps if the field is to finally fulfill its potential?

JEJR: When I started undertaking clinical gene therapy trials 20 years ago, we imagined that viral mediated gene transfer might be able to cure any of the

thousands of rare diseases with no therapeutic options. Today, of course, one of the biggest problems that confronts systemic gene therapy for inherited monogenic disorders is immunological – something we didn't properly anticipate 20–30 years ago. Back then we thought that it's all just a problem of inefficient gene delivery and once we get the gene in everything will be fixed, because that was the logical conclusion to draw at the time. We have been forced to come to terms with the fact that while AAV is perhaps the most efficient, safe, and proven gene therapy vector on the planet, we can't give it to everyone because of the immune challenges it presents. Similarly, in regenerative medicine, were we really so naïve to believe we were going to be able to reprogram cells and simply wave our magic wand and make them into any cell in the body to repair damaged or diseased organs and tissues? That of course is not a straightforward proposition, and that is where the challenges really lie today for the stem cell therapy field.

The next step will be to do the very, very hard work – just like the bone marrow transplantation pioneer, Don Thomas, did 60 years ago – and deal with the challenges that are here and now, instead of claiming we have overcome them by using cells that, frankly speaking, may not be fit for purpose.

In particular, I'm thinking of mesenchymal stromal cells, which are relatively straightforward conceptually but may not be the fix-all that people originally thought they might be. I think a lot of false claims and unrealized dreams have fallen by the wayside as mesenchymal stromal cells have failed to meet the expectations of scientists, industry, and investors. Don't get me wrong – they do show some promise in assisting some relatively rare diseases – but they have not been a widely applicable 'regenerative medicine'.

Q The rise and rise in significance of exosomes for the cell and gene therapy industry seems inexorable – more hype, or will they have a real impact moving forward?

JEJR: I keep an open mind with regard to exosomes, but as someone who has been working in this field for many years, and who has seen many technologies and approaches become trendy and exciting, I do reserve a significant degree of skepticism. But let's set aside for the purposes of this discussion the very significant challenges of defining the particular size of the exosomes, fractionation, and method of manufacture, and just focus on their promise.

If you reflect on the history of medicine, which I think is so crucial to understanding in general terms where we must go in order to address the unmet needs of our patients, it tells us that we are always looking for the essential active agent in any therapy.

A great example of this idea of a reductionist approach to medicines is the drug digitalis derived from the foxglove plant. Famously, nearly 250 years ago, William Withering treated patients with congestive cardiac failure with this plant and it would improve their condition. And of course, over a long period of time and thanks to the efforts of brilliant biochemists, we learnt that there was an active agent that could be extracted and purified from the foxglove plant, digitalis, which is a drug that we still commonly prescribe today.

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"...one of the biggest problems that confronts systemic gene therapy for inherited monogenic disorders is immunological – something we didn't properly anticipate 20–30 years ago ... The next step will be to do the very, very hard work ... and deal with the challenges that are here and now..."

Time and time again, throughout history, we have detected an activity in a clinical scenario, and then worked to identify and isolate the active agent. Think of quinine, penicillin, rapamycin, opiates, and the vinca alkaloids to name just a few. And today, synthetic biology and advances in chemistry mean we can search vast databases and collections of biologically active materials to find their activities.

Pivoting to exosomes, I see it as a continuum – and to some extent, almost an admission of the failure of mesenchymal stromal cells (MSCs), or vascular fraction cells: in one sense, exosomes arise in the context of MSC's failure to demonstrate efficacy in the majority of the diseases in which they have been tested.

When MSCs first entered broad enthusiasm, the claim was you would inject them into the vein, they would magically home to the site of anything that was wrong, whether it be an inflamed joint, a degenerative cartilage, a broken tendon, a damaged heart, a tumor… The cells would somehow find their way to the diseased site. They would then miraculously convert themselves to exactly that which was necessary to treat the particular ailment, and then regenerate and repair the tissue locally by differentiating to the very tissues that were needed.

Now, it is just nonsense the way I've just described that. But I do believe that was the sales pitch 25 years ago. It was. Let's be honest with ourselves.

Then we discovered that MSCs don't last more than a few days in the peripheral blood. We found we couldn't detect them a week or two after we had injected them. We realized that they didn't seem to be actually regenerating any tissue, or undertaking this miraculous differentiation – so what was it that they were doing? Our next conclusion was that they were homing to the damaged tissues and through paracrine mechanisms, were influencing the local environment of the disease process and acting as anti-inflammatories. They were not actually remaining and regenerating the tissue themselves, but they were influencing the local cells in a way that caused them to regenerate. That became the common theme following the initial pitch for regeneration.

Today, we are at a point where the understanding is that MSCs have systemic immuno-modulatory effects, whether they are pro-immune or anti-immune, which may benefit particular aspects of some particular diseases. I speak as someone who has just published, and featured on the cover of *Nature Medicine*, the first ever *completed* induced pluripotent stem cell-derived

"I'm hopeful that mesenchymal stromal cellswill fulfill a role in medicine – but only when proven by empirical clinical trials ... First and foremost, we need to demonstrate utility and activity."

mesenchymal stromal cell clinical study. I'm hopeful that MSCs will fulfill a role in medicine – but only when proven by empirical clinical trials. We showed the successful use of MSCs derived from iPSCs in the case of steroid-resistant acute graft-versus-host disease. So, it's not as though I'm a complete cynic! But I will say that exosomes seem to me like yet another step in the direction of reductionism, where we are taking perhaps the essence of MSCs and seeing whether or not they have a role.

However, like any rigorous scientist, I want to see where the science takes us. First and foremost, we need to demonstrate utility and activity. The problem with the MSC field is the fact it just hasn't proven itself in diseases consistently in the various large pivotal, randomized, placebo-controlled trials that have taken place over the years. And the *post hoc* analysis and approvals here and there are almost admissions of the failure of the field to reach as broad a church as it would have claimed two decades ago.

If exosomes do prove a level of activity in various diseases, which of course I hope they will, then the next logical question will be 'what's the active ingredient of exosomes?' Is it a combination of factors, such as cytokines, or proteins, or glycoproteins, or lipids? And empirical science certainly has the tools to extract those specific agents - that's what modern medicine is all about, going back to the story of digitalis. So I see exosomes as a step towards potentially finding more active ingredients, and maybe necessary combinations of active ingredients, that have true utility in specific diseases.

The issue here, then, is finding biological activity in a clinically meaningful context, in isolating that activity, and then manufacturing it. But why manufacture exosomes if you can recombinantly produce a series of proteins or lipids or something else, and then combine them and give them to the patient?

The point I'm making in conclusion is that I don't exclude the possibility of combinations of agents being used in the future. Although commercial imperatives and intellectual property necessities often prevent the use of combination therapies, that might be something that regulators and the industry just have to deal with. I certainly don't think that simply because I'm personally a firm believer in empiricism and reductionism, which has served us so well over centuries in medicine, that one day we won't come back to the approach of combining of small amounts of drugs that may have a greater benefit in combination than do the single agents by themselves. The idea of 'holistic medicine' is something that resonates with most people.

Q You have touched already on the issue of unregulated stem cell clinics. Do you feel the field has enjoyed any real success in

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countering them as yet? If so, where; if not, why – and is the issue becoming more or less significant as time passes?

JEJR: The issue has not gone away at all - it remains significant as it has been for at least the decade that I've personally been very active in calling out unproven cell therapies. However, while I think that the problem is becoming more significant in some areas, it has been addressed fairly and responsibly by regulators in another sense. Let's talk about the successes first.

Many of us have reflected on the proliferation of direct-to-consumer marketing of so-called stem cells. We published a paper in *Cell Stem Cell* on that very topic a number of years ago, which called out and highlighted the fact that internationally, in almost every country we were able to analyze, there were direct-to-consumer clinics offering unproven cell-based therapeutics. These were usually adipose-derived vascular stromal fraction or mesenchymal stromal-type cells with varying degrees of purity, frequency of administration, and dosage - usually manufactured at the patient's bedside.

It was really a game of 'whack-a-mole'. You would call out a particular clinic for making false claims and that clinic would disappear momentarily, but only to reappear under a different name or in a different location shortly afterwards (often at another clinic literally a couple of blocks away). And the proliferation of those clinics was extraordinary. Make no mistake, it was supply driven by demand. The public was crying out for these simple fix-alls they thought might make a difference, even though they were unproven and not regulated properly.

It took many, many years of direct lobbying to the regulatory jurisdictions worldwide, including in Australia and the US, because regulators had real challenges in overcoming the legal loopholes. But I am very glad to say that overcome them they have, to a large extent. Today, the US FDA, the TGA in Australia, and those other regulatory bodies around the world that have paid serious attention to these unproven clinics have sought to shut them down. Shonky stem cell clinics are no longer able to function because of the tightening of regulatory requirements in many countries.

In terms of our failures and the growth of this area of unproven cell therapy, I think part of the problem is that some otherwise distinguished or responsible academic and industry operators have become much more savvy and able to navigate the regulatory pathways. This has reached a point where some have really started to extend beyond what is acceptable ethical behavior. In particular, I am talking about pay-to-participate clinical trials for certain childhood diseases, where the data is unconvincing at best. And yet families, whether through guilt or through desperation, are paying tens of thousands of dollars to avail themselves of unproven therapies because there is nothing else available.

One of the hardest things that any physician ever has to do is to advise a family there is no current therapy or cure available. And yet that level of honest messaging is unacceptable to some families who will then do anything they can to take matters into their own hands, because they believe – and because they've been led to believe – there are therapies. Its false hope. I don't wish to deny anyone the right to try or to appear paternalistic. However, I do feel a duty to call out medical claims that are unsupported by evidence and can present major financial burdens on patients and their families.

This area concerns me deeply and it is an even harder challenge for the regulators to deal with in an independent and consistent way. I think their job has become even more difficult because of the subtlety of the way some of these unproven cell therapies are being marketed. But deal with it they must.

Q Is the gap between academia and industry widening or narrowing at the present time, for you, and with what impact on the stem cell therapy field in particular?

JEJR: I don't think the gap between academia and industry is widening, I simply think that their roles are becoming better defined.

Decades ago, there was an assumption that if you went from academia into industry, it was a one-way street – you were crossing a point of no return. That's not to say it was a negative thing, it was simply a reality of going into industry and moving away from the need to maintain a publication track record and academic credentials in the grind of academia. But that has changed completely in my opinion. Today, it is very much a revolving door between the two.

For a physician-scientist like myself working in the government health sector, that represents a wonderful opportunity. I can take advantage of working in the basic laboratory and having translational projects covering all aspects of biomedical research. Ultimately, I can't think of a viable alternative to the proposition that industry is the essential destination for any therapy to achieve wide applicability for the benefit of human health. So I work with pharma in a very productive and symbiotic relationship.

It's all very well to manufacture something in one's own academic GMP facility and show proof of principle, but at some pivotal point, value must be added, the necessary infrastructure put in place, and the complex regulatory and market access requirements for getting a drug to market met. And all of those things are best done by industry – I'm a firm believer in that. So, to that extent, I think the separation between academia and industry is perhaps clearer.

I believe there is currently an appetite to greatly increase the connectivity between academia and industry, and I certainly embrace that possibility. I think the solution there is to have a more savvy middle-management in academia that is capable of clearly identifying when spin-outs need to be created.

"...there is currently an appetite to greatly increase the connectivity between academia and industry, and I certainly embrace that possibility."

There is a vast ocean of academic creativity, and those of us in universities and research institutes have the opportunity - the luxury, in fact – to be able to think deeply about issues and explore possibilities. Many of these explorations into the 'what if' will fail – I've had thousands of great ideas, few of which have reached the exhilaration of fruition! But you generally don't have that indulgence in industry.

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However, as an idea does reach fruition, the money gets bigger and financial risk is greatly increased, and then to my mind, industry and commercial pathways are the only way to go. The question is, when does that pivot occur? Early spinning out, with proper incentives and safe protection of intellectual property, is to me a win-win.

I can't emphasize enough that we as a whole community have to have a vibrant, continuous pipeline of basic discovery, married with the bench-to-bedside-and-back philosophy that I think most of us embrace.

Q What are the key trends you see in the evolving regulation of cell and gene therapy products, both with the TGA in Australia and around the globe?

JEJR: I keep a very careful eye on this area and I've published widely on various aspects of regulation, in particular the unproven cell therapy field. However, I want to expand here on aspects of political influence and its impact on regulation, which I find deeply concerning.

Ultimately, I don't think that we can have any higher gold standard for medicinal products and devices than when approval is granted by a government regulator. To me, it's one thing for someone to claim that their clinical trial is showing promise, or it's a good idea, or say "hey look, we've published it in a great journal and that's evidence it's really good". But it's another thing to get past the hard-nosed, critical review by public-sector regulators who are charged with the greatest responsibility: making certain that efficacy and safety are assured to protect the public they serve. It's about vested interests - governments and regulators are there to serve the public, to the best of my understanding; everyone else must have a degree of self-interest, otherwise they wouldn't be successful.

In Australia, the seriousness of this responsibility takes on an even greater dimension, because our social welfare system means that all drugs that are approved by the federal government are paid for by the federal government, in partnership with the States. So, it means that whenever a drug is approved by the TGA in Australia, the taxpayer foots the bill. I know that sounds amazing to people in other parts of the world, such as the US, but if you're a citizen in Australia and you need for example a bone marrow transplant or CAR-T cells, you shouldn't be out of pocket whether you are employed or not. If a baby needs a multimillion-dollar treatment for spinal muscular atrophy, that multimillion dollar treatment is free to citizens of Australia. The point is that the responsibility of approving drugs so that they are efficacious, safe, *and* cost-effective is an enormous one. And that's where I see regulators today needing to deal with issues that may not have been as apparent or confronting in previous times. Marry this with the active lobbying of families and individuals to speak directly to politicians with compelling arguments for approval of ever-increasingly expensive therapies. These issues present real challenges for federal regulators who are required to balance politics and empirical evidence of safety and efficacy.

All of these factors mean that regulators need to be empowered. They need to be given the authority and strength that allows their aggressive independence, so that political factors are minimized when they are making their decisions.

Q What are your key priorities and goals for your work over the foreseeable future?

JEJR: I am thrilled by the fact that Australia has approved commercial CAR T cell therapies, and that ours is one of only two centers in Australia that have been approved to do the commercial rollout in adults. We've already treated a few dozen patients with lymphoma and leukemia. This is a field which is expanding dramatically and influencing the cell and gene therapy sector, because it is driving so much of the excitement in our field.

I would not have imagined 20 years ago that CAR T cell therapies would have been one of the most successful cell and gene therapies in the world, and we owe an enormous debt to those who discovered and developed these therapies because they have been life-changing in a number of diseases. In particular, response rates of above 80% in acute lymphoblastic leukemia are just enthralling. It is so exciting to see this dramatic change.

Of course, at least until there is stronger market competition, these are very expensive therapies. They are also quite demanding in terms of their toxicities. This places demands on other areas of the hospital such as the intensive care unit, hematologists, neurologists, pharmacists, nursing and allied health, and all of the other rehab doctors, to name but a few. But we hope that cell-based immune therapies, like CAR T cells and others, will expand dramatically beyond the hematological malignancies to solid tumors. And as anyone reading *Cell & Gene Therapy Insights* would know, there are hundreds of companies now devoted to trying to achieve that particular dream, as well as the obvious trajectory of making these products off-the-shelf rather than bespoke from every patient's own cells. Ultimately, hopefully in 2–3 decades' time, we'll be looking back and thinking about the history of CAR T cells. Maybe we will be able to reflect that autologous cells were just a stepping stone – a proof of principle that led to off-the-shelf technologies, possibly with gene editing involved, perhaps made with iPSC-derived cells or other allogeneic cells.

That's one key trajectory for the field, and for me personally. For example, our group is undertaking a vibrant and active industry collaboration, as well as an academic initiative, in CAR T cells for pancreatic cancer, which we have been working on for a number of years. That is something that I'm extremely excited about – not least because partnering with industry presents an exciting opportunity to be able to take advantage of a flexible infrastructure that isn't often available to us.

Regarding gene therapy, where I have spent most of my career, I can't help but think there is an incredible future ahead for the field. I simply reflect on the fact that there are thousands of rare diseases with unmet needs – there are perhaps 400 million people on the planet who suffer from rare diseases, and only 5% of them have any therapy at all available to them. The majority can only be managed symptomatically at best – there is no direct therapy. I've worked in the hemophilia gene therapy space for over two decades now, and today I can see – based upon a number of pivotal clinical trials that are currently underway – it is almost inevitable that gene therapy approvals for hemophilia will occur in the not-too-distant future. And we already have miraculous - and I don't use that world regularly – gene therapies for blindness and spinal muscular atrophy. Those two treatments in particular are life-changing for the individuals who

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have received them. When I lecture my medical students, I often remark 'if you had told me 20 years ago that gene therapy would be able to cure blindness, in the case of retinitis pigmentosa, I would have thought you were dreaming' – that it would be impossible to reverse blindness. And yet, here it is – an approved, available therapy. I think one need look no further than that particular example for gene therapy's proof of principle. And that's without mentioning the *ex vivo* gene therapy successes in an expanding range of diseases such as beta thalassemia and X-linked severe combined immunodeficiency (X-SCID).

So, gene therapy is here and now. It's a matter of consolidating and expanding the field as early career professionals take for granted this new set of clinical opportunities. I'm looking forward to us as a community delivering the goals of cell and gene therapy that were set out decades ago, but are now actually being realized in the clinic, changing lives for the better.

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CELL & GENE THERAPY INSIGHTS

CLINICAL TRIAL DESIGN, SUPPLY CHAIN & OPERATIONS

SPOTLIGHT

INTERVIEW

Challenges in the gene therapy of bone marrow failure syndromes

JUAN BUEREN is the Head of the Division of Hematopoietic Innovative Therapies of CIEMAT and CIBER of Rare Diseases. Dr Bueren is also Coordinator of the Mixed Unit of Advanced Therapies CIEMAT/IIS-Jiménez Díaz Foundation and consultant of Rocket Pharmaceuticals Inc, and currently serves as Vice-President of the European Society for Cell and Gene Therapy. Dr Bueren is Scientific Director of gene therapy trials for patients with Fanconi anemia and also for patients with the primary immunodeficiency, leukocyte adhesion deficiency type I, and has participated in the development of therapeutic lentiviral vectors designed as Orphan Drugs by the European Medicines Agency and by the FDA for these two diseases. Both ODs have been licensed to Rocket Pharmaceuticals which is currently developing different global gene therapy programs in Europe and in the USA for Fanconi anemia and LAD-I.

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Q In the context of gene therapy, what distinguishes inherited bone marrow failure syndromes (IBMFS) from other inherited diseases affecting blood cells?

"...only in the case of Fanconi anemia has it been possible to demonstrate that genetic correction results in proliferative advantage of HSCs in humans."

JB: First of all it should be noted that in contrast to the mature cells that circulate in peripheral blood, hematopoietic stem cells (HSCs) constitute a very small population of cells that reside in bone marrow, and which constitute the basis for the generation of all types of blood cells. These are the only ones with self-renewal and multipotential ability to generate all different blood cell types.

As opposed to other monogenic diseases (e.g., hemoglobinopathies or primary immunodeficiencies) in which the genetic defect mainly affects committed progenitors or mature blood cells, in the case of IBMFS such as Fanconi anemia (FA) or dyskeratosis congenita (DC) the HSCs are already affected by the disease. Consequently, the main challenge for the gene therapy of these IBMFS is that the gene therapy target is a cell population that can be severely affected by the disease.

Q In practical terms, what are the direct implications for developing gene therapies in patients with IBMFS?

JB: One of the first implications can be derived from the fact that the number of HSCs present in the bone marrow of diseases such as FA can be very low. Given that HSC numbers from these patients progressively decrease with age, it is recommended that collections of HSCs be performed in early stages of the disease. By doing so, the possibilities of collecting clinically relevant numbers of HSCs – and presumably with a healthier status – increase. Also of significance is that based on the content of HSCs in the bone marrow of these patients, it is possible to predict which patients will provide sufficient numbers of HSCs for gene therapy purposes [1].

Despite the limited content of HSCs in FA patients, we have also observed in experimental models that corrected FA HSCs develop a proliferation advantage when transplanted into immunodeficient mice [2]. These observations allowed us to presume that the infusion of autologous corrected HSCs might engraft in FA patients, even in the absence of any pre-conditioning regimen. These treatments are conventionally given prior to allogeneic transplantation, and also prior to most of the current gene therapy protocols to facilitate the engraftment of corrected HSCs.

In a recent clinical study we had the opportunity to demonstrate that this hypothesis was true, since we could observe in the first four FA patients infused with corrected autologous HSCs an evident engraftment in all hematopoietic cell lineages. Furthermore, a clear correction of the characteristic defects of FA cells, such as hypersensitivity to DNA damaging agents, was taking place in all these patients [3].

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Q Finally, do you think that the findings observed in current FA gene therapy trials will be applicable to other IBMFS?

JB: It is still too early to affirm this. In fact, only in the case of FA has it been possible to demonstrate that genetic correction results in proliferative advantage of HSCs in humans. Also of significance is the fact that not all IBMFS are associated with similar damage at the HSC level. While FA and DC are certainly syndromes in which the HSCs are progressively damaged, in other syndromes such as Diamond Blackfan anemia it is believed that this damage is less severe, at least in cells of the HSC compartment.

Therefore, to define the most appropriate gene therapy protocol to be used in the different IBMFS, detailed studies will be required to evaluate the level of HSC damage in each of these syndromes, and also whether the correction of the genetic defect will confer proliferative HSC advantage over uncorrected populations.

Certainly, the next few years will clarify these uncertainties, and new expectations for patients with IBMFS will appear based on the development of novel gene therapies that hopefully will result in more efficient and less toxic treatments compared to current therapies based on allogeneic HSC transplantation.

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CELL & GENE THERAPY INSIGHTS

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SPOTLIGHT

INTERVIEW

Strengthening the clinical supply chain for individualized therapies

ANDY CASE is a Supply Chain and Supply Chain Technology professional in the Bio-Pharmaceutical space. He is a subject matter expert in Chain of Identity and Chain of Custody for individualized cell therapies and the orchestration platforms designed to control COI/COC and supply chain activities for these therapies. Andy worked for four years at Novartis as Sr. Director of Supply Chain Technology and as a member of the team that launched Kymriah as the System Owner for CellChain the orchestration platform established by Novartis for its Cell and Gene therapies business. He is currently Head of Clinic Supply Chain, Individualized Therapies at Genentech/Roche where he is establishing supply chain capabilities for a portfolio of individualized therapies in clinical development. Andy has a BS in Civil Engineering from Texas A&M University and an MBA from IMD in Lausanne, Switzerland.

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Q What are you working on right now?

JAC: Genentech-Roche has a portfolio of individualized therapies in fairly early-stage clinical development. As the head of supply chain for these therapies, I am working on developing the capabilities for supporting them.

We have an individualized neoantigen-based therapy that is an mRNA cancer vaccine. It is manufactured individually for each patient based on a genetic sequencing of the tumor cells from their cancer. This is in active clinical trials, so we have an established supply chain organization to support that. We are now building additional capabilities to support a broader portfolio of similar products.

We have two different neoantigen-based cancer vaccine products, the mRNA-based therapy that is part of a joint venture with BioNTech in Germany, and one is DNA-based. We also have a pre-clinical T cell therapy program in partnership with Adaptive Biotechnologies.

Q Is there any more background you can give us on the cellular immunotherapy prospect?

JAC: From my point of view, the key is to build the necessary capabilities to manage these therapies going out to treatment centers around the world.

The supply chain challenges of doing this starts with having a very robust chain of identity. Maintaining identity, and maintaining a record of the chain of custody throughout all the different handoffs in the supply chain, is the core thing we need to develop. This is essential to protect the safety of our patients.

The main capabilities we are focused on building right now are the orchestration platform for managing the end-to-end process, establishing the business processes, quality systems, tissue operations, change management, etc., and of course the team to support those processes.

Q You were involved in Kymriah's supply chain during its clinical development and commercial launch - what are the key lessons from that experience that you have taken forward to your current work at Genentech-Roche?

JAC: That journey involved going from a Phase III registrational trial, through the pre-approval inspection of the main manufacturing site, and then to the commercial launch for the first ever CAR-T therapy, which was followed very rapidly by an additional commercial indication in the US. All of that was in turn followed very rapidly by a pivot to launching both of those commercial indications in Europe, and simultaneously in Japan, Canada and Australia.

There were a lot of lessons learned. A key one was that we needed better alignment between the timing of applying for a Biological License Approval and establishing the capabilities needed to support the commercial launches. In other words, the application for commercial approval from a regulatory standpoint, was not always well synchronized with establishing the capabilities and scale needed to support all of these commercial launches when health authority approval was granted. Although it is important to note that those commercial launches were being granted rapidly, so everything was moving very, very quickly.

Another key lesson came from the fact that initially, we built systems from the standpoint of needing to have very tight control over these products, especially in terms of chain of identity.

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"When you design all of your business processes and your orchestration system to prevent things like shipping out-of-spec material back to a patient, it requires you to develop a lot of flexibility into the system that you hadn't anticipated when you designed the system in the first place."

You have to have tight control of transporting the cells through a very complicated supply chain, at cryopreservation temperatures in the specialized shipping containers designed for these conditions. You may have to get it to multiple manufacturing sites, depending on where the patient's cells are originating from and where the capacity is available for the manufacturing.

You create what you think are the right processes to manage this product in a regulatory environment, in a proper GMP way. But then, you learn that individualized cell therapies inherently have a lot of uncertainty around them. There were manufacturing issues and there were processes that we have since learned were a little too tightly controlled. Especially early on, we had manufacturing challenges where we would have successful manufacturing of a drug product that would treat the patient, but it didn't meet the specifications necessary to release it as a commercial product. However, we still had a product for a patient who had no other resort, so we had to work with the health authorities and the treating physicians to develop the necessary process to permit the physician to treat these patients with out-of-spec material.

When you design all of your business processes and your orchestration system to prevent things like shipping out-of-spec material back to a patient, it requires you to develop a lot of flexibility into the system that you hadn't anticipated when you designed the system in the first place. Creating the mechanism to easily convert a therapy from a commercial product to a single-use IND that would allow you to treat the patient safely and legally was extremely complicated to set up and manage.

Q What would you identify as the key challenges in clinical supply chain for personalized cellular immunotherapies today, and what can you tell us about your approach to addressing them?

JAC: There are a lot of ways I could answer that question! One of the key challenges, and one of the things we are trying to focus on at Genentech-Roche, is that there is not a lot of standardization in the industry right now.

By standardization, I mean things like how you qualify the treatment centers for providing the cells we need to do the manufacturing, standardization with labelling, standardization with

the biopsy tissue and apheresis collections that we require, and standardization in how the tissue or CAR T product is cryopreserved. We are dealing with a very large number of treatment centers - I believe Novartis is now aligned with well over 250 treatment centers, maybe approaching as many as 300. At Genentech, we have nearly 100 treatment centers involved in our iNeST product clinical trials. When we launch the T cell therapy, it will be a phase I trial with up to 50 treatment centers.

You are dealing with constituencies that essentially have to be set up in your system as a vendor, because you are acquiring from them the cells that are the key starting material to make the drug product, but then they are also your customer because you are returning that product to them to treat the patient. Standardization simplifies the process in terms of making sure you can identify the cells properly, making sure the quality of the cells that you are getting is suitable for the manufacturing process, and making sure that the type of biopsy you get, in the case of an iNeST product, is sufficient to do the genetic sequencing needed, which defines the drug product that gets manufactured.

Standardizing all of those things will improve efficiency, improve manufacturing success, and it will improve the time it takes for us to do the manufacturing and return the therapy to the patient. We need to build standardization into the process in terms of how the treatment centers operate, how we interface with the treatment centers, how we label products, and so forth. There is a lot of room there to improve the industry, which is of course an extremely immature industry that is really just emerging. This will be an area of focus we will have going forward over the next few years – to try and implement, on an industry level, a lot of standardization where it is appropriate.

Q How are you mitigating that additional risk presented by the current COVID-19 pandemic?

JAC: It is certainly a big thing to add on top of something that is already a challenge.

It is also something that wasn't very temporary. I think everyone was a bit naïve back in March 2020, more than a year ago, when we thought that in a month, we would be past this and then it would be back to business as usual. But here we are, over a year later. This is not a volcanic eruption in Iceland that shut down air travel for 10 days, this is more than 18 months of disruption.

> "We need to build standardization into the process in terms of how the treatment centers operate, how we interface with the treatment centers, how we label products, and so forth."

There are so many challenges that the COVID pandemic has brought. It has limited the number of flights, and of course, everything we do is through air transport. We have had to adapt to reduced airfreight capacity sometimes having to wait for space to become available.

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We have also started to see delays in customs and FDA approvals of incoming materials from outside of the US, which we kind of chalk up to the fact that they are inundated with doing approvals of COVID vaccines coming in. These regulatory agencies are simply overburdened with the current workload.

> "At the very core, we have to have a system that has literally zero chance for failure."

We are also seeing a number of supply issues for what we would consider very mundane materials, like vials, vial caps, sterile gloves and certain raw materials that are in demand because of the massive amount of manufacturing that is going on to create the vaccines. All of those things are causing disruptions that we have to try to adapt to, and be flexible to accommodate.

There are a variety of things that hit you as you work through the problems you have. You see a commonality that all points back to the fact that a year ago, or even six months ago, nobody was manufacturing these vaccines. But now, getting these massive quantities of products manufactured and transported around the world is the meaning of life, literally the meaning of life, for a large part of the industry.

Q How have supply chain technologies evolved to support autologous cellular immunotherapies over recent years - firstly, what have been the most significant advances, for you?

JAC: As I mentioned, the core of this product is that the patient is the raw material.

In the case of a T cell therapy, we are taking their T cells, doing a genetic modification to those cells, expanding them and returning those modified cells back to the patient. If we make a mistake with that, then the Host vs. Graft disease reaction that will occur if you infuse foreign T cells into a patient creates a high mortality risk.

In the case of cancer vaccines, the immediate reaction would not be dangerous, but if we had a switched sample on the way to the genomics sequencing lab, and then we sequence someone else's tumor sample, we will manufacture a vaccine that will have absolutely no efficacy for that patient. I would suggest that the impact to the patient is nearly as bad as infusing them with foreign T cells – it is not an immediate reaction, but it means you are infusing them with a cancer vaccine that has no chance whatsoever of having any efficacy.

At the very core, we have to have a system that has literally zero chance for failure. Being able to create a system that supports a complex process of moving products in cold storage from hundreds of treatment centers to multiple manufacturing centers. Sometimes it is through a daisy chain of manufacturing centers – going from a sequencing lab, to manufacturing a plasmid which is custom-made specifically for that sequence, then transporting that plasmid to a drug product manufacturing setting, then sometimes having to transport the drug product to

a separate fill-finish contract manufacturer, then getting that product back to the treatment center and to that specific patient. It is of course a very complex process.

We have to do this in such a way that we can show we have maintained the identity throughout the entire process - in a way that we can validate the custody of that product every single time it is handed off from one service provider to the next, or from one manufacturer to a service provider, and back to the treatment center. Therefore, the key capability we are working on is an orchestration platform that will support that entire business process. It will also orchestrate all the internal processes that we have to undertake: sequence, manufacture, test, package, release and ship back to the treatment center in a way that we can again demonstrate the full end-to-end chains of identity and custody.

Q Are there any shortfalls in current innovation in allowing you to do that? What could be improved from the technology provider side?

JAC: Going back to the standardization question, one of the key messages we get from the treatment centers – who as I said, are both vendor and our customer at the same time – is this is a very rapidly growing industry with a lot of players participating, especially at the early-stage development level. And if it is not a typical 80/20 rule, I would strongly suspect it is close to it: I haven't done the math on this, but I would bet a significant amount of money that 20% of the key treatment centers around the world are serving probably close to 80% of the patients for which there therapies are targeted. That means a relatively small population of teaching hospitals and large oncology centers are being inundated with any number of Bio-pharma manufacturers that have any number of these types of therapies. They all come to the table with an orchestration system, quality processes, and cell collection or cell cryopreservation processes. The treatment centers are struggling to deal with these interfaces and with all these different companies.

It is very difficult for our partners to manage this. I think that over the mid-term, the industry has to come to some kind of agreement on our collective approach to things like the quality systems we put in place, the audits that we do, and how we are qualifying a cell lab at a treatment center or the qualification of the apheresis center for collecting the T cells, for example.

It is probably relatively intuitive to assume that if a treatment center can collect cells for Kite Pharma, then there is no reason why they can't collect cells for Genentech. But if Genentech goes into that treatment center, we are probably going to show up at the door with our own quality system and they are going to have to go through that and be approved by us. This is a near-sighted approach that we need to address, because it is not just us as the door - it is 50 other manufacturers or more, all with the same type of approach.

The industry is recognizing this but of course, it is going to move slowly. The industry needs to agree on a certain way of doing things that 1). protects the patients, but 2). also makes it as easy and seamless as possible to deal with all these different manufacturers that are bringing these very exciting therapies forward.

Q Lastly, can you sum up your chief goals and priorities in your role for the foreseeable future?

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JAC: My chief goal is to get us, as a company, ready to support these products and establish the capabilities to do that. This is both in terms of launching clinical trials that will prove the products' safety and efficacy and moving through the clinical development phase to a registrational trial and hopefully, a commercial approval beyond. Each of the products has certain requirements or nuances that are different, so we need to put systems in place that are adaptable, flexible, and scalable enough to support those products we develop ourselves, as well as any we might acquire and move into our portfolio. Over the next two to three years, my goal is to stand up these capabilities to support whatever products we end up trying to bring to the market.

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CELL & GENE THERAPY INSIGHTS

CLINICAL TRIAL DESIGN, SUPPLY CHAIN & OPERATIONS

SPOTLIGHT

INTERVIEW

Addressing issues in clinical development of AAV-driven gene therapy

SABAH SALLAH, MD, PhD, current position: Senior Vice President of Gene Therapy, Translational Medicine and Hematology at Freeline Therapeutics, Boston, MA, USA. He is board certified in Internal Medicine, Hematology and Oncology and has published approximately 100 peer-reviewed papers, chapters and books.

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Q What are your working on right now?

SS: My role spans multiple functions, with the main focus being on identifying new indications for liver-directed gene therapy. I'm also involved in evaluating new constructs, and linking research and preclinical studies with the clinical activities in terms of the suitability of animal models, the types of biomarkers to be used, and the end points required.

There is heavy emphasis in my work on better appreciation of the humoral and cellular responses against the capsid, and how we can address their impact in the context of gene therapy trials.

Q Can you give us some more details of Freeline Therapeutics' R&D pipeline?

SS: Our lead candidates are in hemophilia B and in lysosomal storage disorders – Fabry disease and Gaucher disease, more specifically.

Further upstream, Freeline is making really significant progress when it comes to protein engineering, and identifying new variants with high specific activity versus the wild-type transgene.

In addition, there is ongoing effort for deeper understanding of the biology of AAV vectors, which certainly will enhance our knowledge of the behavior of the vector following gene delivery. We believe this will subsequently lead to better designs for our clinical studies.

Q It has been a challenging period for gene therapy clinical developers for a number of reasons – firstly, regarding the COVID-19 pandemic, in what specific areas has the impact of the pandemic been most keenly felt, and how have you sought to minimize the disruption for Freeline's clinical-stage product candidates as far as possible?

SS: It has really been uncharted territory for the drug development field in general. I think a lot of us face the same challenges, although on the whole, I think it has perhaps been more difficult for some clinical development programs outside of gene therapy – in oncology with the use of chemotherapeutic agents, for example – than for gene therapy itself.

The challenges range from obtaining consent to recruiting patients, and from visiting trial sites to facing operational issues. But in particular, in the midst of the pandemic, our number one focus was and still is on maintaining patient safety. With that in mind, Freeline has adhered strictly to the guidance issued by the regulatory authorities concerning the conduct of clinical trials and investigational therapies during the COVID-19 pandemic.

Q The full impact of interruptions to clinical trials during the pandemic is perhaps yet to be felt by drug developers in general – what can gene therapy developers do to prepare for regulators' scrutiny and future requirements in this regard?

SS: Absolutely, the full impact is still unknown, but it has certainly become really important to rethink the way we operate in terms of clinical trial conduct, and to try to adapt accordingly. There has been a renewed emphasis on remote training of everyone involved in the conduct of a clinical trial, including investigational sites, trial managers, patients, and investigators, to mention a few.

In terms of the regulators, obviously, regulatory standards have tightened overall for gene therapy. Consequently, it has become particularly important to have early and open dialogue

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"...regulatory standards have tightened overall for gene therapy. Consequently, it has become particularly important to have early and open dialogue with the regulators so that we can better design and structure our clinical studies, and to understand the impact of certain end points or biomarkers on a clinical trial's success or failure."

with the regulators so that we can better design and structure our clinical studies, and to understand the impact of certain end points or biomarkers on a clinical trial's success or failure. I see this type of interaction as becoming more and more important.

Q Where for you is the 'silver lining' from the COVID-19 experience, and how do you plan to capitalize upon it moving forward?

SS: I think if there is an upside, it's probably having the opportunity to think over our overall strategy. Gene therapy is a very specific field and it is still evolving – taking manufacturing as an example, it's different from other biologics in that we get low manufacturing yields, low production volumes and that puts significant stress on all gene therapy companies, but on small biotechs in particular.

I would also reiterate that the pandemic has taught us the value of remote monitoring and interaction – for instance, replacing some of the physical visits to the patient with having a recorded diary, or interactions via video-conferencing or other methods of communication.

In my view, these are some of the important issues that we need to emphasize as a field moving forward.

Q Turning to the AAV gene therapy field in particular, it's been a bit of an up and down year or two in terms of clinical progress. What for you are key areas of focus for the field as a whole to ensure its promise as an area can be fully realized for patients moving forward?

SS: It has certainly been up and down, but I would say that the initial outcomes from gene and cell therapies have been really encouraging overall, especially in certain incurable diseases. Having said that, I think there is a spectrum of activity that goes from manufacturing through to administration and monitoring of the gene therapy that we really need to work on.

"It is increasingly important to investigate what could constitute appropriate immune management for a cellular capsid response. That becomes a function of Phase 1/2 studies."

As I mentioned, gene therapy differs from other types of biological treatment. Scaling-up platforms is becoming a real necessity but in line with this scale-up of manufacturing, we also need to work on the analytical studies, with a view to maintaining the speed of manufacturing.

In addition, there are several challenges in terms of the immune system response to gene therapeutics, which amplify the importance of designing novel capsids that can evade the immune system. If you think about it, overall, 50% of the patients who could be eligible for gene therapy are currently ineligible because of the presence of pre-existing neutralizing antibodies. So, the mechanism of immune response against the capsid, whether it's cellular response or humoral response, becomes a vital area for investigation – not only to allow more patients to be eligible for gene therapy studies, but to better address issues concerning the management of the immune response after the patients have received gene therapy.

For me, it's really a continuum, a spectrum of challenges that we need to work on in the AAV-driven gene therapy field. But I think we are getting there.

Q How and where is competition for patients in key indications driving innovation in patient recruitment within the cell and gene therapy space – particularly in the rare disease arena?

SS: There is a major focus across the field at the moment on how to effectively characterize the vector production process – for example, in the past year or so, a number of programs have suffered delays because of the FDA's requirement for better characterization of gene therapy products. In the long-term, this might impact patient recruitment and retention.

I think a further important issue is biomarker identification. In gene therapy, we often don't have a secreted protein or measurable transgene available as a marker to monitor the success of transduction and subsequently, the outcome of gene delivery. So, we will have really to be more creative in investigating surrogate markers, which could potentially evolve or be translated into evaluable or appreciable clinical end points. Again, working with the regulators early on in the process to ensure a successful clinical trial design is of paramount importance, and this is especially the case with rare diseases.

Q Where do you see meaningful innovation in the way of clinical trial design and strategy in the gene therapy field today, particularly in early-phase development?

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SS: I believe that for the next few years at least, we will basically rely on the traditional or conventional clinical Phase 1/2/3 model in order to address safety and to define the appropriate dose level of gene therapy.

It is increasingly important to investigate what could constitute appropriate immune management for a cellular capsid response. That becomes a function of Phase 1/2 studies. This and the confirmation of the appropriate vector dose might require a better understanding in the context of a subsequent Phase 2b trial – it really all depends on the size, design, and outcome of the initial Phase 1/2 trial. But ultimately, we will still need a pivotal trial for a complete and hopefully successful gene therapy program.

So for the time being, I think that clinical trial strategy and design will not change fundamentally. However, in future years, I do expect to see some changes coming in, particularly relating to the investigation of gene therapy in pediatric patient populations.

Q Freeline is active on both sides of the Atlantic – are there any particular areas of convergence or divergence between US and European advanced therapy guidelines that you see as being particularly significant at the moment for clinical development?

SS: I would say that overall, there is good alignment between the US FDA and European EMA. There are some differences in terms of the requirements for what should be included in the preclinical package, for example, and perhaps also on the biomarkers side. But again, it's an evolving area and considering this fact, regulators across countries and continents are pretty well aligned, which of course is benefiting the field.

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CELL & GENE THERAPY INSIGHTS

LATEST ARTICLES:

CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

Preparing for pivotal: solving challenges in scale for cell and gene therapy clinical trials

Subbu Viswanathan, Rich Gaeto, Erin Goodhue Meyer, Chris Greenberg & Jim Wise

Advanced therapies – such as cell therapies, gene therapies, and personalized cancer vaccines – emerge from uniquely advanced science. The clinical studies behind these therapeutics are some of the most complex in the history of medicine, and must overcome the operational challenges inherent in their patient-centric paradigm. In addition, the transformative nature of these treatments means that a promising early result often leads to accelerated status and pressure to scale rapidly.

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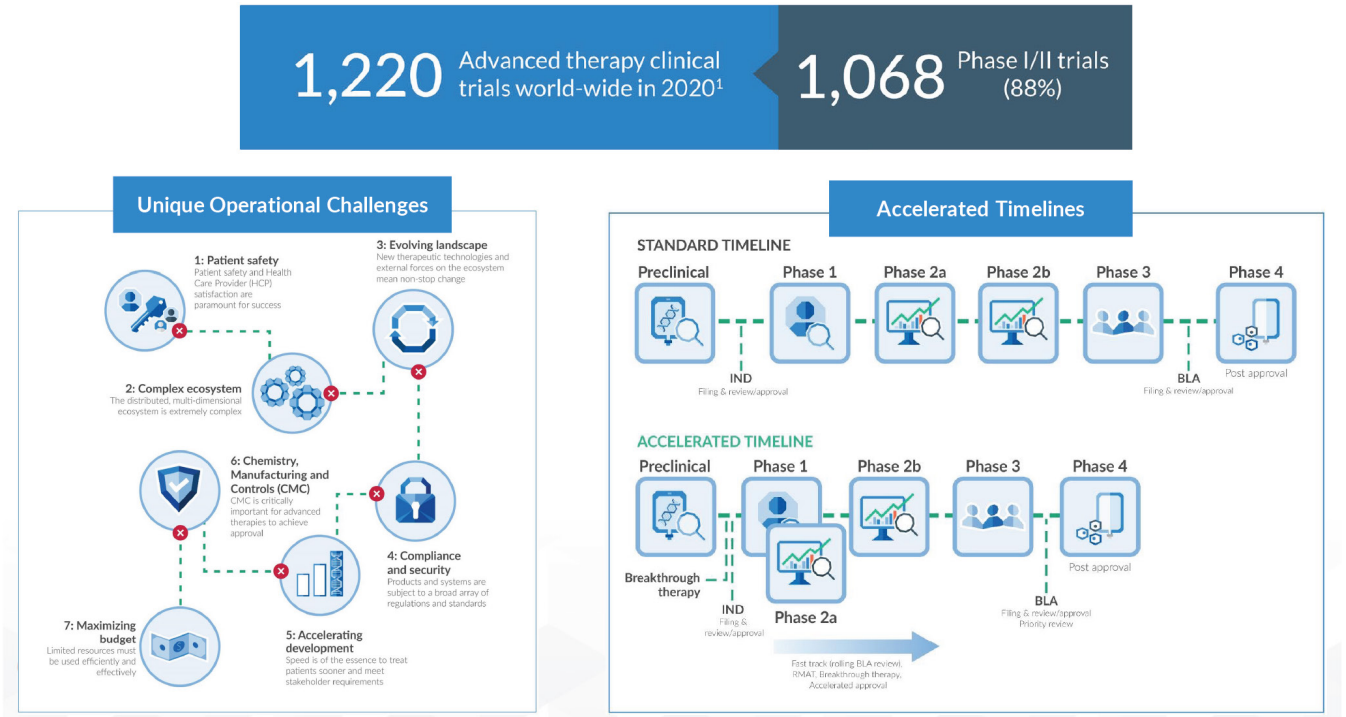
With more than 1,200 advanced therapy clinical trials operating world-wide (Figure 1), the need for solutions that simplify and scale advanced therapy studies is urgent. Veteran experts from the cell and gene therapy ecosystem recently collaborated in a webinar to share proven solutions for clinical scale.

Here are highlights of the insights they shared.

FIGURE 1

Scale and unique challenges of advanced therapy clinical development.



Q & A

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Attending Physician, Transfusion Service and Apheresis Clinic, Nationwide Children's Hospital and Director of Clinical Research and Development, Terumo BCT

Chris Greenberg
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Q How can a data-driven approach be used to optimize cell collections in early phase trials, and how can such an approach help with scale up?

JW: Accelerated scale up is the norm in this space, therefore change is also the norm and we are all in a learning stage. What I think can differentiate sponsors is their readiness for that change, readiness for the need to be inspection ready, and identifying ways to reduce the costs of these expensive, complex products. One of the things that we're always looking at is defining and measuring cycle times for each step along the manufacturing pathway and looking to define those early – understand how we can reduce cost and optimize each of those segments of that pathway. This is where a software platform can optimize manufacturing capacity by overlaying patient scheduling with capacity and weaving in partner data, eventually taking it on a global level. If you are looking forward, beyond your first patient and startup in one country, the more you can look at your country-site mix to establish your logistics and product requirements early, then other target regions can optimize for scale up more readily as the program advances.

EGM: We need the data from collections to see what worked and what didn't, so that we can work to make sure we optimize the collection experience for the patient, make sure source material is appropriate and correct, and the patient has been as safe as possible going through the collection procedure.

RG: It is important to capture the data and identify trends, from site specific trends to the key manufacturing data and logistic issues, then manage the exceptions that you see.

Q Cell and gene therapy studies may receive some form of accelerated status, such as RMAT designation. How does this possibility — or the actual receipt of accelerated status — change trial operations? How can sponsors get ready for scale?

RG: With accelerated studies, it's important to prepare for success and commercialization. You need to hire people early, which can be a battle internally, especially in early stage companies. It is also important to develop an IT roadmap that will take you to commercialization and optimize collection, from the collection of the starting material to manufacturing. Lastly, be prepared for inspection.

JW: It is a balance, but you need to have a long-term strategy so you don't get caught off guard. Start out with simple items that don't add a lot of cost, like inspection readiness. Data is always king here, with lots of eyes on data. Cell therapy in particular drives very heavy, upfront data requirements. Additionally, you need to start testing out your country and site mix, including logistics and shipping requirements.

Q As multiple trials face the need to scale quickly, what should be standardized to improve pivotal trials for cell and gene therapies, and how can our sector support growth and scale?

CG: I'm coming at this from the angle of systems implementation and the underlying processes. It is a multi-part answer for me because you have internal standardizations, and having a manual process to base your systems off of, as well the bigger picture with industry standardization. I'd also like to talk a little bit about configurability of systems – we need better data driven, modular designs – especially for Chain of Identity (COI)/Chain of Custody (COC) and at the front end of the life cycle for order placement and scheduling. We shouldn't be recreating the wheel every time. These are all needed to support growth and scalability. For greater efficiency, simplification is key.

Sponsors must use various standards so the more we can make ours consistent across the industry into a steady state, the better. As you start to scale up and deal with dozens or hundreds of sites, it becomes apparent that they all operate very differently from one another. They have different physical setups, different roles in terms of who's doing what, and different equipment challenges. So we need to kind of simplify and strike a balance between site specific processes and sponsor requirements. Label content, for example – standardizing study specific information is a step in the right direction.

On the industry standardization, I think this is where continued collaboration between sponsors, standards groups, suppliers, investigator sites, and industry forums come into play. The sites are being asked to implement processes and systems from multiple sponsors who are all doing things differently. The more consistent we can make our processes and systems across the industry, the better.

EGM: From a site-specific perspective, we will get recruited or vetted from industry to be a site because we have met certain levels of accreditation. This can be an incredibly lengthy and rigorous process, including COC and quality management plans. If we get approached by an industry partner to start a trial to work with some of our patient population we are already FACT accredited, but in addition, we may have to meet additional standards that are redundant. It can be quite a lot to juggle at one time.

Simplification needs to come from accreditation bodies coming together and making everything as standard as possible. That's just another way we can help the patients get the treatment, because the patients only have a certain time when they will be able to be collected most effectively. It is incumbent upon us to make sure we can pivot and get to them in the right time window.

RG: It is beneficial for the sponsor and the sites to keep it simple, keep the end goal in mind, and understand that you don't need to put your stamp on a facility that is already accredited.

JW: I think that some of these issues are really holding back patients' access to these types of therapies. At PRA we have run a study that was looking specifically to go into the community setting, utilizing non-FACT accredited sites, and it was very challenging

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with everything that was needed to assure patient safety and compliance with the product and COI/COC. There is so much work to be done to really achieve the goal of CRAACO (clinical research as a care option) and providing cell therapies to patients.

Q Could you share one or two key takeaways on how best to scale an advanced therapy clinical trial?

CG: It's extremely important to be in touch with how your sites work. Three years into this, we are going into different regions of the world. We are seeing different looks, so to speak, on how sites physically operate. The more we can do as sponsors to understand how sites operate and try to build our processes and solutions around them, the better. More collaboration with the regulatory agencies will ultimately get us further along in scaling these studies and therapies around the world.

RG: The challenge is to orchestrate multiple layers of complexities and constraints. Key integrations with your partners are really important. You also need to keep processes simple, hire staff early, and get those processes in place, whether it's a manual process at first, then evolving to an integrated solution. This will mitigate your risk across your supply chain, and the patient's journey. And then finally, striving for continuous 'white glove' service for all your external partners, and especially the patient.

JW: We always say we want to keep the patient in mind, and we should be patient-centric. There's so much room for us to really do that with action, versus just saying it. The regulators have given some very specific guidance about what diligence they are expecting sponsors to do towards gene therapy long-term follow-up. But I think that we all need to start that process earlier, in terms of figuring out how to decentralize it. How can we have standardization around registries in this space? How do we make this easier for patients, and easier to show the diligence and follow-up of collecting that long-term safety information and gene product persistence?

EGM: Keeping the patient and the family central and pivotal in the conversation is key. Often they have very long disease and treatment journeys. If we keep it as simple as possible, particularly for those sites, who already have pretty rigorous national accreditation, that would go a long way to being able to scale and make the treatment protocols and processes truly feasible. Additionally, keeping transparency across all parts of the treatment team to make sure patients get collected, treated quickly and efficiently with the right product, and receive the care and monitoring they need.

We hope you've found these insights valuable as you consider your own clinical trial plans. If you have further questions or would like to talk further, please contact us: info@vineti.com

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Subbu's area of specialty is compliance in the cloud, from GxP to data privacy and security regulations (such as HIPAA, GDPR) and he now leads this effort for Vineti. Additionally, he has led software development, process automation, agency inspection preparedness, agency compliance, and remediation efforts for a variety of life science companies.

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Rich has been a Technical Operations Executive in the biotech and the Cell and Gene therapy industry for over 30 years. He has an extensive background in commercial launches such as Enbrel, Provenge, Neulasta, and Recothrom, global supply chain strategies, and systems integration regarding personalized medicine, Chain of Custody and Chain of Identity. He has held executive positions at Iovance as Sr. Vice President of Technical Operations, Vice President of Technical Operations at ZymoGenetics and Vice President of Commercial Operations at Dendreon. In addition to on-going consulting roles, Rich has recently completed a full-time Head of Operations position at Imvax focusing on CDMO selection, build out of internal manufacturing, and establishment of an integrated solution regarding CRO, Manufacturing, and Patient Scheduling. Prior to these activities Rich has held positions at Amgen, Immunex, and Centocor.

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Dr. Erin Goodhue (nee Meyer) is a national leader in therapeutic apheresis. She is the Director of Clinical Research and Development at Terumo BCT and is leading a team of Clinical and Laboratory Scientists who will collaboratively evaluate, prioritize, and implement developed strategies including clinical trial protocol development and post market studies. Dr. Goodhue continues to work part-time as an attending physician at Nationwide Children's Hospital covering the Transfusion Service and Apheresis Clinic. In her previous position as the Executive Medical Director of Direct Patient Care at the American Red Cross, she developed Red Cross's national educational offerings surrounding therapeutic apheresis, hematopoietic stem cell, and immune effector cells. In collaboration with her medical office colleagues, Red Cross therapeutic apheresis procedures increased significantly through her tenure to over 15,000 procedures per year. Dr. Goodhue was part of the core team launching Red Cross's COVID-19 convalescent plasma collection program in 2020. Dr. Goodhue received her medical degree from the University of New England College of Osteopathic Medicine. She then went on to dual residencies in Anatomic and Clinical Pathology as well as Preventative Medicine at the Dartmouth-Hitchcock Medical Center while earning her MPH at the Geisel School of Medicine at Dartmouth College. Dr. Goodhue then completed a fellowship in Transfusion Medicine and Apheresis at the Joint Program in Transfusion Medicine at The Harvard Medical School. Her first position was as a transfusion medicine and apheresis attending physician at Emory University and Children's Healthcare of Atlanta.

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Jim has long-term experience managing early through late clinical development, with a primary focus on hematology/oncology indications and advanced therapeutics. Currently, he heads PRA's Center for Immuno-Oncology, Cellular & Gene Therapy which centralizes cross-functional knowledge expertise and global capabilities in these treatment modalities.

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Cell and gene therapies present serious CMC risks, but proactive systems and planning can protect your success.

Vineti

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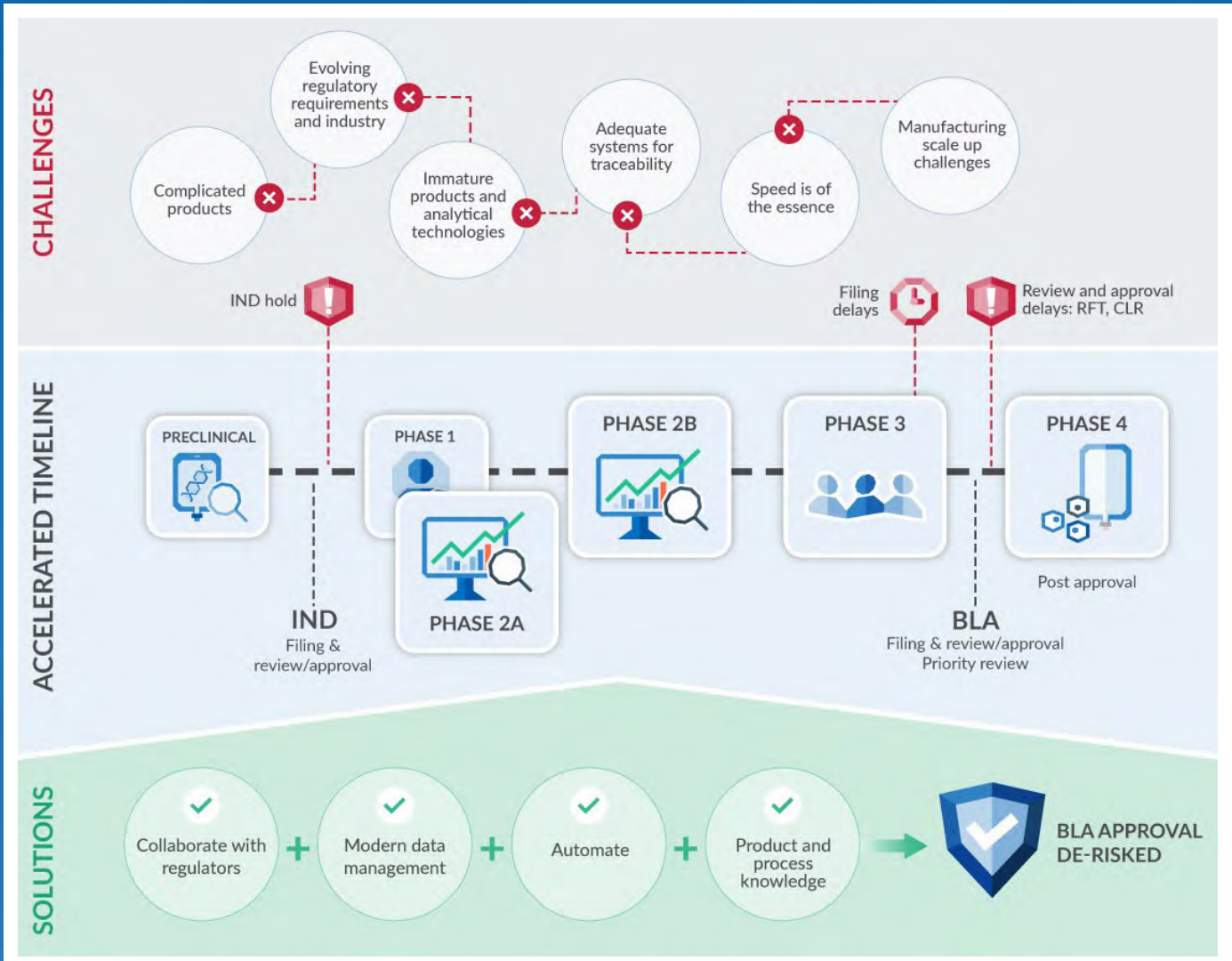

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CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

When using a closed and automated manufacturing platform, is there an option to maintain flexibility?

Kaman Kim, Carlos Yuraszeck & Joseph O'Connor

To allow greater flexibility and better targeting of CAR T cell therapies, Astellas developed *convertible*CAR™ T cells, which kill antigen-expressing target cells only in the presence of an activating bispecific adapter. Here, we will discuss the clinical manufacturing of autologous *convertible*CAR T cells, with a special focus on automation of the process using the Lonza Cocoon® Platform.

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THE ASTELLAS *convertible*CAR PLATFORM

Kaman Kim

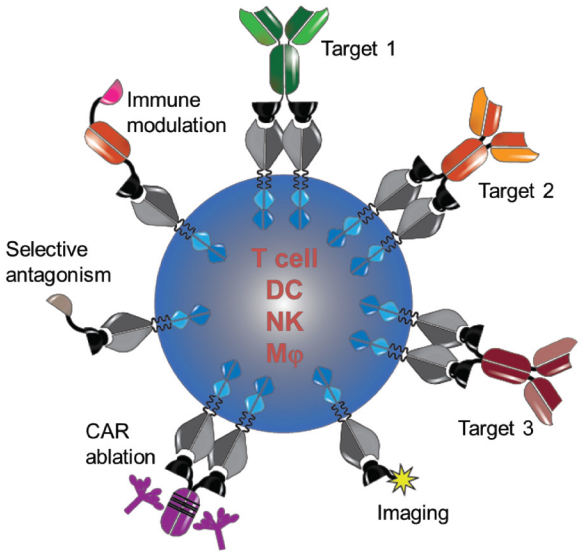
The pioneering CAR T therapies initially approved for clinical use are technically limited. They have a single-purpose scFv receptor, no way to control the dose of any given cell, and no mechanism to address tumor heterogeneity or antigen loss. All of these issues can cause CAR T therapies to fail – either during treatment or due to relapse and antigen loss after administration.

To address these limitations, Xyphos Biosciences – an Astellas company – created a universal chimeric antigen receptor (CAR; Figure 1).

Our platform provides a multifunctional receptor, addressing the single-purpose limitation of an scFv CAR and allowing for easy retargeting of our chimeric antigen-bearing cell to

FIGURE 1

Range of possible functions with the universal chimeric antigen receptor.



any tumor target of interest using a bispecific adaptor molecule. We are also able to control the function of the CAR T cell by changing the ratios of adaptor molecules as needed. Lastly, by combining receptors we can multiplex and target multiple antigens simultaneously.

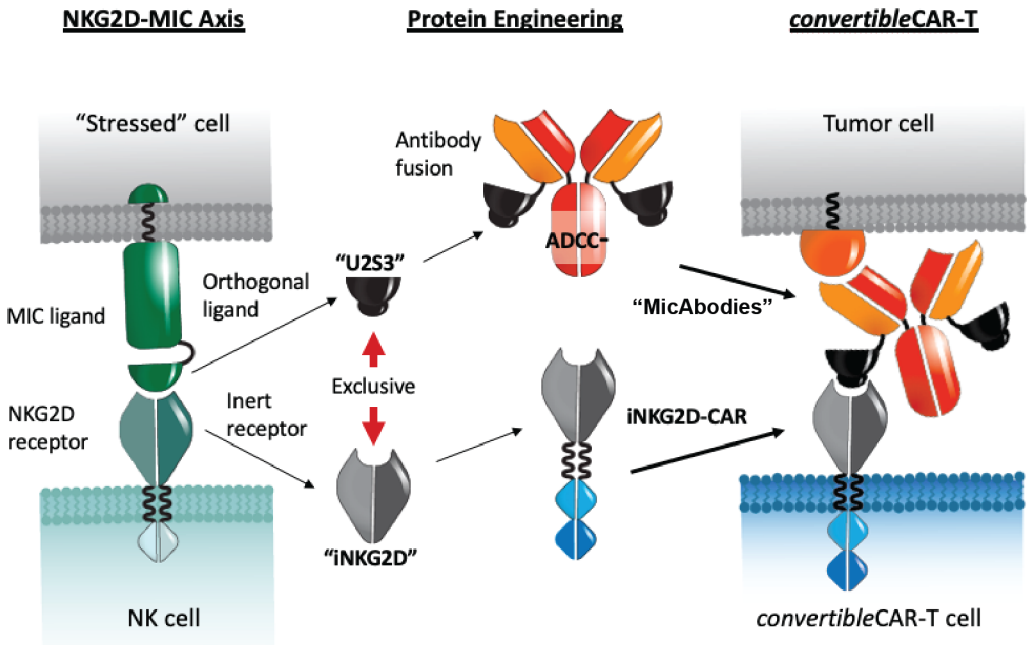
Developing the platform

Our starting point was the NKG2D-MIC signaling axis. NKG2D is an activating receptor that is present on natural killer (NK) cells and allows them to survey the body for cells that are stressed, often due to viral or oncogenic transformation. Stressed cells upregulate MIC ligands on the cell surface, which bind to NKG2D receptors on NK cells and prompt them to eliminate the unhealthy cell.

Applying a structure-based engineering approach, we mutated the extracellular domain of NKG2D to render the receptor inert (iNKG2D) and incapable of binding to any natural human ligands (Figure 2). We

FIGURE 2

The Astellas convertibleCAR T platform.



The extracellular domain of the NKG2D receptor is mutated to become functionally inert (iNKG2D). iNKG2D is associated with trans-membrane hinge and costimulatory domains and introduced into CAR T cells. The U2S3 (ULBP2 S3) orthogonal ligand, which has an exclusive affinity to iNKG2D, can be fused to tumor-targeting antibodies to create bispecific molecules (MicAbodies).

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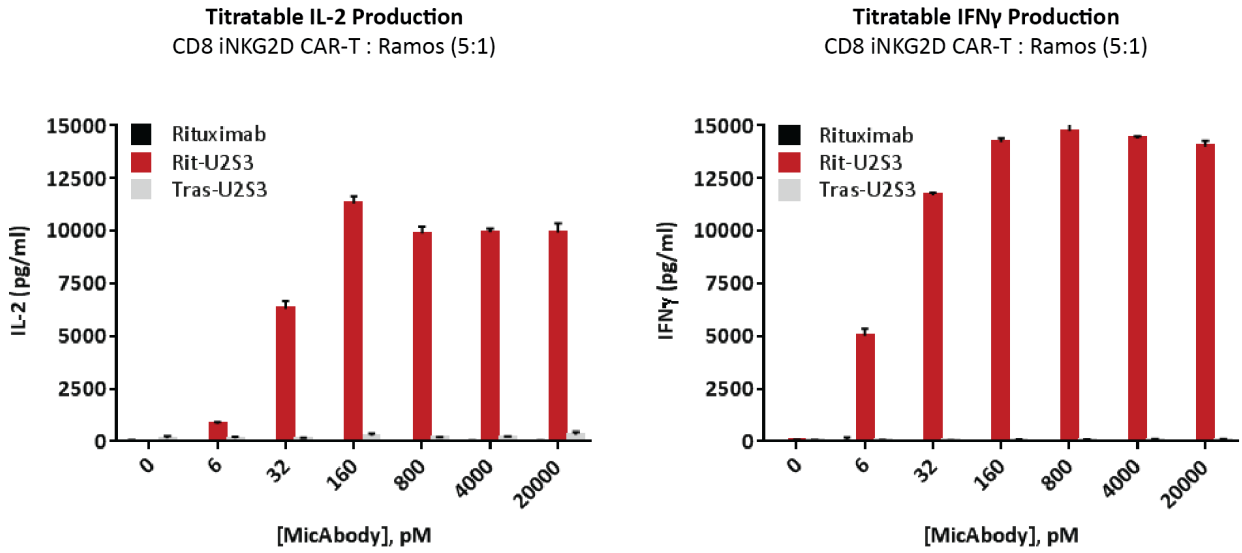
FIGURE 3

Activation is MicAbody- and target-dependent.



Changes in IL2 and IFNγ secretion with increasing MicAbody concentration in CD20⁺ Ramos human B-cells cocultured with *convertible*CAR T cells (CD8 iNKG2D CAR=T), after introduction of CD20-targeting rituximab antibody (black), HER2-targeting trastuzumab MicAbody (gray), or rituximab U2S3 CD20-targeting MicAbody (red). Cytokine release happens only with the appropriate tumor-targeting MicAbody.

introduced the iNKG2D CAR construct into our *convertible*CAR T cells through lentiviral transduction, with highly efficient expression of the CAR construct on the T cell surface (on par with an scFv CAR).

Next, we turned our attention to the MIC ligands and used a phage display-based strategy to identify variants with very high specificity and affinity for iNKG2D but not wild-type NKG2D. Essentially, we created a novel bio-orthogonal interaction. These MIC ligands can be attached to a tumor cell-targeting antibody to form a 'MicAbody' (Figure 2).

It is also possible to create a bivalent format, with two copies of the ligand on the bispecific molecule, while maintaining selectivity. Regardless of whether there is a heavy chain or light chain fusion on the targeting antibody we retain high binding to the iNKG2D (below picomole level) with no binding to the wild-type NKG2D.

When tumor cells are co-cultured with *convertible*CAR T cells, the CAR T cells are incapable of recognizing the tumor cells until the appropriate tumor-targeting MicAbody is introduced, prompting cytokine release and other measures of activity (Figure 3).

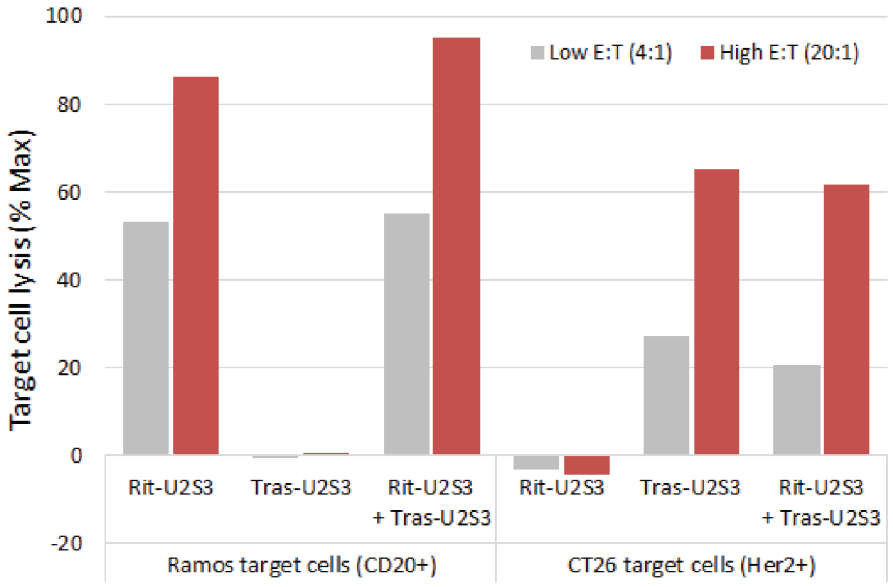
Multiplexing capabilities

Receptor saturation occurs at 5 nanomoles of MicAbody, with cytotoxicity seen at concentrations as low as 30 picomoles. That leaves a lot of space on the surface of the *convertible*CAR T cells to combine multiple MicAbodies. An example can be seen in Figure 4, where combining an equal molar concentration of rituximab and trastuzumab MicAbodies results in killing of both CD20⁺ and HER2⁺ cells, at the same level as when they were individually armed. In other words, multiplexing does not compromise activity.

In an animal model of B cell leukemia, treatment with rituximab CD20 targeting MicAbodies plus *convertible*CAR T cells was well tolerated and led to robust tumor control, and we hope to start our first clinical trial in 2022.

FIGURE 4

Dual arming of *convertible*CAR T-cells.



Percentage cell lysis is shown for CD20+ and HER2+ cells when exposed to *convertible*CAR T cells and MicAbodies targeting CD20, HER2, or both. Results are shown for low (gray) and high (red) effector:target ratio.

MANUFACTURING *convertible*CAR T CELLS

Carlos Yuraszeck

Figure 5 shows the process for producing conventional CAR T cells versus *convertible*CAR T cells. Our process is similar to that of producing conventional CAR T therapies, but with the important additional step of adding MicAbodies to arm the cells prior to harvest. As with any complex cellular therapeutic product, the priority is creating a consistent manufacturing process – the more we can reduce the variability of manufacturing, the better the end product will be. The challenges to consistency include working with living cells, which respond to their environment, and the use of aseptic techniques, since sterilization is not possible. An overview of our cell manufacturing process can be seen in Figure 6.

Why automate?

Compared with traditional pharmaceuticals, the clinical development time for these cell therapies is much shorter, leaving very little time for process development, or chemistry, manufacturing, and controls (CMC). That means that manufacturing decisions must be made early, process translation must be quick, and the system must be scalable from Phase 1 trials to commercial manufacturing. Time is of the essence and you don't want to lose time changing the process between trials.

An important factor for us as cell therapy manufacturers is that moving biological materials across borders can be easily disrupted (as highlighted by the impact of the COVID-19 pandemic), making centralized manufacturing very challenging. For that reason, we believe a regional manufacturing model will serve us best. However, a major challenge of regional production is compatibility – proving that products manufactured at different sites are the same. Automation can improve confidence in this regard.

For Astellas, another consideration was that we are working on a number of different cell types, with different targets, and finding a flexible solution that can be applied across

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many different products would be highly advantageous for us.

Considering all these factors, we felt that automation was the right choice for us, but with a platform that also provides flexibility to accommodate our various requirements.

Having decided to automate the process, we set several criteria for selecting our preferred system. Our top five reasons were:

1. Good technical support in both process and analytical development
2. A closed system, to reduce the potential for contamination
3. A customizable, flexible platform
4. Product quality and yield within the required range (>1 × 10^9 CAR^+ cells)
5. Clinical use experience

Applying those criteria, we opted to use the Cocoon Platform from Lonza, due to its flexibility and small footprint. Lonza brought great depth and breadth of experience in manufacturing T cells and autologous products, and the collaboration has been seamless.

With a closed, automated process in place, we are confident that we will be able to deliver our *convertible*CAR T cell therapies to patients around the world.

AUTOMATING THE PROCESS WITH COCOON

Joseph O'Connor

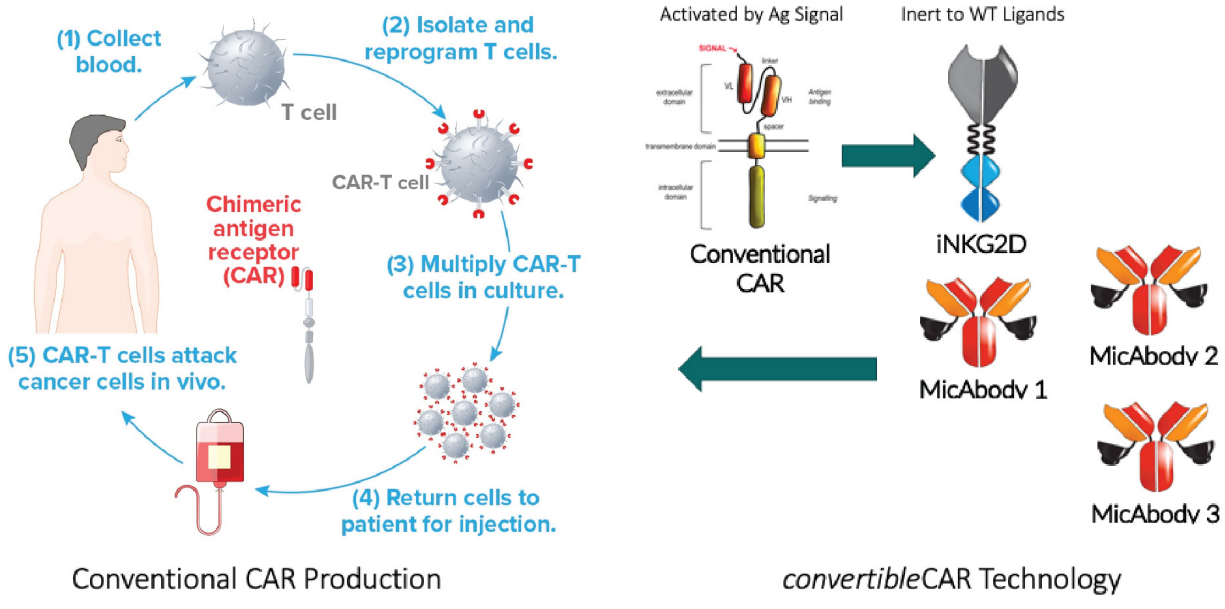
It quickly became clear that the biggest risk of translating the process into Cocoon Platform was the non-standard MicAbody unit operation. Therefore, this operation needed to be assessed, optimized, added to the automated protocol, and later tested.

The targets for successful process translation were:

- Subject dose greater than 800 million CAR^+ cells
- Transduction efficiency greater than 50%

FIGURE 5

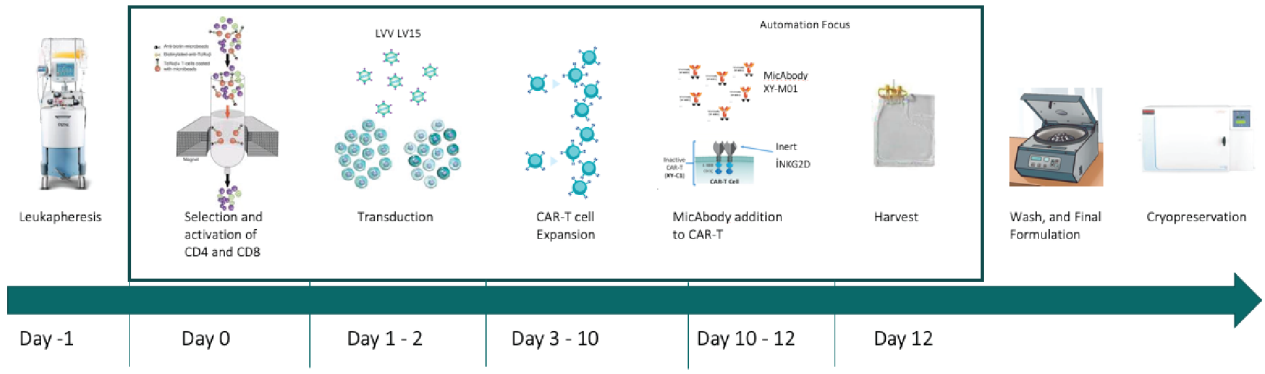
Producing conventional versus *convertible*CAR T cells.



Producing *convertible*CAR T cells requires the additional step of adding MicAbodies to arm the cells.

FIGURE 6

Manufacturing *convertible*CAR T cells.



The process begins with leukapheresis, followed by isolation of CD4 and CD8 T cells, transduction with a lentiviral vector, expansion, adding or arming the NKG2D receptors with one or more MicAbodies, harvest, final formulation, and cryopreservation.

- Greater than 70% viability post-thaw
- Purity of over 95% $CD3^+$ cells
- Efficient wash-out, with less than 0.1 nanomolar of MicAbody remaining post-harvest
- More than 20% of receptors occupied by the MicAbody, proving the efficacy of that unit operation

In automating the MicAbody unit operation, there were some special considerations. For one, MicAbody arming appears to be temperature sensitive, so we used cold reagents. Everything was done at room temperature and any heating elements were turned off. Plus, to speed up the process, the standard harvest protocol was modified. The automated protocol is outlined in Figure 7.

We have now performed four Cocoon runs of the Xyphos process. Cell viability was

FIGURE 7

Manual (top) versus automated (bottom) process overview.

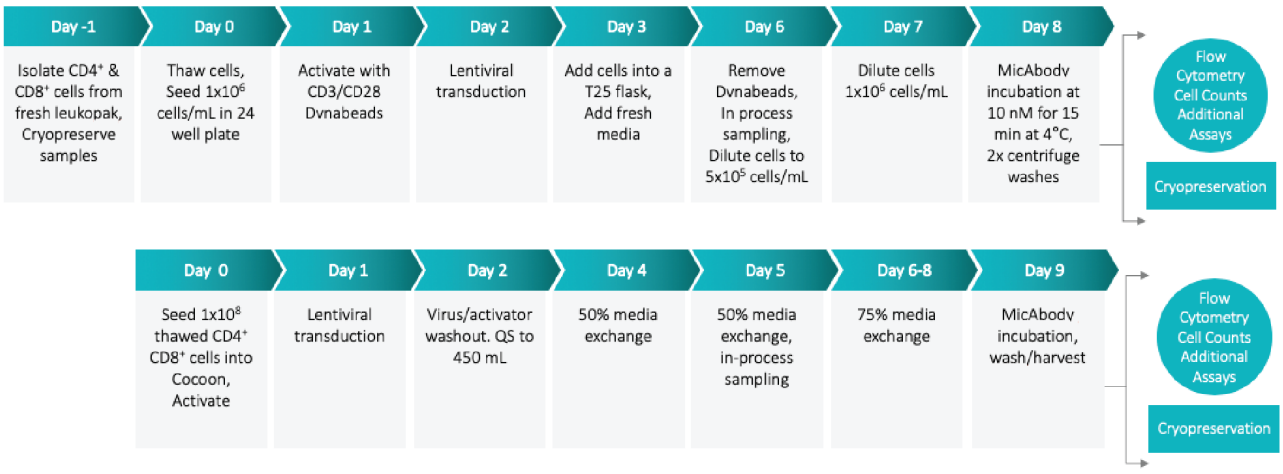


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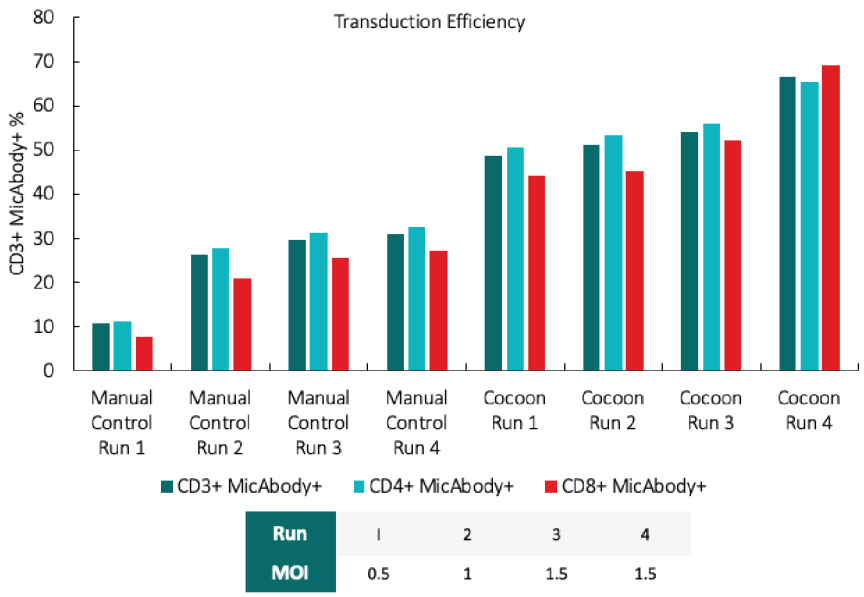
FIGURE 8

Transduction efficiency for manual and Cocoon runs.

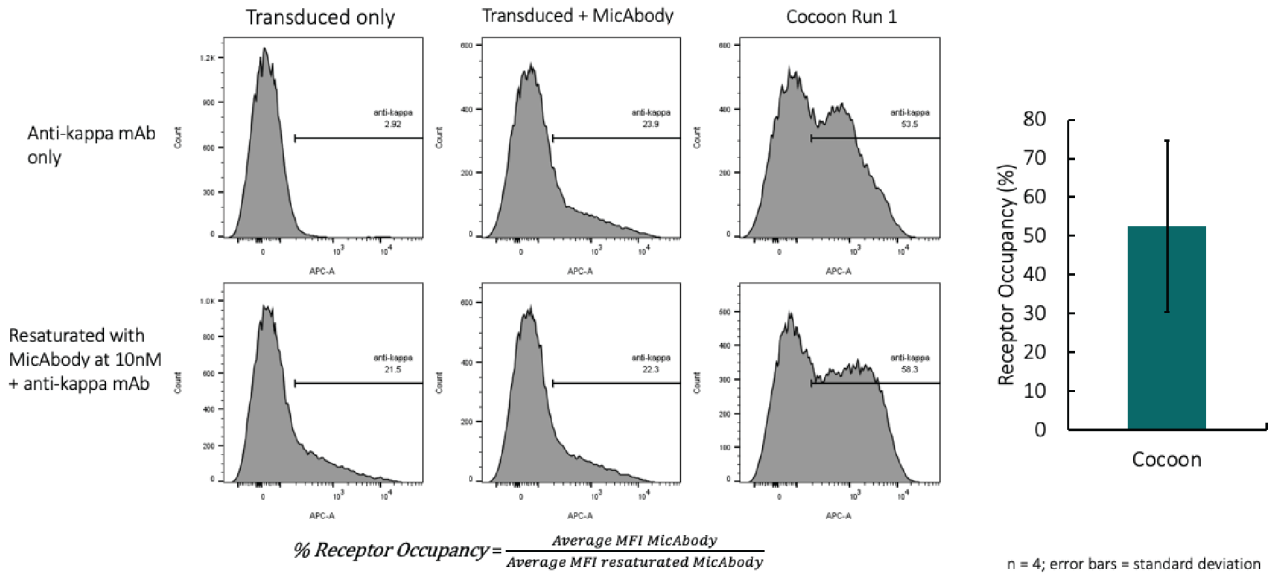


within the target range and cells from Cocoon runs exhibited increased transduction efficiency compared with manual runs (Figure 8).

We are still investigating the reasons behind this increased transduction efficiency, but we believe it may relate to the increased surface area of the cassette growth chamber

FIGURE 9

MicAbody receptor occupancy.



The percentage of receptors armed with the MicAbody was determined by measuring the average MFI of the detected MicAbody (top), divided by the average MFI after MicAbody re-saturation (bottom).

and/or the ability to mix cells periodically during transduction.

One of the most important assays is the MicAbody receptor occupancy assay (Figure 9), which ensures we have an effective therapy. The average MicAbody receptor occupancy was over 50%, demonstrating that the correct therapy is being manufactured, and the addition of the MicAbody incubation unit operation is working as expected.

The concentration of non-bound MicAbody was about 0.015 nanomolar, which passes the acceptable criteria by almost an order of magnitude and proves we have effective washing.

Overall, the data from the four Cocoon runs (with two donors) was highly reproducible (Table 1) and met all the translation targets.

BOX 1

Enabling cell and gene therapies: from concept to patient.

Introducing The Cocoon Platform from Lonza

Joseph O'Connor

There is wide agreement among cell and gene therapy manufacturers that automation will play an important role in the future of the field. Our survey of cell and gene therapy professionals suggests that the key considerations for implementing automated manufacturing are:

- Flexible platform
- Compatibility with existing process
- Staffing
- Equipment costs
- Scalability

To address these needs, Lonza has developed The Cocoon Platform. The platform is flexible enough to be implemented during preclinical R&D or later in the development lifecycle, and is fully customizable, allowing the end-user to create or modify their processes. Our goal is for the Cocoon to serve as an end-to-end solution for cell therapy manufacturing. We didn't want a system that sacrificed flexibility by automating. It was critical that the system be flexible enough to use in the development of the process, and then seamlessly transition into manufacturing using full automation. We also wanted to provide a system that could expand as needed with minimal changes.

The Cocoon consists of three primary components.

1. The environmental unit, which has the ability to control the temperature in two zones – 37°C for culture and 4°C degrees for reagents such as media. It also maintains gases.
2. A single-use disposable cassette, which is a closed system and can be tailored to any individual process. The flexibility of the cassette makes it suitable for both suspension and adherent processes. A bidirectional peristaltic pump moves fluid through the disposable cassette and integrated sensors measure pH, and dissolved oxygen, in real-time.
3. The software, which controls and monitors various process parameters. It allows the option for protocol design and controls the fluidic pathways. Importantly, it is 21CFR part 11 compliant, providing product traceability and audit trails. Plus, the software can generate fully customizable batch records for each individual process. The time savings generated by reducing paper batch records should not be underestimated.

The Cocoon Platform has already been used for CAR T cells, engineered TCR T cells, dendritic cells, CD34 cells, mesenchymal stem cells, and more.

Scale-out

As more autologous cell therapies are approved for larger patient groups, scaling up/out manufacturing will become a key challenge. To treat 10,000 patients per year, you would need to initiate 30 new patient processes per day on average, meaning you have 330 patient processes running in parallel. Manual production at that scale would require around 1,700 full-time employees – automation is needed to make scale-out feasible.

Some companies are investing large sums to create facilities that can manufacture 4,000 patient doses annually, but our vision for autologous cell therapy manufacture involves moving to a much smaller footprint with the Cocoon Tree – an array of units on a central vertical axis, with each individual Cocoon representing a separate process (Figure 1).

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TABLE 1

Cocoon platform translation data summary.

Test	Success criteria	Cocoon Run 1 MOI = 0.5 45 IU/mL IL-2 Donor A	Cocoon Run 2 MOI = 1 45 IU/mL IL-2 Donor A	Cocoon Run 3 MOI = 1.5 100 IU/mL IL-2 Donor B	Cocoon Run 4 MOI = 1.5 100 IU/mL IL-2 Donor B
Subject dose ($CD3^+MicAbody^+$ cells)	>8 x 10^8	1.16 x 10^9	1.00 x 10^9	1.09 x 10^9	1.24 x 10^9
% Transduction efficiency	≥50%	48.7 (control = 10.7)	51 (control = 26.2)	54.2 (control = 29.5)	66.4 (control = 30.9)
% $CD3^+$ cells	≥95%	97.5	97.4	96.5	98.2
Concentration of non-bound MicAbody (nM)	<0.1 nM	0.048	0.002	0.000	0.009

Q & A

Kaman Kim
Director of Research, Xyphos Biosciences – an Astellas company

Carlos Yuraszeck
Executive Director of GMP Operations, Astellas Institute of Regenerative Medicine

Joseph O'Connor
Senior Scientist, Personalized Medicines Process Development Team, Lonza

Carlos Yuraszeck, Kaman Kim and Joseph O'Connor answer your questions about *convertible*CAR T cells, cell manufacturing automation and the Coccoon Platform.

Q Does using a two-part system of mAbs and CAR T mean a more difficult regulatory path, because now there are two drug products, or is the final frozen cell product considered a single drug product?

CY: The strategy that we're pursuing, which has to be yet proven, is that this is a single agent. It's in two parts, but both the INKG2D receptor and MicAbody alone are inert.

Q What was the origin of the *convertible*CAR T/MicAbody system?

KK: A lot of so-called switch or adaptor-based technologies raise concerns with regards to immunogenicity. If you start with something as human as possible, that is less likely to be an issue, so we reviewed a number of human receptor-ligand pairings, and focused particularly on those with a lot of structure-function information in the immunology space. NKG2D MIC ended being a perfect fit.

Q Can you pool different lots or batches of cells to reach a yield, and is this acceptable to the regulatory bodies?

CY: In my personal experience, although not with this particular program, it's common to pool batches. As each lot of material meets your specifications, there's nothing in the regulations that says they can't be pooled and given as a single dose.

Q Can you retrieve in-process samples from the Cocoon to monitor cells?

JO: Yes, you can sample cells or sample media.

Q Are there regulatory concerns with the Cocoon Tree having multiple patients' cells in the same space?

CY: I don't think that's a concern only with the Cocoon. The current standard approach is manufacturing multiple patients in the same space, so the issue goes beyond whether you are automating or not automating.

I'm a big fan of the ISBT 128 standards, which help not only with the manufacturing but also in moving products from the clinic and into manufacturing, then back to the clinic.

It's likely that regulators will come on board to manufacture the same therapy with different patients in a closed system like the Cocoon. What we generally hear from regulators is that it's the use of different vectors in the same suite that gives them pause. Lonza is working on experiments to prove that this shouldn't be a concern, but ultimately, we may need to consider suite set up for manufacturing one therapy. Multiple suites for multiple therapies.

Q Is there published data using the Cocoon platform?

JO: Not yet. There are some white papers out, but we are actively working, myself included, in giving some out this year.

Q How does harvesting cells work in the Cocoon system?

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JO: The cells are currently settled along the proliferation chamber so we can remove media without disturbing the cells. We add and remove buffer several times without disturbing the cells. We then use the Cocoon to rock back and forth to resuspend the cells, then collect the cells in an output bag. All the user really needs to do is press go, and then wait.

BIOGRAPHIES

Joseph O'Connor
Senior Scientist, Personalized Medicines Process Development Team, Lonza

Joseph O'Connor, PhD, is currently a senior scientist in process development for Lonza's Personalized Medicine Business Unit. His focus is on translating and optimizing manual autologous cell therapies into the Cocoon® Platform, a closed and automated cell therapy manufacturing solution. Joseph earned a doctorate in chemical engineering from the Pennsylvania State University while researching the mechanical regulation of gene expression. He has been with Lonza since 2017.

Kaman Kim
Director of Research, Xyphos Biosciences – an Astellas company

Karman Kim has extensive training in molecular biology, microbiology, and immuno-oncology. She successfully led a startup research team to develop Xyphos' convertibleCAR platform, and as Director of Research in Astellas, continues to coordinate all research and discovery efforts to expand upon the functionality of the *convertible*CAR platform, and promote its application into a variety of cancer indications.

Carlos Yuraszeck
Executive Director of GMP Operations, Astellas Institute of Regenerative Medicine

Carlos Yuraszeck leads production of HESC and IPSC-derived cell therapy products at the Astellas Institute of Regenerative Medicine. Over his 25-year career in the pharmaceutical biotech industry, he has held leadership positions with corporate compliance QA, QC, validation, and technical operations, at companies including Merck, Pfizer, and CellGene.

Lonza

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

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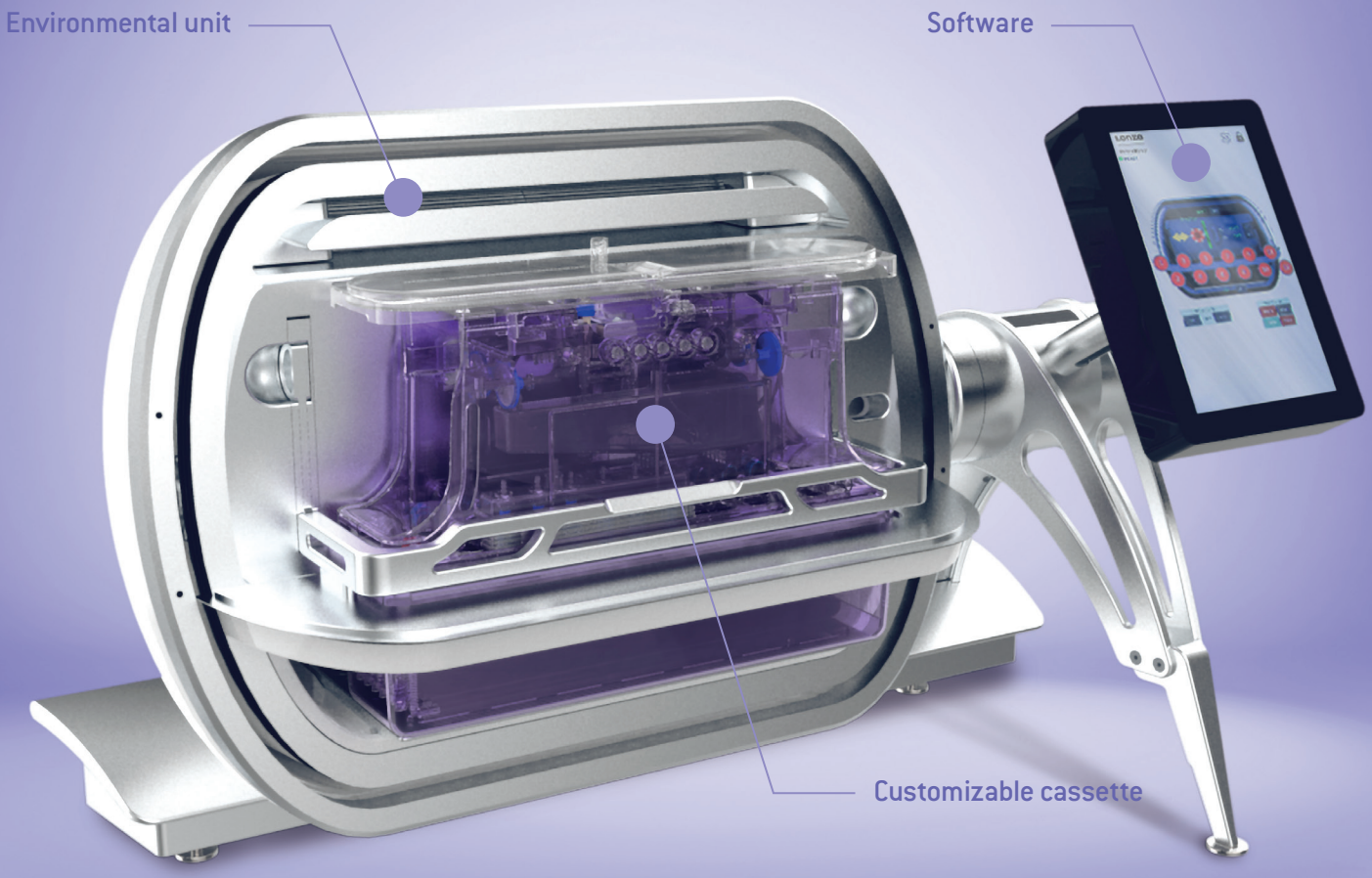
Lonza
Cell & Gene

The Cocoon® Platform

- Automated and closed cell therapy manufacturing
- Superior scalability
- Higher quality product with in-process analytics
- Lower cost of production



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Supply Chain Channel

Honing global commercial strategies

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SUPPLY CHAIN CHANNEL: Honing global commercial strategies

AUGUST 2021

Volume 7, Issue 7

INTERVIEW

CELL & GENE THERAPY INSIGHTS

INTERVIEW

Evolution and innovation in autologous cell therapy supply chain

SADIA L'BAOUCH has more than 20 years' experience in manufacturing operations, supply chain management and external supply. She has a successful track record in devising strategy and infrastructures for new products and managing multiple sites. Sadia joined Ixaka from Sangamo Therapeutics where, as Senior Director of Supply Chain and Manufacturing, she managed CMOs for delivery of early phase programs using CAR-Tregs (chimeric antigen receptor regulator T cells). Prior to Sangamo Therapeutics, Sadia spent 17 years at GlaxoSmithKline in roles such as Operations and Supply Director, Director of Manufacturing and Supply, and Supply Chain Senior Director where she led on supply chain for the launch of the first *ex vivo* gene therapy Strimvelis. She transitioned to Orchard Therapeutics in 2018 following its acquisition of the GSK Rare Diseases portfolio to act as Supply Chain Senior Director. There she continued to manage global supply chain operational aspects for autologous cell and gene therapy products for both clinical and commercial supplies.

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Q What are your working on right now?

SLB: I joined Ixaka (formerly known as Rexgenero) six months ago as Chief Manufacturing Officer.

My role here is to look after various CMC aspects. That includes looking after the process and analytical development teams, as well as the GMP operations teams for manufacturing and QC release on our lead program, REX-001, for CLTI (chronic limb-threatening ischemia). REX-001 is an autologous multi-cell therapy, with no transduction using viral vectors required. In this role, I supervise all the manufacturing and supply aspects of our Phase 3 clinical trials – with our manufacturing team based in Seville, Spain. One of my first objectives is to establish and develop the supply chain team.

We have another platform at Ixaka – at a much earlier stage – called the Targeted NanoParticle (TNP). This is currently in pre-clinical development with the development team based in Paris, France. The TNP program, in contrast to REX-001, is an *in vivo* gene therapy, and it is an off-the-shelf product with a traditional pharma supply chain.

Autologous products such as REX-001 require tight control at all levels, with a highly personalized and considered approach to supply chain aspects, from patient planning for manufacture to delivering the drug to patients. In addition, REX-001 employs the 'fresh in/fresh out' model, which is one of the most challenging supply chains to manage, in comparison to other autologous processes or products that have tended over recent years to move towards a 'frozen in/frozen out' model.

Q During your time at GSK and then Orchard Therapeutics, you took the lead on supply chain for the launch and roll-out of Strimvelis. How do you reflect today on how cell and gene therapy supply chain has evolved since then – firstly, in strategic terms?

SLB: When I was involved in the launch activities for Strimvelis, there was barely anything in place for that type of product. Strimvelis was the first *ex vivo* gene therapy launched in Europe and so, many of the commercial aspects were new for this type of product and supply chain, from designing the financial trade routes to packaging and labeling requirements. Tailor-made solutions and very often manual processes had to be used.

"Autologous products such as REX-001 require tight control at all levels, with a highly personalized and considered approach..."

What I see today is that the entire industry has caught up and there are many CGT products now being commercialized. There are also lots of IT companies now, many of whom developed their solutions by focusing on one sole aspect (e.g. track-and-trace) and who now provide systems that can support inventory management, commercial financing, and

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customer relationship management (CRM) – all of which are required when we are getting ready to launch a product. So, I would say there has been great progress on supply chain technology systems, where many companies are now emerging to support the day-to-day supply chain management activities in cell and gene therapy.

"...there has been great progress on supply chain technology systems, where many companies are now emerging to support the day-to-day supply chain management activities in cell and gene therapy."

Q ...And in terms of supporting logistics services and general infrastructure?

SLB: Regarding logistics, I don't think there has been much change lately. We have some fairly well-established key players in the cell and gene therapy space – logistics providers that everyone knows and goes to.

In the early days, when I started in cell and gene therapy, I talked to a number of the logistics companies and proposed to some that they create a cell and gene therapy department, because our product was not a traditional pharma product or even a traditional biological product. My view was that we needed them to apply some personalized logistics services to suit our personalized medicinal products. Some of those companies have followed through and a lot of the logistics providers today have a dedicated cell and gene therapy department. They are very knowledgeable now, very experienced. They understand the challenges. But I think there are some internal limits to what these specialist companies can do and we have seen some of these limitations become issues during the COVID-19 pandemic. For instance, they tend to be tied to using commercial flights because some don't have their own planes and they don't really have control on whether our package will be getting onto the scheduled plane or not. Now, of course, such general flight plans have been massively disrupted. At the moment, unless we as the sponsor go with what we call an on-board carrier (which is having someone escort our package onto the plane and making sure they always know where it is – an extremely costly option) then we simply can't be sure we'll get our pack to its destination on time.

So for me, there are still challenges in terms of logistics, which require the sponsor to do a lot more micro-managing and issue-handling. I don't think that this will be sustainable if and when we reach the scale of providing products to thousands of patients a year – we will need to have something better. These companies need to continue growing and improving their systems and their services for this type of product.

Q You mentioned the IT piece and how that has advanced in recent times. Are there any other key areas of technological innovation that have evolved?

SLB: One of the bottlenecks we have always talked about since I've been in cell and gene therapy is not having enough liquid nitrogen available to cater for the whole industry. With everybody turning to cryo now, we may not have enough liquid nitrogen nor dry shippers to cope. Some companies already know this and are reserving and validating their own dry shippers. It is going to be a major bottleneck at some point.

There is innovation happening in this space, however, where some small companies are starting to develop cryo storage and transportation without using liquid nitrogen. There are also technologies now emerging that aim to preserve products without involving the DMSO-type of technology traditionally used for cryopreservation. I don't know how far along these approaches are – whether they are fully validated and usable as yet – but they are a step in the right direction, which could open up new ways of both preserving and transporting our cell therapy products.

Q Can you distil one or two key learnings for supply chain that you take forward to Ixaka?

SLB: The supply chain is vast. I consider it to comprise four different areas: Planning, which deals with scheduling patients and the manufacturing slots at the CMO or internally; Logistics, dealing with the transportation of the product; Packaging and Labeling, which is also very tricky and can cause lots of headaches to people working in this area; and the IT system and what I call the supply chain technology, which supports all these activities. Without sufficiently strong IT support, when we go up in volume, we simply wouldn't be able to cope. For instance, some products could be shipped before release, and this would cause compliance issues time after time.

So, for me, an IT system is an absolute must when we grow in volume and near commercialization. Most cell therapy companies that are at the stage of dealing with low numbers of patients on a one-by-one basis can still do manual processes. They can use Excel, use whatever technology systems they have got without too many problems. As you grow in volume, however, the proper IT systems really need to be in place.

Another important thing for me is that when a platform is quite small – like ours is at Ixaka currently – when we first build a supply chain platform, we need to have people who are versatile. They need to be able to do all four of the areas I described, because the volumes are not big enough to warrant a more specialized approach. As we grow the platform, however, then we will need to have our people specializing in each one of these areas. We need to be able to develop and grow them in this way, because those who work in each of the four areas are very specialized. A logistics person is not necessarily knowledgeable around the supply and demand planning, for example. A key part of this specialist knowledge is understanding what the differences are between clinical and commercial, because they can be considerable for each area.

I am using all these learnings to build the platform at Ixaka and to develop a strong network for the company, especially on the logistics side. As I mentioned, we have a fresh in/fresh out product and very tight timelines in our production process. This means that we usually have

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"...Brexit has made things more difficult if we want to have products shipped between the UK and Europe. Equally, if we work with countries outside of Europe, there is more documentation and other things that need to be in place ... It's a big challenge to get it all right to make sure that our product is not held up at any stage during transportation."

less than 24 hours to transport patient bone marrow to the manufacturing site, then once the product is made, we have less than 48 hours to transport the final product back to the clinical site for administration. As a result, we need extremely personalized logistics and are increasingly looking to the smaller companies that can perhaps provide such a service.

Q We have discussed a number of bottlenecks in the cell therapy supply chain – which one would you identify as the most significant, currently?

SLB: For my current role, I would say that would be on the logistics side, for the reasons I've just explained. Not only regarding transportation but also the customs side and all the documentation that needs to be in place there. We know that Brexit has made things more difficult if we want to have products shipped between the UK and Europe. Equally, if we work with countries outside of Europe, there is more documentation and other things that need to be in place (i.e. export permits, import permits, etc.), which are key. It's a big challenge to get it all right to make sure that our product is not held up at any stage during transportation. Having a key partner as a Custom broker is paramount here.

Q ...And are there any other bottlenecks that you haven't mentioned yet that spring to mind?

SLB: Looking to the future, if we want to make the type of product we currently have in Phase 3 available on a truly global basis, which is our intent, then we will probably need to change the formulation so that we can freeze the final drug product at least.

The alternative to this is to look to a bedside or point of care solution. For some autologous products in particular, moving manufacturing closer to the patient will become important in

the future. I'm not sure yet what the solution there will look like, though, because I know that most hospitals are not set up to do GMP manufacturing.

Q We have touched on the considerable impact of COVID-19 on cell therapy supply chain. How has your approach to supply chain development and management altered as a result of the pandemic?

SLB: We have changed our approach by getting alternative suppliers in place for our research activities, especially for the procurement of starting materials. Most of the starting materials we use come from the US and through the pandemic period, those shipments and even just the availability of those materials became extremely difficult. The same goes for back-up logistics providers – having alternative suppliers in place for every part of the supply chain has become really important.

Q ...And what will be the key next steps of the cell and gene therapy field in general in terms of preparing future supply chains for a more uncertain world?

SLB: Getting a much stronger logistics network and service provision in place will definitely be a priority – that means working closely with the logistics providers to explain our needs and discuss how they could be met.

In the early days of the London Regenerative Medicine Network (LRMN) and the Cell and Gene Therapy Catapult, there was a network around logistics that I was a part of. We discussed what would be the future logistics for this type of product – whether we would need to create 'biological passports' in order to move these products more quickly across borders, for example. I think this sort of idea is still applicable today – something needs to be done so that these products are not held up.

Once again, I'm quite convinced that we need to bring manufacture of these time-sensitive autologous cell therapy products closer to the patient – to where the treatment is happening.

Q Finally, can you outline the chief goals and priorities both for yourself in your own role and for Ixaka as a whole over the coming 12–24 months?

SLB: One of my key objectives is to define the manufacturing and supply chain strategy for both the REX-001 and TNP programs.

For REX-001, we will be moving towards completion of the Phase 3 trial and preparing for EMA MAA and US FDA BLA filings in the next few years. My focus will be on building the appropriate manufacturing and supply network to support the development and commercialization of that product.

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For the TNP program, which is much earlier stage, it's really a case of understanding the supply chain and building that supply chain map. It is less complex in terms of logistics, because it's an off-the-shelf product, but the complexity comes in the various manufacturing steps, which will require management of various suppliers across the supply chain.

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COMMENTARY

EXPERT INSIGHT

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BUSINESS INSIGHT: JULY 2021

COMMENTARY/OPINION

Critical need for establishing value that justifies the current rising costs of cell and gene therapy

Richard T Maziarz

Autologous and allogeneic hematopoietic cell transplantation (HCT) remain valuable tools in the treatment of patients with advanced hematologic malignancies, some solid tumor cancers, immune deficiency syndromes and genetic inherited disorders. The confirmation of the allograft graft versus malignancy effect observed after the administration of donor leukocyte infusions to patients with relapsed chronic myelogenous leukemia has been highlighted by many as the birth of cell therapy. With the emergence of clinical cellular immune oncology over the past three decades, cellular and now gene therapies have expanded dramatically, with indications beyond the scope of HCT. The cost of care of HCT has been heavily scrutinized and since become a barometer for new cellular therapy interventions. Cell and gene therapy innovations are changing the landscape of care for many individuals, but it remains unclear if access to care will be limited by the high costs. Value frameworks may provide the appropriate tools to determine and guide valuation and pricing of these emerging agents.

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The delivery of high quality, high value care is the principle that remains the focus and goal of all healthcare providers [1]. However, there also exists the recognition that the delivery of care particularly within the United States is generally based on contractual agreements of coverage, whether the source of that coverage is through a governmental or private insurer.

Certainly, within a single payer system as seen in multiple countries, access to care remains a priority but the distribution of benefits can be effectively regulated.

Healthcare delivery currently is undergoing a dramatic evolution, catalyzed by advances in molecular medicine and advancing bioinformatics, possibly as direct results from the human genome sequencing project. New diagnostics and new therapeutics continue to emerge. Clinically, everyone demands high quality outcomes as well as expects exceptional value for offered products. No individual is excited to accept an intervention with perceived lower value or lower quality product, but it remains an enigma to clearly define high quality or high value products in healthcare and particularly in the complex field of HCT or clinical cellular immune oncology. *Quality and value* have become terms that many individuals and organizations focus upon and have developed matrixes to characterize, but, if one does try to strictly define the concept, we often run into the oft quoted comment regarding the definition of pornography from United States Supreme Court Justice Potter Stewart "I shall not today attempt further to define the kinds of material I understand to be appraised within that shorthanded description and perhaps I could never succeed in intelligibly doing so, but I know it when I see it" [2]. That being said, as a general rule of thumb, overall value is commonly defined as the ratio of the quality of care and the cost of the intervention(s) and that healthcare delivery is a balance between levels of quality, service, and the course involved in the delivering of healthcare [3].

HCT has a long history of being recognized as a procedure that is costly, with high healthcare utilization, of which long-term outcomes are compromised by relapse of the underlying disease or by complications of the procedure [4]. The Affordable Care Act (ACA) had a significant impact in United States on decreasing the number of uninsured, nonelderly patient population from a peak of 46.5 million in 2010 to a nadir of 26.7 million in 2016. Important aspects of the ACA also relate to the fact that prior to the changes that were written into the law, that patients who were insured, often still had suboptimal coverage with restriction of the availability of HCT or other expensive technologies based upon restrictions placed by pre-existing condition clauses and lifetime or procedural maximum payments allowable by private payers [5]. With the expansion of benefits to the previously uninsured and the elimination of some restrictive clauses from coverage plans, greater numbers of patients pursue HCT than ever before.

That being said, even before the ACA was enacted, significant scrutiny on the transplantation field had developed, first in the 1990s when the rapid expansion of high-dose therapy with autologous HCT was applied to high risk or metastatic breast cancer patients, with the downstream fears that the system could financially break under the volumes of patients that could be eligible. As well documented, the failure to demonstrate benefit beyond standard of care therapies in randomized Phase 3 trials led to rapid cessation of these procedures across the US and the world [6]. However at the same time, the emergence of reduced intensity and nonmyeloablative allogeneic HCT dramatically changed the landscape of allogeneic HCT. As reported by the Agency for Healthcare Research & Quality (AHRQ), bone marrow transplantation was the single principal procedure category associated with the highest percent increase in total costs and hospital stays over a 48-month period ending in December 2007 with an 84.9% increase in cost and 51.3% increase in hospital stays. Interestingly, of the top 10 identified procedures, cancer was associated with 5 of those reported, the performed procedures [7].

With this recognition, greater scrutiny was and remains focused on the cost of care of the transplant patient. It has recently been recognized that the fastest growing demographic undergoing allogeneic transplantation is the over 70-year-old, with patients over age 60 (an age that in the past was felt the maximum for alloHCT) now accounting for 40% of all

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transplantation procedures [8]. Majhail *et al.* reported a detailed analysis of course during the first 100 days post HCT demonstrating the significant greater expenditure was associated with allogeneic transplantation versus autologous procedures [9]. Analysis of transplant associated charges by the Milliman group, demonstrated over 50% increase in associated charges between 2005 and 2017 for both allogeneic and autologous procedures [10]. Using available claims databases, examination of short-term and long-term payer costs demonstrated that over 5 years, the cost of care still remained higher than age-matched healthy individuals with a median of approximately $418,000 of payment claims by the end of the first year for adults undergoing alloHCT for large cell lymphoma with continuing significant paid medical expenses between $70,000 and $90,000 a year over the next 2 years [11]. Similarly, in a pediatric study, a median of approximately $650,000 paid out by the payer in adjudicated claims for pediatric patients undergoing alloHCT for acute lymphoblastic leukemia in the first year of transplantation with approximately $40,000 to $105,000 annually in paid claims over the next 4 years [12]. It is critical to understand these costs of care in effect are interpreted as 'costs of cure'. These historical numbers are the new comparators for cell therapy, developed and targeted as curative therapy. However it also remains important to remember that HCT is reimbursed often by contract as a procedure covering an incident of care with a number of days of care strictly defined. In contrast cells as drugs will be reimbursed as a single component of a claim that covers a particular incident of care. Thus, the cost of the drug is only one expenditure in the delivery of care to an individual as opposed to the cost of HCT which is designed to cover both inpatient and outpatient healthcare costs.

The past 10 years have clearly been the decade that confirmed the emergence of immunotherapy as the accepted 4th arm of cancer therapy. Sipuleucel-T was first approved in 2010 as a dendritic cell vaccine for advanced prostate cancer. Soon thereafter, the emergence of checkpoint inhibitor and bispecific antibodies gained approval for clinical use and now, autologous cell and gene therapy with chimeric antigen receptor T cells have emerged. Currently, 5 independent products are approved for multiple indications (Table 1) in the US and across the world. Notably a study that has gained significant attention was an analysis performed prior to any official regulatory approval of a CAR-T therapy, anywhere in the world, by the National Institute of Health & Care Excellence (NICE) before FDA or EMA approval was obtained for these cellular drug products. Specifically, after performing an analysis of utilizing CAR-T therapy for the treatment of B-cell acute lymphoblastic leukemia, a hematologic malignancy typically affecting younger patients, it was modeled that based on quality adjusted life years (QALY) analysis, that acquisition cost if used as a bridge to transplant would be acceptable at £356,100 or if used for primary curative intent, a potential acquisition cost of £528,660 would be within an acceptable price range [13,14].

Quality adjusted life years (QALY) saved is an accepted value framework that can be used to guide pricing or alternatively, guide decisions regarding whether pricing is appropriate [15]. QALY is a beneficial tool that is used to identify how interventions may reduce the burden of disease and increase the quality of life of populations. Thus, 1 QALY is considered equal to 1 year of perfect life. If life is compromised during that time, then the QALY is discounted (< 1) with death, QALY = 0. QALY has become a key central measurement in cost effectiveness analysis as it combines assessment of length of survival with health-related quality of life. Notably, it is also reported that it will discount for patient health gain in the future being worth less than health gained today. With this being said, various groups have used dollar expenditure/QALY gained to determine value. One report from the American College of Cardiology/American Heart Association task force on performance measures and practice

TABLE 1

CAR T products and indications.

Disease	Diffuse large cell lymphoma	Acute lymphocytic leukemia	Mantle cell lymphoma	Follicular non-Hodgkin lymphoma	Multiple myeloma
Drug	Axi- cel Tisa- cel Liso-cel	Tisa-cel	Brexu-cel	Axi- cel	Ide-cel
Market	1000s	100s	100s	1000s	1000s
Cost	$399,000 $373,000 $410,300	$475,000	$399,000	$399,000	$419,500

Axi-cel: Axicabtagene ciloleucel; Brexu-cel: Brextucabtagene autoleucel; Ide-cel: Idecabtagene vicleucel; Liso-cel: Lisocabtagene maraleuecl; Tisa-cel: Tisagenlecleucel.

guidelines recommends that high value is defined as better outcomes at a lower cost, or incremental cost effectiveness ratio < $50,000/ QALY gains [16]. Intermediate value is defined at outcomes achieved at expenditures of $50,000 to <$150,000/ QALY gained and that low value is > $150,000/QALY [16]. These numbers have been utilized by payers often to guide self-funded insurance plans in defining pharmacy benefits.

The Institute for Clinical and Economic Review (ICER) and the California Technology Assessment Forum (CTAF) collaborated to perform the first assessment of chimeric antigen receptor-T (CAR-T) cell therapy for B-cell cancers to model their effectiveness and value with the goal of determining benefit based in terms of incremental cost for responder as well to assess QALY and health outcomes of life years. In general, their organizations specifically choose to target new drug assessments, with their hypothesis that the current landscape of pricing and evaluation of drug benefit particularly at the time the FDA approval, is a "black box….don't know if we are getting good value at these higher prices." [17].

Thus, their first CAR-T therapy assessments performed in 2018, were comparisons of tisagenlecleucel versus clofarabine as advanced salvage chemotherapy for young patients with ALL and as well, the assessment of axicabtagene ciloleucel compared to ongoing salvage chemotherapy for adults with advanced relapsed/refractory large cell lymphoma [18]. Again, these were performed before FDA approvals were in place. Their final analyses demonstrated that for young patients with ALL, that CAR-T therapy was associated with an incremental cost effectiveness ratio/ QALY at an estimate of $45,871 which would fall into the category of high value. However, the axicabatagene incremental cost effective ratio/QALY was estimated at $136,078 which is actually closer to the low value target number. Recently ICER performed the same type of analysis on the newly approved multiple myeloma CAR-T idecabtagene and the second agent that is under FDA review, ciltacabtagene, and their analysis suggests that costs/QALY gained were $247,000 and $110,000, respectively [19]. Their conclusion was that the preliminary evidence suggested that ciltacabtagene would meet commonly cited acceptable thresholds but that idecabtagene with its current market price of $419,500 should be discounted by greater than 37% from the current price to fall within acceptable value frameworks. Some clinical experts would even state that the discount should be higher, based on the hypothesis that it would be more reasonable in the market today to use a target of <$100,000/QALY as a drug price that would be considered more reasonable to base funding support upon, rather than the >$150,000 definition of low value [20,21].

It is critical that these issues be addressed immediately and rapidly. Regarding CAR-T applications, pediatric and young adult ALL is relatively uncommon. High-grade lymphoma is more common but multiple myeloma

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with its increasing incidence and prevalence and long expected median survival, can impact and potentially bring CAR-T therapy and its cost to many more patients. It has been well documented that cancer care and cancer drugs are rising faster than inflation and other healthcare expenditures in general [22]. We also recognize that there are fewer than 10 cell and gene therapies approved and in use in the United States currently but that there are greater than 10 products expected for approval within the next 12 to 24 months with advanced phase trials in multiple indications including cancers, blood disorders such as hemophilia and thalassemia, as well as other inherited disorders. Certainly what has brought recent heightened attention is the approval of the gene therapy Zolgensma®, by the FDA and the UK's National Health Service at a cost of approximately $2.48 million per dose [23]. It was estimated in Great Britain that as many as 80 infants and young children could potentially benefit from the gene therapy, clearly a rare event. However when one considers gene therapy for hemophilia, thalassemia or sickle cell anemia, these costs could be rapidly prohibitive for health systems. In treating individuals, cost is often not felt appropriate to consider. When managing populations however, addressing these costs of care become front and center.

Pricing remains under scrutiny. It is not linked to FDA approval in United States but this is not the same in other countries. It is often stated that the course of drug development is expensive and that pricing is often based on recapturing the cost of research and development. A recent study of 10 recently approved oncology drugs, suggested that the cost of drug development was exaggerated and the return on investment often far exceeded the cost of goods and manufacturing [24]. Sometimes, it is also important to recognize that there can be pricing backfires. For instance, for alipogene tiparvovec (Glybera®) the first approved gene therapy for lipoprotein lipase deficiency was initially priced at approximately €1.1 million. After 5 years, only one patient was treated in the world and due to inability to maintain a functional and adequate drug supply, the company discontinued its availability [25]. There is certainly very visible backlash against drug costs within the US, as the Trump and Biden administrations have both reported need for legislation to lower pricing. The Trump plan considered linking governmental payer drug payments to overseas prices while the Biden plan suggested allowing CMS to begin to independently negotiate drug prices and to give consumers the ability to import medicines from abroad. In one interesting publication, even the providers have become activists. This study evaluating the costs of tyrosine kinase inhibitor agents for the treatment of chronic myelogenous leukemia across multiple countries, the comparison outlined the price of imatinib, nilotinib, and dasatinib acquisition across 50 countries showing the dramatic variation in price [26]. This statement, published by the consortium "119 experts in chronic myeloid leukemia" addressed multiple factors involved in cancer drug pricing and their impact on individual patients and healthcare policies and argued for the need to lower pricing to allow more patients to afford these life-changing therapies and to maintain sound long-term health care policies. They endorsed the doctrine of *justum pretium* (Just Price) to determine fair market value of commodities advocating that by moral necessity, the price must reflect worth and not what the market could bear.

What is to then be expected over time? Normally we would anticipate that competition will lead to lower prices. The emergence of competitors for treatment of hepatitis C has been successful at reducing the initial target price. Similarly, the emergence of generics and biosimilars has been associated with driving down the price of commercial products [27]. We understand that many of the new agents have extended the survival of patients with cancer and changed the natural history. However, it is also important to reflect that estimates of the cost of cancer care in United States in 2010 was approximately $125 billion [28], estimated

to approach $200 billion by 2020, at which time lymphoma itself was estimated to have expenditure of between $15 and $20 billion [29]. There are now projections regarding the US cancer incidence and death rates continually extending to 2040 [30]. Cancer is not going away, and neither is the costs of cancer care. We will continually see advances but we must also expect changes in the healthcare and overall payer industry systems, particularly as costs of care increase. Already we are experiencing demands for value and quality often achieved with reproducible and well-defined pathways of care. Centers of excellence are selected and increasingly patients, payers and employers are demanding transparency across healthcare including visibly publishing the prices of drugs and outlining choices. Value based contracts are growing with real-time monitoring for patient outcomes for contract adjudication [31]. Performance-based risk sharing agreements between payers and manufacturers are commonly found in the United Kingdom and the European Union but have been less frequently used in the United States, although they are now increasing. Consequently manufacturers are now sharing the financial risk where drug clinical failure occurs and there is payback from the manufacturer to the payer. In our cell therapy world, Novartis with its drug tisagenlecleucel has entered in such an agreement where if ALL patients do not gain standard clinical remission determination by day 42, then payment is not collected. Similarly, for example with gene therapy, Voretigene neparvovec-izyl (Luxterna®) has value based contracts regarding visual milestones that must be met before payments are provided.

We recognize that the demand for healthcare remains a priority and even more so, assuring access to healthcare for all is critical. What is necessary as a universal goal is to make patients healthcare delivery efficient and assure that value is confirmed. The American Society for Quality (ASQ) has defined Healthcare Services that neither add value, nor improve patient outcomes, to be considered waste [32]. In a previous study published in 2012, it was estimated that the US healthcare system wastes approximately $750 billion annually. One of the 6 domains used to define the pricing failures in the above study was 'market value for no reason'. Estimates in this category for the US was a median estimate of $169 billion [32]. Shrank *et al.* updated this analysis in 2019, from information obtained from the public domain and after the development in implementation of the ACA [33]. Their conclusions were that estimates of waste still range between $750–900 billion but as a country, we were more efficient where only ~25% of healthcare dollars fall in the waste category as opposed to 33% in 2010.

We will continue to see novel approaches on how to assess value and also, novel means by which payment for healthcare can be delivered, possibly even by amortization over time. An interesting proposal for management of expensive drugs that are often on accelerated approval tracks from the FDA was published by Gellad and Kesselheim [34]. In effect, they report that many of these agents emerging in the gene and cell therapy are approved with limited evidence. They proposed models for how to assure that patients in healthcare systems are getting value for their expenditure of both time and dollars. They had 5 different suggestions including:

1. That companies would be reimbursed only the actual cost of the manufacture of the drug and some agreed-upon percent markup until confirmatory trials demonstrated clinical benefit;

2. That confirmatory trials conducted after receiving accelerated approval must be performed in a timely fashion and be designed optimally to limit the period of uncertainty about clinical effect;

3. All drugs that moved to the accelerated approval pathway and cost overall $100,000 per year or other agreed-upon threshold, must be subject to formal economic impact analyses after 1 to 2 years on the market;

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4. That additional price concessions to public insurance programs for drugs receiving accelerated prove should be granted until confirmatory trials are completed; and

5. That a portion of drug payment be held in escrow until efficacy is confirmed and if the drug is found later to be clinically ineffective, that payers be reimbursed.

We are all excited about the profound changes in the rapidly evolving cell therapy market. We see multiple autologous and allogeneic products emerging for a multitude of malignancy types. There is also potential of extension to other organ systems (for example myocardial infarction repair), for treatment of autoimmune diseases, and certainly for replacement therapies with approvals on the near horizon for gene modified cullular therapies like sickle cell and thalassemia. It has been standard for drug development to focus on safety and efficacy, but we believe that cost and value assessments will also emerge as critical to perform before drugs reach market approval. It is important to recognize whether agents are being developed for one-time use or for repeated treatments, and if they are stand-alone therapies or a bridge to alternative therapies. We understand that CAR-T therapy for relapsed refractory large cell lymphoma has led to the FDA approval of 3 independent agents, but we also recognize that 50 to 60% of patients who receive those agents will have disease progression and will often go on to further therapeutic interventions. As such, we are recognizing that CAR-T therapy may not be a stand-alone therapy but may be given in combination with other agents. Alternatively, randomized trials are awaiting determination of whether CAR-T therapy should be offered to patients experiencing first relapse of large cell lymphoma, rather than for those with advanced relapsed refractory disease. As such, it is appropriate to question if the current CAR-T prices are acceptable, or if they should be lowered. As such, it will be critical that we continually endorse and utilize value and quality assessments and various framework tools that exist to determine value and quality, particularly in the oncology world, including ASCO, ACC/AHA, NCCN, ICER, MSKCC Drug Abacus and Avalere-FasterCures Patient-Perspective Value frameworks. How to define? As Vanness reported in 2018, the ideal framework needs to be comprehensive in scope, patient-oriented, incentive-compatible, expedient, forward-looking and dynamic (Box 1) [35]. For now the current tools each provide some, but not all, of these targets thus necessitating technology assessment programs to utilize multiple approaches to provide their final assessments of value and quality.

In conclusion, the observation remains that there are multiple emerging gene and cellular therapies with anticipated enhanced efficacy justifying patient utilization but also

BOX 1

Ideal value-based framework.

- **Comprehensive in scope:** Consider the comparative comprehensive costs and outcomes of treatments, including ancillary services, and future related medical events
- **Patient-oriented:** Value health outcomes (including death) from the patient's perspective
- **Incentive-compatible:** Incentivize development of technology that improves population health without further increasing the share of GDP allocated to healthcare
- **Expedient:** Provide the earliest possible access to treatment for which evidence indicates positive expected net benefit
- **Forward-looking:** Guide the subsequent gathering of evidence, including long-run, confirmatory, and real-world outcomes studies
- **Dynamic:** Transparently update payment schedules and clinical practice guidance reflecting updated comparative evidence

with attributed acquisition cost ranging from approximately $400,000–2,000,000. All are increasingly recognizing the critical need for value frameworks and technology assessment programs to balance the expenditures versus the burden of disease over lifetime. What remains challenging is the implementation. From health policy perspectives, cost containment makes sense from a population management viewpoint. When faced with single individuals, directly under care, stringent guidelines will likely remain difficult to enforce. Thus, comprehensive, patient oriented, incentive compatible, expedient, forward-looking and dynamic value frame works (Box 1) are predicted to become more frequently used tools by which medical practice is managed.

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BUSINESS INSIGHT: JULY 2021

EXPERT INSIGHT

Solving the problem of financing one-time treatments with evidence uncertainty: which types of outcomes-based payment models could work best for novel CAR-T therapies in multiple myeloma? A systematic review of the published literature

Cassidy-Candice Dietrich, Clare Hague & Stefan Boes

Managed entry agreements (MEAs) are arrangements between a manufacturer and payer/health care provider that grant access (coverage/reimbursement) to a health technology, subject to fulfillment of specific conditions. An increasing number of payers in different countries are implementing MEAs to enable timelier access to cancer therapies. Novel chimeric antigen receptor (CAR) T-cell therapies are one such example where MEAs can play a prominent role in accelerating patient access. CAR-T therapies are administered to patients as a single, one-time treatment. 'Spread payment' models can help to reduce the

(front-loaded) cost impact on payers' annual health care budgets. Furthermore, CAR-T therapies are associated with uncertainty around their clinical and economic value proposition, whilst data on their long-term safety and clinical effectiveness are pending. Such uncertainty can be ameliorated, in the most part, through outcomes based MEAs, where payments can be made in installments, according to patient outcomes that are observed in routine clinical practice. Well-validated and objective measures are however prerequisite to successful outcomes-based schemes, as is high quality data together with the ease of implementation. A systematic review of the published literature over a 5-year period (2015–2020) was performed to better understand the nature of outcomes-based MEAs employed to date, as a conditional requirement for the reimbursement of CAR-T therapies. Their applicability to, and suitability for, a future generation of CAR-T therapies in development for multiple myeloma (MM) are considered, drawing on the recent experience from regulatory approved CAR-Ts in acute lymphocytic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

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INTRODUCTION

The development of CAR-T therapies for multiple myeloma

Cancer remains a devastating global public health challenge. Scientific research has focused on gaining an enhanced understanding of disease, genomics and molecular characterization of tumors which has led to the development of innovative cancer treatments [1] which include advanced therapy medicinal products (ATMPs) [2]. ATMPs consist of gene therapies, somatic cell therapies, and tissue-engineered products [3].

Chimeric antigen receptor (CAR) T-cell therapies are ATMPs made up of a patient's own T cells (a type of white blood cell) that have been genetically modified in a laboratory so that they make a protein called chimeric antigen receptor (CAR). With this receptor on their surface, the modified cells, called CAR-T cells, can attach to a target on the surface of plasma cells called B-cell maturation antigen (BCMA). When the modified T cells are infused back into the patient, they are expected to attach to this target and kill the abnormal plasma cells, thereby helping to clear the cancer from the body [4].

Those CAR-T therapies that have received Marketing Authorization from the European Commission (EC) include Kymriah® (tisagenlecleucel), Yescarta® (axicabtagene ciloleucel) and KTE-X19.

- Kymriah® is indicated for the treatment of pediatric and young adult patients (up to 25 years of age) with B-cell acute lymphocytic leukemia (ALL) that is refractory or in second or later relapse, and in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy [5];
- Yescarta® (axicabtagene ciloleucel) is indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy [6];
- Conditional authorization was recommended by the Committee for Medicinal Products for Human Use (CHMP) on October 16th 2020 for KTE-X19, which is indicated for adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor [7].

Following in the footsteps of the CAR-T therapies for ALL, DLBCL and MCL, are over 100 clinical studies investigating the use of CAR-T cell therapies in a variety of treatment lines and settings for multiple myeloma (www.clinicaltrials.gov date 18.02.2021 [8]). 119 trials were identified using the search terms of title: multiple myeloma; other terms; CAR T (Figure 1).

Multiple myeloma is a cancer of the plasma cells. Plasma cells are produced in the bone marrow (the spongy tissue inside the large bones in the body). In multiple myeloma, the division of plasma cells becomes uncontrolled, resulting in abnormal, immature plasma cells multiplying and filling up the bone marrow. This interferes with production of normal white blood cells, red blood cells and platelets (components that help the blood to clot), leading to complications such as anemia (low red blood cell counts), bone pain and fractures, raised blood calcium levels and kidney disease.

Multiple myeloma is a debilitating and life-threatening disease, particularly because it disrupts the normal functioning of the bone marrow, damages the bones and causes kidney failure [4]. According to the latest Global Cancer Observatory (GLOBOCAN) statistics, there were an estimated 160,000 cases of multiple myeloma globally in 2018, accounting for 0.9% of all cancer diagnoses [9]. Approximately 90,000 of those cases were in males and 70,000 in females, which equates to an age-standardized incidence of 2.1/100,000 and 1.4/100,000, respectively [10].

Novel treatments for myeloma have significantly improved survival rates over the years, however most patients will suffer multiple relapses. These relapses present clinical challenges and economic costs. An exploratory study by Hulin *et al.* [11] highlight the devastating impact that relapse has on patients from a psychological, physical, financial, and logistical perspective.

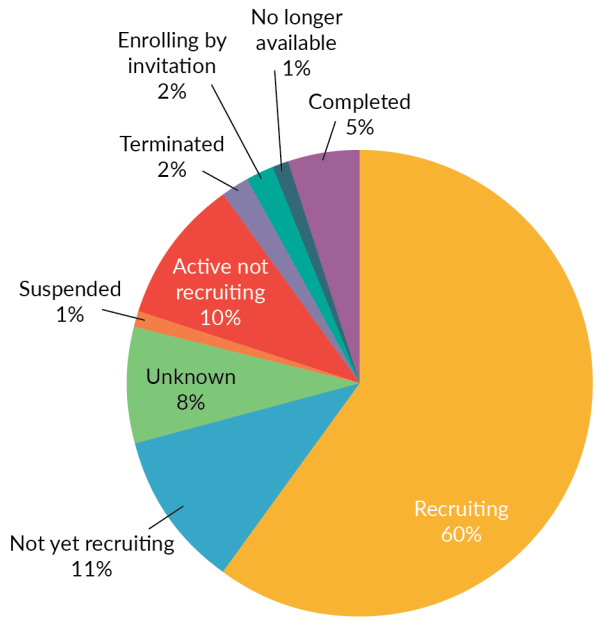
Whilst CAR-T therapies have been described as representing a 'breakthrough' for patients with cancer that have failed to respond to prior therapies [12], there remains some uncertainty around their economic value proposition, whilst data on patients' longer-term safety and survival outcomes are pending [13].

One has to consider these uncertainties however in the context of the bigger picture. Global expenditure on cancer is increasing [14,15] and questions raised as to whether such levels of spending are sustainable and justified [16–19]. Instances where medicines have failed to demonstrate their effectiveness in the post-authorization setting, when reimbursement has been conditional upon this, further fuels a debate and reluctance towards early access and conditional approvals of (potentially) innovative cancer medicines [20].

Agreeing on a single (one-time) fixed price for complex and high cost treatments can indeed pose a financial risk for both payer and manufacturer [21]. This risk may be ameliorated however through spreading payments over time using outcomes-based managed entry agreements (MEAs), where payments are typically made in installments, according to (pre-specified) outcomes that are observed in routine clinical practice. Managed entry agreements are defined as "arrangement[s]

FIGURE 1

Clinical trials of CAR-T therapies in multiple myeloma (as of 18/02/2021) (n = 119).



between a manufacturer and payer/provider that enable access to (coverage/reimbursement of) a health technology subject to specified conditions" [22]. Following the definition of Wenzl and Chapman [23], there are two types of MEAs:

1. Financial; and
2. Performance-based MEAs.

Financial agreements can take various forms from simple discounts or rebates, to more complex payment schemes such as annual budget caps or price-volume agreements [23]. Performance-based or outcomes-based payment (OBP) models are characterized by payments related to outcomes observed in real-world clinical practice. Figure 2 provides an overview of the taxonomy for MEAs.

Which types of outcomes can be used in OBP models?

There is a range of possible outcomes that can be used in OBP models. Clinical outcomes are still preferred by payers; and whilst patient-reported outcomes (PROs) such as health-related quality of life are also of great interest, these are challenged by current data collection systems as PROs are not generally captured in routine clinical practice. In general, objective outcomes are needed, and therefore validated measurements are required when implementing patient-reported outcomes, otherwise 'gaming of the system' may occur [21].

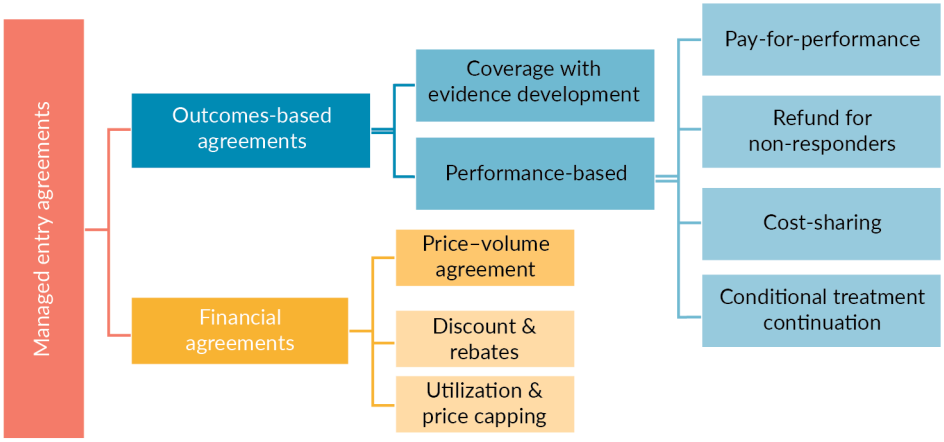
In the report of Cole *et al.* [21], the introduction of OBP schemes for cancer drugs in the UK National Health Service (NHS) was explored. They propose an outcomes framework which is shown in Figure 3 illustrating all the possible outcomes for OBP schemes. They also describe several contextual factors, like individual (patient) preferences, the type of cancer, and drug type to play an important role when defining an outcome as 'important'. Clinical outcomes have been found to be preferred by older patients, whereas outcomes measuring 'functioning' are rated as more important by younger patients [21].

Lorgelly *et al.* [24] identified the four most important core outcomes for cancer patients and carers:

1. Survival;
2. Disease progression, relapse or recurrence;
3. Long-term side effects; and
4. Return to normal activities.

FIGURE 2

Managed Entry Agreements categories.



Modified from [90, 91].

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The most preferred options (survival and (disease) progression) are defined as 'hard' outcomes that can be measured objectively, but progression as an outcome can also be considered 'subjective' regarding the degree of tumor growth. Side effects and return to normal activities are not currently collected during routine practice, which can represent a barrier for using these measures in OBP schemes [21].

WHAT ENABLES OBP SCHEMES & WHY ARE FINANCIAL SCHEMES ARE STILL PREFERRED?

The right data infrastructure and technical framework is needed to enable the broad use of OBP schemes. With the introduction of the Standard Monitoring Registries (SMRs) in 2005, Italy represents a great example of a country with the right infrastructure in place to enhance access to innovative treatments. The Cancer Drugs Fund in the UK also enables MEAs or 'coverage with evidence development schemes' and is thus able to shorten the time to patient access. Public Health England's National Cancer Registration and Analysis Service (NCRAS) contains the National Cancer Registry for England and linked data sets including Hospital Episode Statistics (HES), the Systemic Anti-Cancer Therapy (SACT) dataset which includes all anti-cancer treatments and death registration and geographic data provided by the Office of National Statistics (ONS) [25].

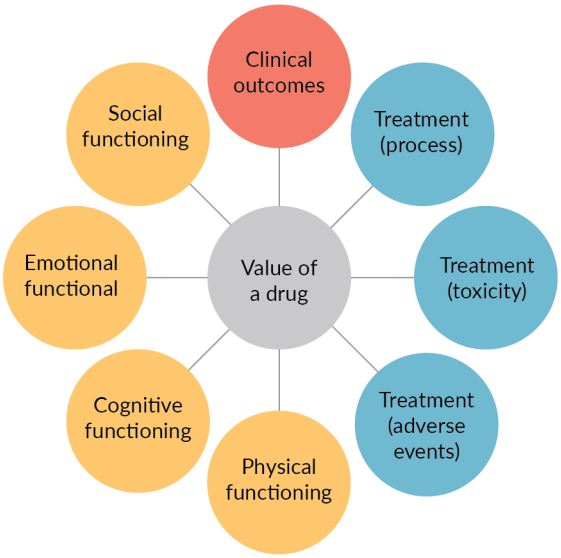
More than half of all ATMPs in Germany are reimbursed under a MEA which suggests that dealing with uncertainty in ATMPs represents a new challenge for which old ways of addressing uncertainty in the value assessment do not work [26]. In Middle and Eastern Europe, the most stated reason for MEAs was to overcome budgetary challenges [27].

Advantages of OBP schemes

OBP schemes can help to manage high one-time treatment costs where there is uncertainty

FIGURE 3

Possible outcomes which can be used in OBP schemes Cole *et al.* [21].



of the underpinning evidence (as it relates to efficacy/safety/cost–effectiveness) and be a conduit for improving and accelerating patient access to cell and gene therapies [28].

Challenges of OBP schemes

There are some challenges to using OBP schemes, however. Concerns around data quality has been cited as a barrier to implementing OBP schemes, as is the absence of the right infrastructure needed to collect the data which may include hiring new staff [21]. High administrative burden and costs, lack of transparency, conflicts of interest and problems in measuring the right outcomes have also been cited as potential challenges [29].

Collecting real-world data quickly to inform pricing decisions can also be considered a barrier, as few countries have sufficiently robust patient level databases to enact such schemes [30]. In an ideal world, a common data source would be used at a country-level to capture data to support OBP schemes to avoid different mechanisms of data capture to support the evidence requirements of (multiple) individual treatments. Yet,

not every OBP scheme is based on observational (real-world) data; some coverage with evidence development (CED) schemes focus on new information from ongoing clinical trials, as seen in Australia for 'Keytruda' where new data on progression-free and overall survival were collected from the ongoing KEYNOTE-006 trial for patients with advanced melanoma [21,31]. In countries where patients can move from one insurance company to another from one year to the next, this can also pose challenges to implementing OBP schemes – since the company that pays for the initial treatment may not be the one that re-coups the benefit of the treatment.

In anticipation of a future scenario whereby there are regulatory approved BCMA and/or other CAR-T therapies licensed for patients with multiple myeloma, it will be important to determine which types of MEAs may be most appropriate (given the one-time treatment administration) to secure reimbursement. There have been very few known examples of OBP schemes for patients with multiple myeloma, with the exception of Velcade® (bortezomib) for the treatment of multiple myeloma. In the case of Velcade® (bortezomib), a pay-for-performance scheme was implemented in 2007 in the UK based on treatment response. In cases where patients did not respond to the treatment the company rebated the full costs (n.b responses measured as a 25% or greater reduction in serum M-protein levels [21].

This systematic review, therefore, aims to provide an overview of existing OBP schemes for cancer therapies and consider their application to novel CAR-T therapies for multiple myeloma.

METHODS

Search strategy

A systematic search of the grey and published literature was performed (September–October 2020) to identify which OBP schemes had been implemented after 2015 in different countries between payers and manufacturers for the reimbursement of cancer medicines.

All articles published from Jan 1, 2015 until October 31, 2020 were included. Clinical trials and purely theoretical studies were excluded. To be considered eligible, an article had to have an objective analysis of a MEA in one or more countries and needed to differentiate between the type of MEA (whether it be a financial and/or outcomes-based MEA). MEAs for diseases other than cancer were excluded, as were outcomes-based schemes that were implemented before 2015. The search strategies for this review are described in Suplementary Material 1.

Those databases searched include:

- Cochrane Database of Systematic Reviews (CDSR) via Cochrane Library, searched on September 07, 2020;
- Medical Literature Analysis and Retrieval System Online (MEDLINE) via EBSCO, searched on September 07, 2020;
- PubMed, for relevant journals not indexed in MEDLINE, searched on September 07, 2020;
- Web of Science Core Collection, searched on September 07, 2020;
- Scopus searched on September 07, 2020.
- Search alerts have been checked until the end of October 2020.

A search strategy based on synonyms for four keywords was applied: Outcome-based, pricing, cancer, treatment. Filters were applied to restrict the year of publication from 2015–present day. No filters were applied to study types. An EBSCO MEDLINE search strategy was developed. This strategy was modified to fit the syntax of the other databases. The reference lists of eligible articles

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were searched by hand. Furthermore, relevant references provided by the Janssen-affiliated author were screened.

Searches of Google scholar and Google were conducted to complement the database searches. The first 60 hits were screened.

Furthermore, targeted internet searching of key organizational websites was also performed:

- The Organization for Economic Co-operation and Development (OECD) [32] (searched on 07/09/2020 "performance-based managed entry")
- Institute for Clinical and Economic Review [33] (searched on 08/09/2020 "gene therapy")
- The Office of Health Economics [34] (searched on 07/09/2020 "outcome-based")
- European Medicines Agency [35] (subsequential searches for different drugs)
- Websites of regulatory/HTA agencies which contain public information on MEAs
  - England: National Institute for Health and Care Excellence (NICE) [36] (searched 17/8/2020, 25/09/2020, 16/08/2020 "NICE-recommended technologies that include a commercial arrangement")
  - Italy: Agenzia Italiana del Farmaco [37] (searched 14/09/2020, 08/10/2020 "Lista aggiornata dei Registri e dei Piani Terapeutici web based")
  - Germany: Gemeinsamer Bundesausschuss [38] (searches for specific drugs)
  - France : Haute Authorité de Santé [39] (searches for specific drugs)
  - Belgium: National Institute for Health and Disability Insurance [40]

Data collection & extraction

The main researcher conducted the database searches. Articles not written in English, German, or French were translated using online software. At first, the titles of the articles were screened, and articles not related to the topic were excluded. Second, the abstracts of all remaining articles were screened. If no abstract for the article was available in the database, the full-text article has been searched on the search portal of IDS Lucerne [41] and then full-text articles were screened. In the last step, the main researcher read the remaining full text. Duplicates were removed using Endnote X8.

An Excel File sheet was prepared including the following information: Generic and brand name of the drug, implementation year/country, manufacturing company, cancer type, respective OBP scheme and a detailed description and the source of information. Information from the Excel File was used to fill summary tables which then formed the basis for the analysis. Bias was minimized by double-checking the included references and ensuring only necessary exclusion was made. Furthermore, weekly meetings with the second author were held to discuss the selection process. To deal with missing data because of the confidentiality of concrete reimbursement contracts, the respective drug was searched up in the relevant grey literature to find more information. Available information varied between countries.

The ideal attributes for a successful outcomes-based scheme were deemed as follows:

- Outcome measures should be clinically meaningful
- Outcome measures should be objective (and auditable)
- The methods by which the outcomes are measured should be non-invasive (from a patient perspective)

- The operationalization of the outcomes-based scheme should not be burdensome to implement for data collectors
- The outcome measures should be routinely captured in clinical practice

These criteria formed the basis by which to evaluate which types of OBP models could work best for novel CAR-T therapies in multiple myeloma.

RESULTS

The literature search for OBP schemes in databases, websites of regulatory authorities, grey literature including google scholar, reference scanning, and input from company meetings, yielded 2626 articles. After removal of 1209 duplicates, 1417 references titles and abstracts were scanned which resulted in the exclusion of 1321 references. From this, 96 articles were considered potentially relevant. After the full-text screening, 62 articles were excluded because they did not meet the predefined inclusion criterion based on the time frame and the exclusion of purely theoretical papers. For some studies, updated and more detailed information on the number and types of MEA in some countries could have been found in other articles. Following the selection process shown in the PRISMA flow diagram (Figure 4), 34 (1.3%) articles were included.

Categories of OBP schemes

An overview of the different categories used in OBP schemes are described (Table 1) [21].

FIGURE 4

Prisma flow diagram.

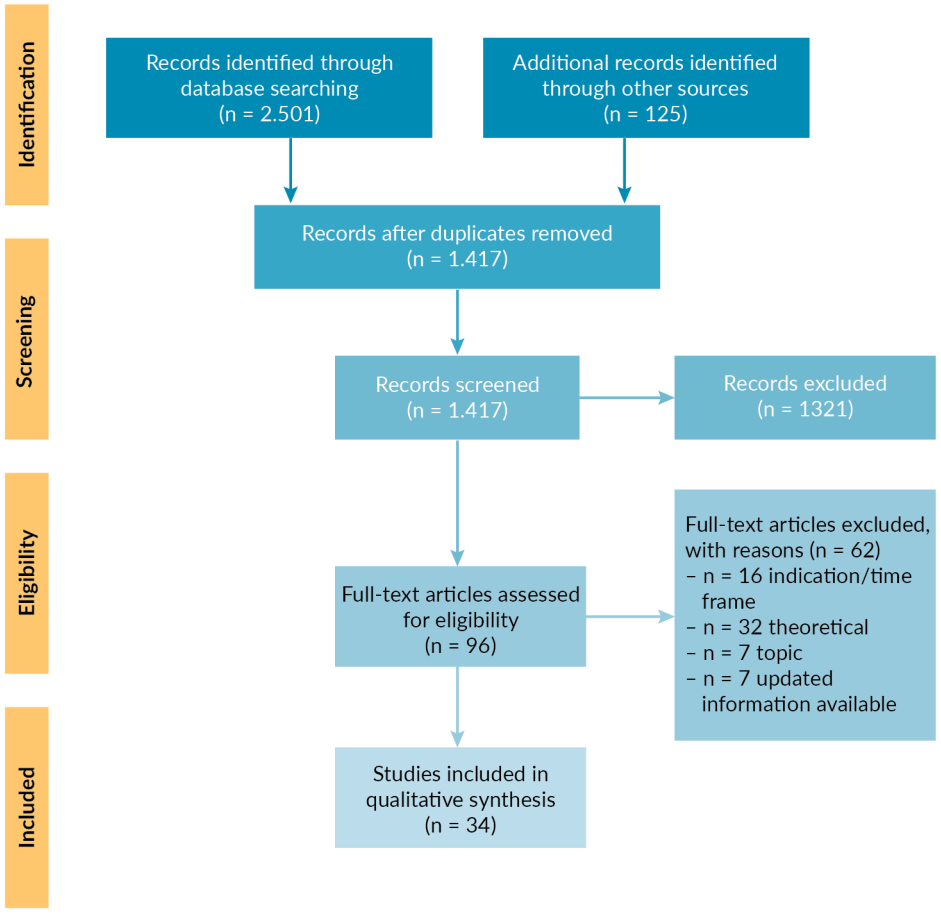

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TABLE 1

Categories of OBP schemes.

Category	Definition	Example
Refund for non-responders (payment-by-results or risk sharing)	Total or partial reimbursement by the manufacturer for non-responders	**Imnovid® (pomalidomide), multiple myeloma** Paybacks of full drugs cost for early dropouts due to progression or unsustainable toxicity [85]
Pay-for-Performance (outcome-guarantee)	Rebates, refunds or price adjustments for patients not reaching pre-defined outcomes	**Velcade® (bortezomib), multiple myeloma** Rebates of total costs for patients who do not have a 25% or greater reduction in serum M-protein levels [21]
Coverage with evidence development	Initial access is provided but further population-level data needs to be collected, reassessment after a specific time period	**Ninlaro® (ixazomib), multiple myeloma** Included in the CDF. Further data need to be collected to address the clinical uncertainty of overall survival (OS), duration of treatment and quality of life (QOL) [86]
Conditional treatment continuation	Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level	**Revlimid® (lenalidomide), myelodysplastic syndrome** Initial treatment is up to 16 weeks. Patients are eligible for continuing treatment until there is evidence of disease progression to acute myeloid leukemia or if the patient is unable to achieve or maintain adequate red blood cell transfusion response. Patients receiving lenalidomide under the PBS listing must be registered in the i-access risk management program [87]
Cost-sharing	Reduced price paid at the beginning of the treatment; further payments are only made if the predefined clinical outcome is achieved	**Kymriah® (tisagenlecleucel), ALL, DLBCL** 50% paid at administration and 50% after 1.5 year for patients with a complete response [51]

Adapted from [21].

Table 2 provides more specificity in relation to oncology. N.B. To provide relevant insights, the experiences of other CAR-T reimbursement schemes are described (Table 3).

Detailed lists of drugs with an OBP scheme were available in Italy and an overview of drugs included in the Cancer Drugs Fund was available for the UK. For all other countries, information was mainly based on published articles and therefore limited to the time frame of the source. CED schemes are mostly frequently applied followed by 'Payment by Results'. Countries have their own preference for a given type of scheme which is shown in the following and is concluded with an example per country.

The specific cancer-related outcomes of potential relevance to multiple myeloma CAR-T therapies are described (Table 4) and evaluated further according to pre-specified criteria of whether the measures are clinically meaningful, objective, non-invasive, non-burdensome to implement and routinely captured in clinical practice (Table 5).

As one can see from Table 5, there are only two outcomes/endpoints used in the outcomes-based schemes that meet the specified criterion: overall survival and duration of treatment. Progression-free survival (PFS) and response (to treatment) both require invasive means to measurement and can pose a burden on the patient and health care system if not part of routine clinical practice. Adverse events/toxicity may be measured in a different way outside of a clinical trial setting and may not be consistently captured, explaining why some of the boxes have question marks in them.

Evolution of the use of OBP schemes in different countries

The numbers of OBP schemes for cancer therapies clustered for different countries is shown (Figure 5).

TABLE 2

OBP schemes in oncology in some EU countries.

Country	Time frame*	Total Nb.	Preferred option	Outcomes	Ref.
Italy	2015 to 29/09/2020	11 active	Payment-by-result	Response	[85]
UK	2015 to 31/12/2020	53	Coverage with evidence	OS, PFS, quality of life, duration of response	[21,44,45,86]
Spain	2015 to 2019	6	Payment-by-result	Response	[50,57,73]
France	2015 to 2019	4	Coverage with evidence	Efficacy	[52–55,57]
Germany	2015 to 2019	2	Risk-sharing	Survival	[26,56,57,73]

*Due to the different availability of public information in the different countries some information is restricted to limited time frames.
**The preferred OBP scheme is based on the category with the highest total number identified in this review. It can, therefore, only be seen as a predictor for the actual preferences of the respective country.

United Kingdom

In the United Kingdom, MEA are called Managed Access Agreements (MAAs) and can include an agreement on data collection and either a commercial access agreement (CAA) or a Patient Access Scheme (PAS). A PAS can be a simple (discount) scheme or a complex scheme.

In contrast to a simple PAS, a complex PAS is not confidential. By definition, it will involve a more complex reimbursement proposal that, in turn, will be more complex to administer within the NHS. The requirement for transparency is to ensure the administrative burden and cost to the service of implementing such schemes is minimized and helps ensure the value of the treatment, as determined by NICE, is achieved [42].

In addition, 'commercial access agreements', which unlike complex PAS schemes, are confidential, can include rebates, free stock, dose capping, or outcome-based schemes [42]. The Cancer Drugs Fund (CDF) covers the cost of cancer treatments that do not meet NICE's criteria for baseline commissioning. Patients receive access to new drugs within the CDF via MEAs which represent some kind of coverage with evidence development (CED) agreement [21], where there is uncertainty around the effectiveness of the new treatment and therefore further data is collected. With this approach, patients get earlier access to promising new technologies [43].

A well-documented example of an OBP scheme from 2007 in the UK is Velcade® (bortezomib) for the treatment of multiple myeloma which represents a pay-for-performance scheme based on treatment response. For patients not responding to the treatment the company rebates the full costs with responses measured as a 25% or greater reduction in serum M-protein levels [21]. At the end of 2020, there were 53 drugs with an MAA included in the CDF [44]. Simple patient access schemes are preferred because of the perception that complex PAS are more burdensome for the manufactures and the NHS and therefore are only considered in special cases [42]. Kymriah® and Yescarta® are both included into the CDF for a limited time period and are reimbursed under a CED model [45].

Italy

The second most frequently observed country using OBP schemes is Italy. Italy is very experienced with MEAs – both financial and outcomes-based [46]. By the end of September 2020, there were 11 active cancer drug approvals with an outcomes-based agreement implemented after 2015 (28; from 2008–now). 16 OBP schemes for cancer drugs have been closed after 2015 (19; 2014–now). The drug 'Avastin® (bevacizumab)' for cervical cancer was implemented in 2016 but is already closed. All identified MEAs represent payment-by-results schemes with rebates for non-responders, except for Kymriah® and Yescarta® for which a new modification from the previous payment-by-result schemes has been

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used, 'Payment-at-results' where payments are staged for responders [47]. By the end of 2019, performance-based MEAs in the form of payment-by-result schemes represented 53% of all MEAs [48].

Spain

In Spain, Catalonia is the region with the most experience in OBP schemes [49]. Four payment-by-result schemes were signed in Catalonia in 2017 for cancer drugs [50]. Agreements for Kymriah® and Yescarta® were made on the basis of staged payments based on patient's response and survival [51].

France

For France, very limited information on MEAs is available in the public domain as most of it is confidential. In an OECD survey from 2019, France reported using 4 OBP schemes [23]. An OBP scheme for 'Imnovid® (pomalidomide)' in treating multiple myeloma was implemented, where the manufacturer (Celgene) needed to create a real-world data collection registry and coverage by the health insurance was made if the value for patients was demonstrated, otherwise Celgene was required to reimburse the health insurance company [52]. A CED scheme was also

TABLE 3

Examples of MEA for CAR-T therapies.

Brand name	Country	Category	Definition	Outcome	Ref.
Kymriah®	Italy	Payment-at-result	Payments are made for responders only, at infusion, 6 and 12 months	Response	[73]
Kymriah®	UK	Coverage with evidence	Kymriah® was included in the CDF with an MAA that includes a PAS+CAA to collect further data on OS and PFS	OS, PFS	[88]
Kymriah®	Belgium	Coverage with evidence	Additional data on the response to treatment and the condition of the patient need to be collected at 6, 12, 18 and 20 months after infusion	Response, condition of the patient	[73]
Kymriah®	Spain	Cost-sharing arrangements	50% (160,000 Euros) at administration, 50% after 1.5 years but only if the patient has had a complete response to treatment and is 'disease-free'	Response	[51,57]
Kymriah®	USA	Pay-for-performance	Payment only if the patient achieves the anticipated complete remission status by the 35th day after infusion. Applicable for all eligible patients, regardless of their insurance payer (limited to the pediatric indication)	Response	[70]
Kymriah®/ Yescarta®	France	Coverage with evidence	▶ Follow-up data from ongoing trials, data from post-authorization efficacy studies (Kymriah®) and data from ATU ▶ Establishment of a register for all eligible patients in France for short and long-term efficacy, safety and response ▶ Collection of clinical data of patients eligible for treatment under the post-ATU scheme	Efficacy	[54,55,73]
Kymriah®	Germany	Risk sharing	A partial refund of the treatment costs if the patient dies of the indicated disease within a specified period	Survival	[73]
Yescarta®	UK	Coverage with evidence	Yescarta® was included in the CDF with an MAA that includes a CAA to collect further data on OS and PFS	OS, PFS	[89]
Yescarta®	Spain	Cost-sharing arrangements	Staged payments at first 118,000 Euros (36% of the total) and then 209,000 euros based on patient survival	Survival	[51,57]

TABLE 4

Outcomes-based MEA for multiple myeloma.

Name	Country/ date*	Category	Definition	Outcomes	Ref.
Imnovid® (pomalidomide)	Italy (2015)	Pay-ment-by-result	Paybacks of full drugs cost for early dropouts due to progression or unsustainable toxicity	Treatment response	[85]
Darzalex® (daratumumab)	UK (2018)	Coverage with evidence	Included in the CDF with an MAA (+PAS +CAA). Data need to be collected based on OS, treatment duration and subsequent treatments following daratumumab	OS PFS Duration of treatment	[86]
Darzalex® (daratumumab with bortezomib and dexamethasone)	UK (2019)	Coverage with evidence	Daratumumab was included in the CDF with an MAA that includes a PAS+CAA to collect further data on OS	Updated OS data	[86]
Ninlaro® (ixazomib)	UK (2018)	Coverage with evidence	Ixazomib was included in the CDF. Further data need to be collected to address the clinical uncertainty of overall survival (OS), duration of treatment and HRQoL	OS, duration of treatment and HRQol	[86]
Imnovid® (pomalidamide)	France (2015)	Coverage with evidence	Creation of a real-world data collec-tion registry, reimbursement if not shown to be beneficial	Treatment response	[52]
Ninlaro® (ixazomib in combina-tion with lenalidomide and dexamethasone)	France (2017)	Coverage with evidence	New evidence from ongoing trials with primary endpoints of progres-sion-free survival	PFS	[49,53]

*Based on the approval of the MEA

agreed in 2017 for 'Ninlaro® (ixazomib)' in combination with lenalidomide and dexamethasone for treating multiple myeloma in 2017 [49,53]. Kymriah® and Yescarta® also are reimbursed under CED schemes therefore a registry was needed for the CAR-T therapies for all eligible patients in France [54,55].

Germany

Germany has had limited experience with implementing MEAs, with the exception of the recently approved CAR-T therapies. The first agreement for an ATMP was agreed for Kymriah® [56]. Currently five MEA are in place for ATMPs for various indications, with three OBP schemes having pre-defined rebates based on patient survival or staged payments and two OBP schemes based on the duration of treatment or need for subsequent treatments [26]. The agreement for Kymriah® include a partial refund of the treatment costs in case the patient dies within a specified time period [57].

Belgium

Since 2010 for treatments without a recommendation for reimbursement or with a negative recommendation from the reimbursement commission, Belgium permitted the use of MEAs (so-called 'conventions'). Conventions are used to collect additional information when there are therapeutic or budgetary uncertainties. In 2019, 53 MEAs were implemented for which no differentiation between financial or outcomes-based MEAs is made, as payments are combined with conditions that the health insurance only covers the costs if there is a benefit to the patient or when there is sufficient scientific evidence of its efficacy and safety. Most of the conventions are concluded for antineoplastic and immunomodulators drugs [58].

Portugal

From 2014 to 2016 Portugal celebrated around 80 MEAs but these were mostly

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financial in nature. Outcome-guarantee and CED schemes were used in OBP schemes. MEAs are increasingly used to tackle uncertainty in Portugal [59].

Sweden

Between 2015–2019, the literature found 56 MEAs of which 14 were in oncology but none where rebates were based on outcomes. For orphan drugs, the main concern is affordability rather than uncertainty around clinical effectiveness [60].

Central/Eastern Europe

The survey of Ferrario *et al.* [27] involved key informants from 16 CEE countries; of which 12 had implemented MEAs. Albania, Kosovo, Russia, and Slovakia have no MEAs in place, but Slovakia is discussing new ways to increase access to innovative medicines. All 12 countries have implemented financial MEAs and 8 countries (Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Poland, Romania) have allowed the use of outcomes-based MEAs. A more recent study reported that only Hungary and Poland are using outcomes-based agreements but did not analyze the situation in Estonia and Latvia [61]. Most MEAs in Central/Eastern Europe are for antineoplastic agents and are implemented in Estonia. Nevertheless in Slovenia, Hungary, Latvia, Estonia and Romania financial agreements are clearly preferred; only around 1% (10) are payment by results schemes [27]. In the survey by Wenzl and Chapman [23] Estonia reported eight OBP schemes for various indications which are under payment-by-results schemes. Hungary reported using seven OBP schemes which are payment-by-result schemes or based on conditional treatment continuation.

Australia

The National Pharmaceutical Benefits Scheme (PBS) provides access to medicines in Australia [62]. Public information on MEAs reports only the existence of an MEA since detailed information is confidential [63]. From the literature, Australia is identified as a country with a lot of experience in implementing MEAs [31,46,63,64]. Despite this, from 2012 to mid-2016 only 5% of all MEAs were based on outcomes, with 81% based on simple financial agreements. Anticancer or immune-based diseases represent the majority of MEAs [63]. Tuffaha and Scuffham [31] reported three hybrid agreements (CED with rebates) to collect more data to tackle clinical uncertainty. Financial MEAs seem to be still the preferred option where they rely on already existing simple datasets as the PBS claim dataset and are therefore less costly to implement than MEAs requiring capture of clinical patient data [63]. The CAR-T therapy Kymriah® is publicly funded and manufactured in Australia where information on an MEA could not be identified [65].

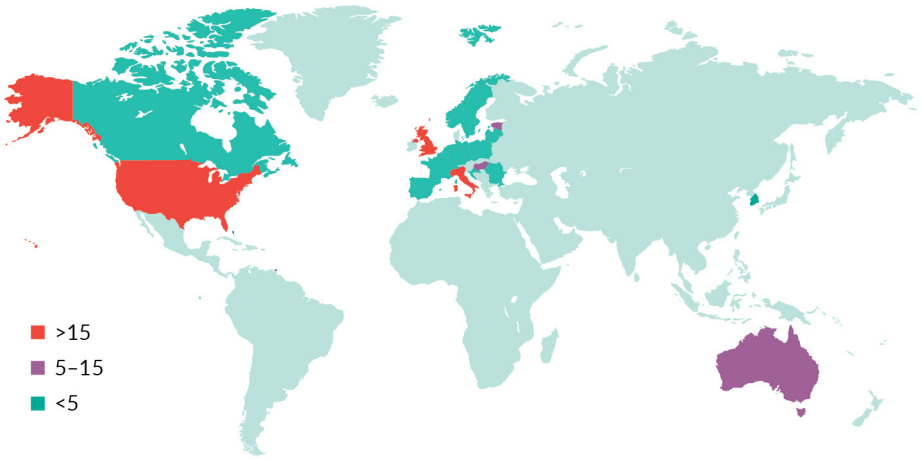
TABLE 5

Evaluation of relevance to outcomes-based schemes in multiple myeloma.

Outcomes/ endpoints used in the outcomes-based schemes	Outcome measures should be clinically meaningful (Y/N)	Outcome measures should be objective (and auditable) (Y/N)	The methods by which the outcomes are measured should be non-invasive (from a patient perspective) (Y/N)	The operationalization of the outcomes-based scheme should not be burdensome to implement for data collectors (Y/N)	The outcome measures should be routinely captured in clinical practice (Y/N)
Response to treatment	Y	?	N	Y	?
Overall survival	Y	Y	Y	N	Y
Progression-free survival	Y	?	N	Y	?
Duration of treatment	Y	Y	Y	N	Y
Toxicity	Y	?	Y	?	?

FIGURE 5

Overview of outcomes-based MEAs across the world.



The overview is based on the included articles in this review and shows the total number of Outcomes-based MEA in different countries for all indications. Due to confidential information on MEAs in some countries, the numbers are probably underestimated.

South Korea

South Korea implemented MEAs in 2013 and is reported as having a lot of experience in MEAs [64]. In a survey by Wenzl and Chapman (2019) Korea reported using 58 MEAs but only one that was performance-based for 'Evoltra®' using a CED scheme [23]. Financial MEAs such as expenditure caps and money-back guarantees are the preferred options [66].

United States (USA)

The US is cited as a country with some experience of MEAs [26] but oncology is an area with only a few OBP schemes with less than 10% were reported in 2018 [67]. There were 36 publicly disclosed value-based contracts from 2015 to mid-2018 [68]. Within the contract of 'Iressa®' in treating lung cancer, the company (AstraZeneca) was required to reimburse costs if the treatment was discontinued before the third prescription fill [69]. For the pediatric indication of Kymriah®, payments are linked to the clinical endpoint of 'complete remission' status by the 35th day after infusion [70]. Challenges in applying outcome-based MEA in the USA arise because of the fragmented insurance market and legal restrictions [71].

DISCUSSION

Innovative personalized medicines like CAR-T therapies offer new hope for patients with cancer yet pose some challenges for health care budget holders due to the high up-front costs, due to the one-time administration. But besides these costs, their real-world effectiveness outside of the clinical trial setting – specifically the long-term benefits of these innovative treatments – are currently uncertain.

Limited follow-up data exist for these treatments currently and the sample sizes of the trials, relatively small [72,73]. This can add additional uncertainty to the economic evaluations which in turn can become a barrier to timely reimbursement decision making and adoption [74].

The challenges and potential solutions to value assessment and reimbursement of CAR-T therapies in Europe are described in detail by Hague and Price [72] but in summary the challenges can be categorized under five main headings:

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1. Challenges facing the clinical value assessment
   - Clinical trial evidence from single arm (non-comparative) studies
2. Challenges facing the economic value assessment
   - Difficulties in accurately estimating overall survival gains due to immature overall survival data
3. Patient and carer value assessment
   - Some limitations in the validated patient-reported outcome measures where the experience of patients receiving CAR-T therapies may not be fully reflected
4. Budget impact
   - Affordability
   - The cost offsets of CAR-T therapies may not be fully realized within the short time frame of the budget planning cycle
5. Barriers facing the acceptance and implementation of innovative payment models
   - Having an infrastructure in place to capture high quality, clinically meaningful real-world data using reliable, trusted data sources.

This study focuses on innovative payment models and seeks to determine what type of MEA would best be suited to a CAR-T therapy in multiple myeloma. What we know is that OBP schemes have been successfully implemented in certain jurisdictions to enable timely patient access to Kymriah® and Yescarta® (see [73]; Table 4), however the design of such schemes needs to be tailored for the disease(s) in question.

One of the limitations of this review is that due to confidentiality reasons, some information may not have been made available in the public domain for it to have been included in our study. Having said that, there have been many published papers describing the types of MEA that have been employed in different countries in different therapeutic areas [21,46,49,60,75–78]. Only one review focuses specifically on OBP schemes [21].

The paper by Pauwels *et al.* [79] provides an overview of financial and outcome-based MEAs for oncology drugs in Europe between 2008–2015 where they conclude that the importance of MEAs in the future will likely increase. Comparing the findings of our review with Pauwels *et al.* [79] they identified 40 outcomes-based MEAs, 37 of them in Italy and three in England, Scotland and Wales. Our review found 27 schemes, eleven active and 16 closed schemes in Italy and 53 schemes in the UK. Comparing the time frame of Pauwels with this review, the increased use of OBP schemes in Italy and the UK is visible. With the introduction of MAA and the CED approach to resolve uncertainty into the CDF in 2016, the UK has led the way in introducing MEAs for access [80]. Italy and the Netherlands were the first countries to adopt MEAs in 2006, but that Netherlands had stopped using such OBP schemes thereafter [79,81]. Similar experiences can be found for Sweden, whilst very active at least prior to 2010, use of OBP schemes declined, due to concerns about obtaining clinical evidence from CED schemes [60].

Many of the outcome measures employed in MEAs in oncology are similar to those used for multiple myeloma treatments as well as the regulatory approved CAR-T therapies. Clinical outcomes are still generally preferred by payers over patient reported outcomes and relying on data from ongoing clinical trials represents an option to fill some of the evidence gaps, e.g. long-term overall survival (OS), with lower costs because no additional implementation and administrative costs are needed [63].

Based on the findings of the systematic review, only survival meets all of the criteria that we had developed to assess the suitability of such outcomes for a CAR-T in myeloma. Duration of treatment does not apply to CAR-T therapy with it being a one-time treatment. Time to next treatment has not been an outcome measure used in outcomes-based

schemes in multiple myeloma or other CAR-T therapies to date, but this would also be a measure that would meet all of the criteria identified. It is also a measure that can help support the economic value proposition of a CAR-T therapy in delaying the need for subsequent anti-cancer therapy.

The difficulty in using measures such as PFS and response rates for outcomes-based schemes is that for the data to be accurate and robust, patients need to be assessed at the same time (every 3 months or so – for example) and in the same way (using the same methodology/definition often employed in clinical trials) and this may not constitute routine clinical practice. Payment-by-results schemes based on response are difficult to establish because of less strict criteria for measuring response in the real-world [82]. Furthermore, to measure a complete response in multiple myeloma bone marrow has to be taken from the patient [82,83]. This represents not only additional costs but also an invasive burden on patients.

CONCLUSION

In conclusion, MEAs have shown to advance patient access and to enhance budget management [84]. Outcomes based payment schemes should however be tailored to the health system, the type of cancer, the nature of the treatment, and the ease at which these schemes can be implemented (and audited) in routine clinical practice, with minimal burden to both patient and health care provider and payer.

Based on the results of this study and the ideal attributes identified for a successful outcomes-based scheme, an outcomes-based payment model based on survival (at a given time point) and/or (anti-cancer) treatment-free (at a given time point) may work best for novel CAR-T therapies in multiple myeloma. It is important that the outcomes-based scheme captures data where uncertainty exists (in this case, long-term overall survival) and using measures that are captured routinely. The time points for assessing the survival status of patients and for determining the time points where patients remain treatment-free need to be aligned with the data from clinical trial(s).

Most important is that outcomes-based MEAs should be designed with well-validated and objective measures and as simple as possible to overcome barriers [21]. It is expected that more ATMPs will enter the market in the future [56]. This new way of treating patients necessitates different reimbursement models for which the right infrastructure and guidelines need to be put into place. Some countries as Italy and the UK have a good infrastructure already in place but other countries will be learning from their experience with the more recent CAR-Ts.

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