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Singapore
Cell & Gene Therapy
Conference 2023

ENABLING CELL AND GENE THERAPIES FOR ASIA

Singapore Cell & Gene Therapy Conference 2023

Enabling cell and gene therapies for Asia

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Contents

Preface

Themed "Enabling cell and gene therapies for Asia", the inaugural Singapore Cell and Gene Therapy Conference 2023 was jointly organised by the Advanced Cell Therapy and Research Institute, Singapore (ACTRIS), Agency for Science, Technology and Research (A*STAR)'s Institute of Molecular and Cell Biology (IMCB) and SingHealth Duke-NUS Cell Therapy Centre (SDCT).

Held on 4-5 August 2023, this hybrid Conference was attended by more than 600 clinicians, researchers, manufacturing experts, and industry players who came together to showcase ground-breaking research and development (R&D), and share practical insights into the curative roles of cell and gene therapies (CGTs).

In conjunction with the conference, Guest-of-Honour Minister for Health Ong Ye Kung also officiated the launch of ACTRIS' new 2,000 sqm cell therapy manufacturing facility. Located at the new National Cancer Centre, Singapore (NCCS) building, this game-changing, state-of-the-art CGT process development and manufacturing facility is expected to play a pivotal role in shaping the next era of CGT manufacturing, and contribute towards making a positive impact on economic outcomes in Singapore and beyond.

The two-day conference offered ample opportunities for fruitful learning and networking, and provided numerous platforms for the forging of partnerships between industry and academia. Amongst the strong line-up of international and local subject matter experts were our keynote speakers, Prof Bruce Levine (Immediate Past President, International Society for Cell and Gene Therapy & Barbara and Edward Netter Professor, University of Pennsylvania), who outlined a trajectory of recent developments in CGT; and Prof Mark A Kay (Dennis Farrey Family Professor of Paediatrics & Professor of Genetics, Stanford University), whose presentation discussed the clinical translation of adeno-associated virus (AAV) biology.

Other key conference themes also included, but were not limited to, topics in regenerative medicine, haematological malignancies, cellular immunotherapy for solid tumours, next-generation CGTs for paediatrics, biotech and start-up, cell therapy manufacturing, cell therapy funding, immune monitoring and diagnostics, as well as clinical quality attributes.

We hope that all participants enjoyed the opportunity to celebrate our collective advancements in the field of CGT, and look forward to more conversations with you on how we can forge ahead towards the next generation of leading-edge therapies.

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Foreword

With world-class research facilities, a regulatory environment that fosters innovation, and strategic partnerships with esteemed global institutions, Singapore is well on its way to becoming a regional powerhouse for CGT.

Indeed, the inaugural Singapore Cell and Gene Therapy Conference 2023 is a testament to the local ecosystem's unrelenting commitment to pioneering revolutionary advances in this transformation science, and Deloitte is proud to support this significant initiative as its Knowledge Partner.

Having played a role in the commercial launch of every single CGT product that has been approved to date, Deloitte has had a front-row seat to the global CGT sector's dynamic evolution over the last decade. We are committed to continue providing thought leadership on next-generation therapy areas by leveraging our extensive experience and expertise accumulated from the Asia Pacific region and beyond.

At this juncture, I would like to take this opportunity to extend my gratitude and deepest thanks to the organisers– ACTRIS, A*STAR, and SDCT – as well as all the partners, speakers, and sponsors who made this pre-eminent conference possible. Your dedication and contributions to the field of CGT are, and will continue to be, pivotal to driving progress and fostering collaboration in this emerging domain.

I look forward to witnessing a flourishing CGT ecosystem in Singapore, and wish all of its players the very best.

Ashish Mahajan
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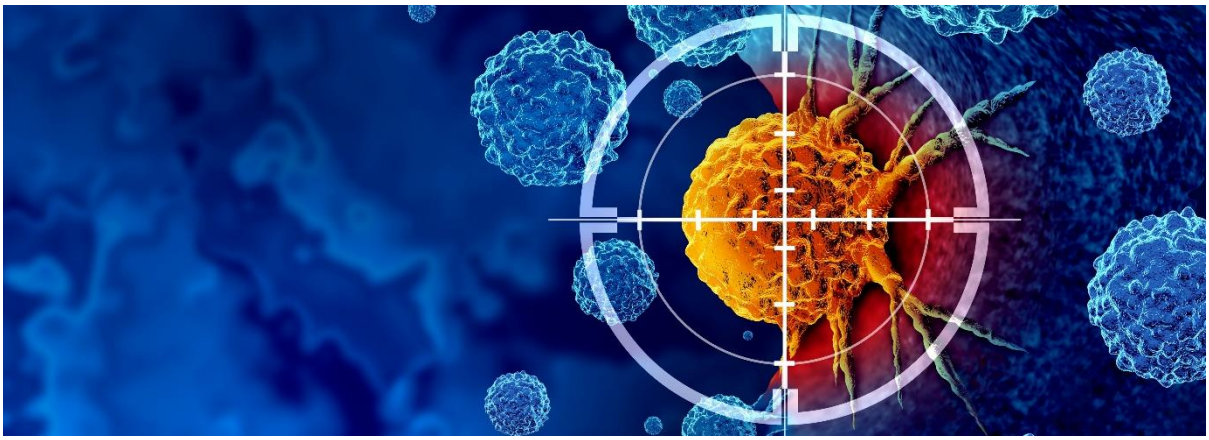
CONFERENCE HIGHLIGHTS

Welcome address

Presented by Prof Chee Yam Cheng, Chairman, ACTRIS



"The field of CGT has experienced unprecedented growth in recent years, bringing us closer to realising the promise of personalised, targeted, and curative treatments for a myriad of diseases and conditions. Singapore has always been at the forefront of recognising the potential of new biomedical advancements and its associated emerging industries – and CGT is one such example."

United by a shared vision of unlocking the healing potential of CGT and revolutionising the landscape of next-generation medicine, the local CGT ecosystem had embarked on a journey of exploration and collaboration. Between 2008 and 2012, small facilities were set up by the Health Sciences Authority (HSA) and National University Hospital (NUH) to manufacture cells under Good Manufacturing Practice (GMP) conditions.

Later in 2017, the Ministry of Health (MOH) formed an advisory committee to perform a feasibility study of developing and operating a national-level cell therapy process development and manufacturing facility to centralise our manufacturing capabilities and capacities. The team went to Canada and the UK to learn more about such manufacturing and enabling centres, studied the clinical trials landscape, and noted the rapid growth of the CGT industry in these jurisdictions.

Following the trip, several recommendations were provided to MOH. These included the need to groom highly skilled local manpower, as well as develop and build a state-of-the-art centralised manufacturing facility to manufacture products that are regulatory compliant and safe for clinical use.

Other key recommendations also included the need to develop and implement a robust business plan to ensure the sustainable running of the manufacturing facility, as well as consolidate resources and capabilities from the two pre-cursor manufacturing facilities at HSA and NUH to ensure cost and operational efficiencies.

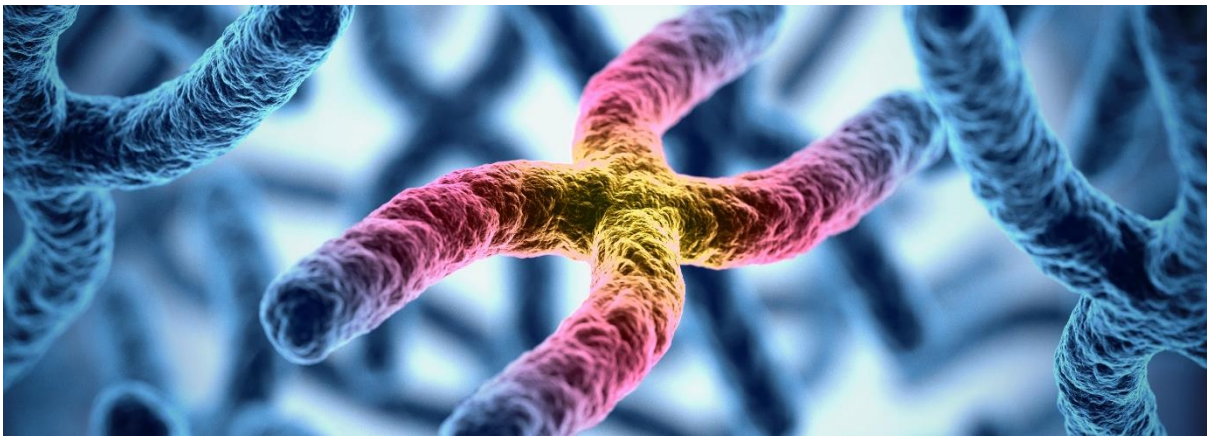
Lastly, the committee also emphasised the need to develop clinical capabilities at our hospitals and forge relevant public-private partnerships to shape our local CGT ecosystem. With the launch of ACTRIS, many of the recommendations put forth by the committee have now been realised.

Ultimately, ACTRIS' new facility will be a game-changer for Singapore's cell therapy ecosystem: being able to manufacture high quality cell therapies locally means that treatments can reach our patients in less time, and they get access to life-saving therapies sooner.

CONFERENCE HIGHLIGHTS

Guest-of-Honour speech

Presented by Ong Ye Kung, Minister for Health, MOH Singapore



"We may well be at the cusp of a major breakthrough in health care. That is why words like 'medical moonshots' are used to describe this development, and why we are also witnessing a strong flow of global funds into this sector, as well as significant developmental efforts by both pharmaceutical companies and biotech start-ups."

Nevertheless, all breakthroughs come with uncertainties and risks. Many precision medicine treatments are experimental in nature and only work on a select group of patients. They are also very costly, which limits access. In some situations, modifying genes and cells raises ethical questions. Hence, there are multiple issues that we need to overcome.

But this does not mean we ignore this major development and simply sit on our hands. Quite the contrary, we need to make it a big part of the public health care agenda so that, in time, precision medicine can bring about an advancement in the health of societies.

There are two reasons for this. Firstly, we have invested much R&D and know-how in this sector. One major project is the ongoing SG100K project. We have nurtured and attracted a considerable pool of precision medicine talent in Singapore, and need to press on. Secondly, and more importantly, we need to adopt the right mindset and approach when confronting promising but potentially disruptive technology.

Five aspects to nurture and grow precision medicine

There are five key aspects to nurture and grow precision medicine in the way that will fulfil its potential while safeguarding against the downside. First, we need to establish a proper end-to-end clinical governance framework that adapts research innovations into clinical applications, covers the appropriate use of screening and diagnostic tests, and provides safe, clinically efficacious, and cost-effective treatments.

Our research infrastructure also needs to be strengthened. This includes growing the capabilities and capacity of our laboratories to support our research and clinical needs, and develop CGTs for clinical use. In manufacturing CGTs, we need to ensure that these treatments are engineered in a way that is safe and effective for patients, as well as of high quality. This is necessary to enable the public to have full confidence in the new medical technology.

Second, we need to ensure both clinical efficacy and cost-effectiveness – a tricky subject. This is no different from what we do for all clinical treatments today, but there are more challenges when it comes to CGTs. The evaluation of clinical efficacy could be harder, because precision medicine so far targets a small segment of patients compared to traditional pharmaceutical products. The database is considerably smaller. While treatments may have immediate or early good results, we also need to see if the good outcomes are sustained over time.

It may be even more tricky when evaluating cost-effectiveness. We need to recognise that a treatment may give rise to very significant clinical benefits for individual patients. However, the high costs of some precision medicine treatments may mean that they are not cost-effective. In particular, CGTs are costly because they are often developed for rare genetic conditions, are customised to the individual, and do not enjoy the same economies of scale as traditional pharmaceutical products which are for more common conditions.

Third, we need to develop a sustainable way to finance precision medicine. This is a policy matter: as the cost of precision medicine will be considerably higher than traditional treatments, it can cause a major disruption to our health care financing framework. We will therefore need an appropriate and sustainable financing framework that will prevent a schism from forming between those who can afford precision medicine and those who cannot.

Fourth, we need to establish legislative safeguards. New technologies are always double-edged swords. The fact that we can now do something new with technology does not mean we have to do it. With new territories comes the need for new limits and boundaries, so society can decide what can or cannot be done with the new technology.

Finally, we need to continue to build our know-how and capabilities. This is where ACTRIS comes in.

ACTRIS

In 2006 and 2009, HSA and NUH had respectively set up small facilities for cell therapy production to serve our hospitals and the pharmaceutical industries. With the continued developments in precision medicine, we decided to consolidate the facilities and grow it further. To give focus to this effort, ACTRIS was therefore set up in April 2020 as a business unit under the Consortium of Clinical Research and Innovation, Singapore (CRIS).

After extensive collaboration between government agencies, research institutions, and industry players, we have arrived at a significant milestone. ACTRIS will consolidate the NUH and HSA cell therapy facilities, and will be established as the national centre for development and production of CGTs. It will be physically located at the new NCSS building.

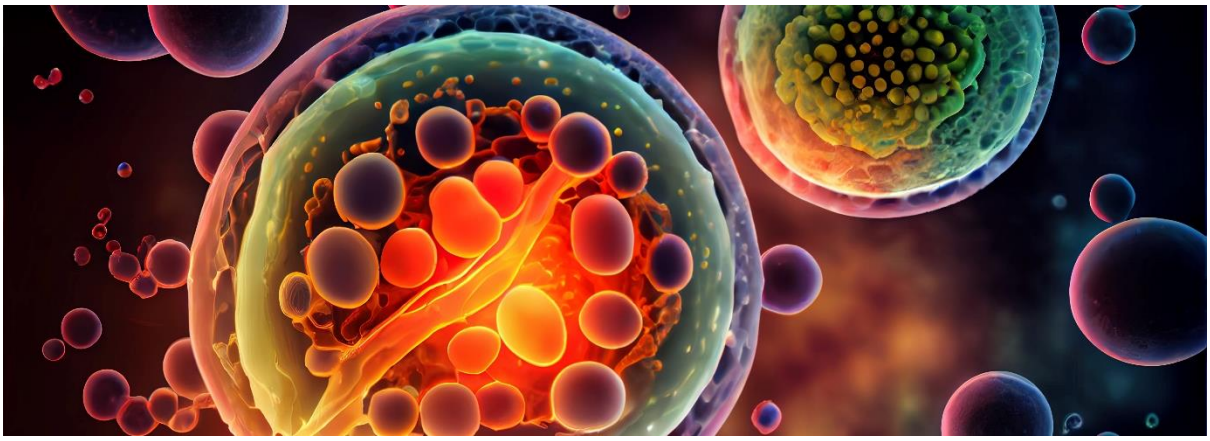
By centralising resources, manpower and capabilities, we can scale up manufacturing, develop talent and improve operations. Through the National Medical Research Council (NMRC), MOH will continue to support good research projects involving cell therapy and ACTRIS.

ACTRIS will be working with its sister business unit, the National Health Innovation Centre Singapore (NHIC), on a joint grant call to accelerate the translation of cell therapies from the lab to the clinic. It is also working with A*STAR and equipment companies to develop production capabilities further. We aim to significantly shorten production times and lower costs in the near future, so that CGTs can become more accessible and affordable to Singaporeans who need them.

CONFERENCE HIGHLIGHTS

Sustainability of CGT in Singapore

Presented by A/Prof Danny Soon, CEO, CRIS & Interim Executive Director, ACTRIS



"CGT is an exciting new field in medicine. The buzz around how doctors and scientists can engineer cells into 'super soldiers' capable of attacking cancer cells was the stuff of science fiction until not too long ago. But the important question remains: how do we deliver these therapies in a sustainable fashion?"

Conventional drugs are manufactured in batches and at scale – often times, in millions of doses. It is also much easier to assure their quality because these are carried out in centralised facilities. In the current autologous CGT paradigm, however, a therapy is created for a single individual patient, which makes it extremely costly. The manufacturing of a chimeric antigen receptor (CAR) T-cell therapy, for example, is a multi-step process that requires a large team of specialists and weeks to complete a single cycle.

Nevertheless, there are a variety of different manufacturing strategies that can be deployed to achieve cost and scale. Work is also ongoing for some ancillaries, such as raw material choice, use of non-viral vectors, and development of in-house release testing to reduce the cost of the final product.

One of the greatest impediments for the manufacturing of cell therapies remains the issue of cell source. Currently, we are taking cells from patients themselves, which creates a high amount of variability in the starting material. By moving towards allogeneic cell sources, we can take cells from healthy donors, modify them, and store them in a cell bank where they can be deployed for use when necessary. There remain many challenges associated with this approach, but there are clear advantages: it will significantly simplify the cell manufacturing process, while ensuring feasibility and quality.

So, what is the role of ACTRIS in this? ACTRIS is supported by MOH and NMRC. Our key customers and partners are the national health care clusters, public health care institutions (PHIs), research institutes, biotechs, and equipment companies.

We will work with PHIs to provide access for our patients, and support cell therapy manufacturing at scale for greater efficiency. We will develop talent for this important and growing field, and support efforts for value-based outcome assessments. We will collaborate with the institutes of higher learning (IHLs), PHIs, and A*STAR on novel asset development with relevance to patients in Singapore.

We will work with the innovators of novel manufacturing technologies, and partner with NHIC to support the grant call for developing new cell therapies. We have also been working with biotechs to support local and overseas companies with their asset development and manufacturing processes. The potential establishment of joint laboratories could also create opportunities for us to testbed new technologies and deliver greater cost efficiencies.

DELOITTE'S PERSPECTIVE

Serving a "market of one"

One central theme across the entire lifecycle of CGTs – from their clinical development and manufacturing to their final delivery – is the imperative to cater to each patient as a unique "market of one". Each CGT patient presents a set of unique requirements, and there can be significant variations in terms of the administration methods for different types of therapies, depending on the location of the specific gene manipulation and source of raw materials.

In this respect, the primary challenge for CGT stakeholders lies not only in understanding and addressing each patient's individualised requirements, but also constructing highly personalised manufacturing processes around a "market of one".

As they embark on this journey, CGT stakeholders will need to begin by placing their patients at the heart of their value chains – not least by delineating specific details of the entire patient journey, including unique touchpoints, transitions, and the various stakeholders that are involved throughout the care pathway as patients receive their therapy and related care.

From a "hospital-focused" to an "individual-focused" approach

At this juncture, it is imperative to emphasise the importance of adopting a seamless and collaborative approach to uniting all involved parties in the shared objective of providing the highest possible level of care and support to patients within this highly personalised construct.

To this end, several Asia Pacific markets, such as Japan and Singapore, are already transitioning from a traditional "hospital-focused" health care system to a more "individual-focused" approach, with this transformation being facilitated by the introduction of national health data platforms prioritising data privacy and security.

Given the high stakes and tight timelines associated with CGTs, stakeholders must also adopt a proactive communication approach. Regular updates on manufacturing progress and order details to care teams and health care facilities are vital to addressing the concerns of both patients and physicians within a personalised "market of one".

Investing in digital ecosystems

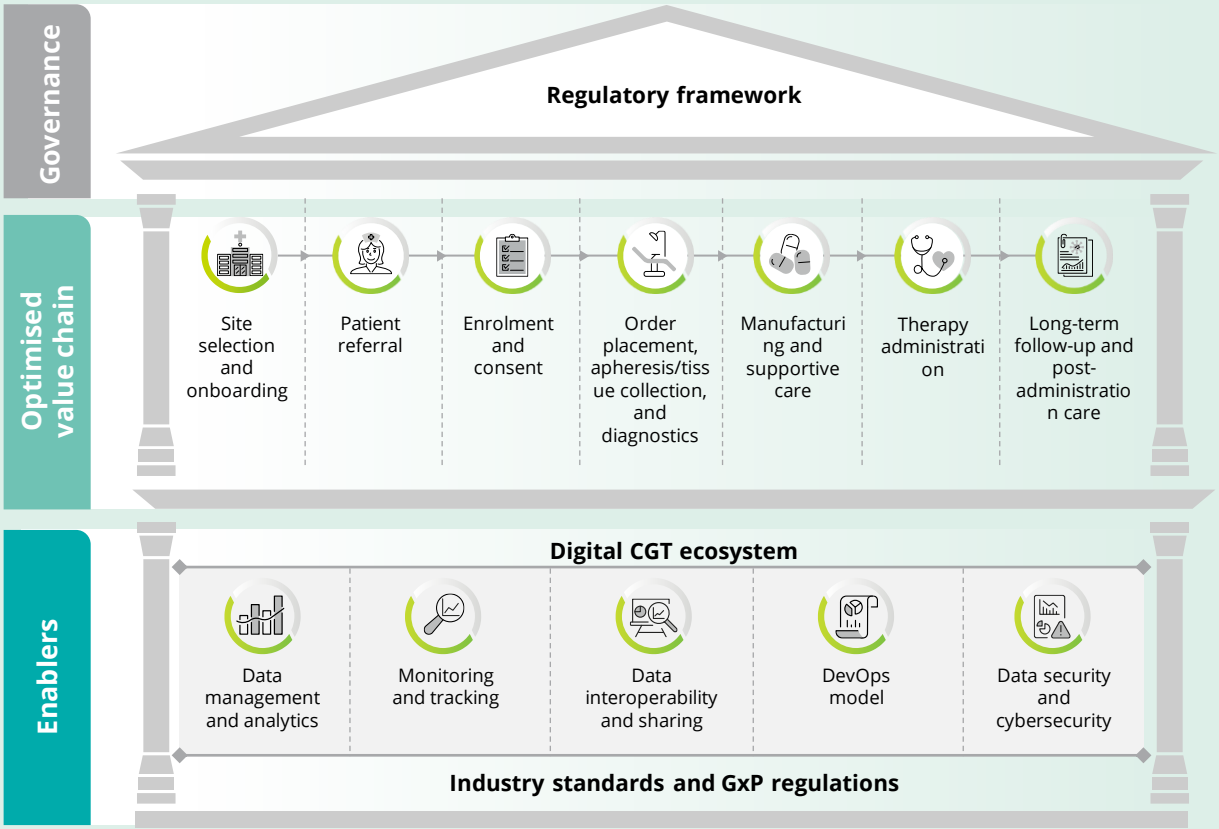
To tackle the multi-faceted challenges presented by CGTs – which include, but are not limited to, safety concerns, affordability, and the need to foster a patient-centric approach – digitalisation will be essential. Currently, leading CGT players can be observed to be proactively investing in the development of digital ecosystems, especially around critical process areas such as patient enrolment, scheduling, and materials tracking.

The incorporation of real-time tracking technologies, in particular, has an important role to play in enhancing patient experience and safety. Specifically, by providing the capabilities to facilitate more effective communication amongst stakeholders, support more timely deliveries, and enable the issuance of prompt notifications to clinical staff, these technologies can contribute significantly to the optimisation of the CGT value chain (see Figure 1), while empowering health care providers to respond promptly to patient and caregiver needs.

Indeed, the long-term success of the CGT field is likely to hinge on the ability of its stakeholders to develop robust data management and analytics processes, and collect long-term follow-up data[1] to demonstrate the durability of treatment responses[2]. Achieving this will, in turn, necessitate the consideration of several strategic aspects relating to data, such as patient data selection, its use throughout the care pathway, and the role that it plays in providing insights to inform upstream product and process development processes.

All things considered, it must be acknowledged that this journey to serve a "market of one" will remain very much a work in progress for the foreseeable future. Given that the CGT landscape is inherently dynamic and characterised by multiple nuances in terms of therapy-specific requirements, market access, and patient journey enhancements, ongoing digital innovation will likely be a key factor impacting not only stakeholders' ability to secure market access, but also their ability to maintain a long-term competitive advantage.

Figure 1: A future-state view of an optimised CGT value chain designed for a "market of one"



1. "Realising the promise of cell and gene therapies in Asia Pacific". Deloitte. 2023.
2. "How to create a stand-out CGT customer experience". Deloitte. 2022.

CONFERENCE HIGHLIGHTS

Official launch of the ACTRIS cell therapy manufacturing facility

Launched on 4 August 2023 by Minister for Health Ong Ye Kung, the ACTRIS cell therapy manufacturing facility is a new 2,000 sqm cell therapy facility that has been developed to meet the increasing clinical demand for CGT treatments in Singapore.

The facility comprises 14 GMP-compliant clean suites, four translational laboratories and one quality control laboratory – the largest national facility of its kind which will support hospital services, academic institutions for research, and biotech start-ups in Singapore.

Its state-of-the-art equipment can support end-to-end cell therapy process development and manufacturing steps such as cell selection, genetic modification, closed-system manufacturing, and product storage. The facility's advanced infrastructure, such as its air-handling systems, allows ACTRIS to manufacture different cell therapy products concurrently, speeding up patient access to these novel treatments.

DELOITTE'S PERSPECTIVE

Point-of-care (POC) manufacturing for CGTs

POC manufacturing – or the production of CGTs at or near the actual treatment site – is an innovative approach poised to revolutionise CGT manufacturing. Nevertheless, the exact definition of POC or "bed-side manufacturing" can vary significantly: in some instances, it refers to manufacturing that takes place at the patient's bedside; in others it refers to manufacturing carried out within the same health facility, campus, or even city or state. While they all aim to achieve a similar objective of 'democratising' manufacturing, each interpretation comes with its own unique set of considerations and challenges.

What is clear, however, is that POC manufacturing in its various forms is rapidly becoming a reality in clinical settings; at this time of writing, a number of pilot programs have already been scheduled for launch within the next 12 months. Should they prove successful at yielding breakthrough results, we could potentially expect POC manufacturing to move into the mainstream within the next few years, notwithstanding several pivotal factors that currently remain unresolved:

- **Quality and process controls:** Determining the appropriate quality and process controls standards, as well as compliance obligations for the drug developer and hospital site
- **Cost optimisation:** Optimising costs through standardisation and a reduction in value chain complexity
- **Regulatory harmonisation:** Collaborating with international regulatory bodies to harmonise standards and streamline approval processes for POC-manufactured CGTs
- **Cell therapy centre readiness:** Evaluating the readiness of cell therapy centres to undertake the corresponding new roles and responsibilities, such as those relating to inventory management, capacity planning, and material sourcing
- **Investment readiness:** Evaluating the willingness of sites to invest in new facilities, talent, equipment, and protocols, as well as the potential suitability of forging collaborative models with drug developers

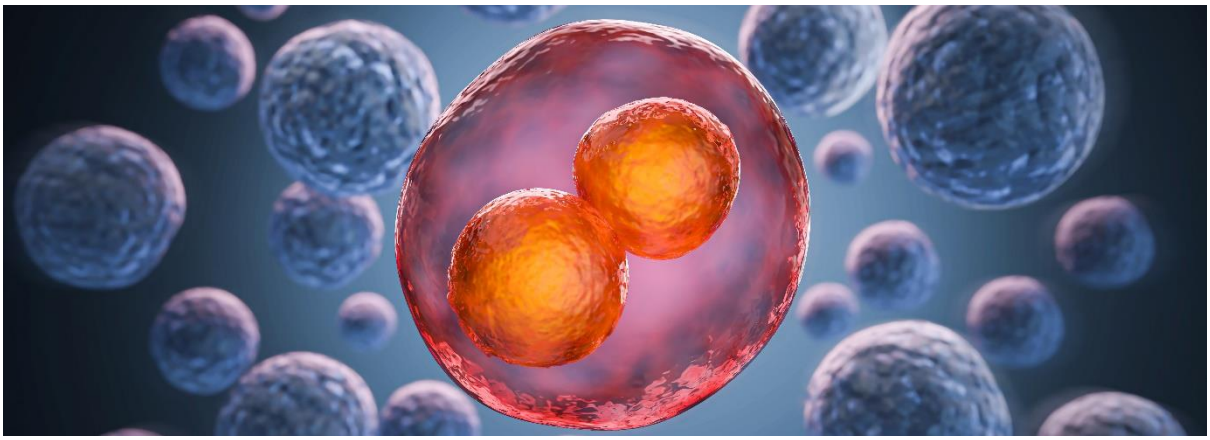
To tackle these issues, CGT stakeholders could consider the adoption of several proactive strategies. These include, for example, engaging with clinical site providers to gauge their preferences and capabilities, fostering collaborative business models that bring together drug developers and POC developers, and considering the use of innovative approaches such as co-investments with contract development and manufacturing organisations (CDMOs), hub-and-spoke configurations, and mobile units. It is also crucial that players address the issue of evolving talent requirements – for example, through the cross-training of clinical and manufacturing expertise – in order to stay ahead of the curve.

Looking ahead, government and health care ecosystem players alike will need to consider the need for policy reform, infrastructure investments, and regulatory adaptations, and work collaboratively with each other to speed up patient access to these novel treatments.

Ultimately, the future of POC manufacturing holds immense promise as a revolutionary concept that could reshape the landscape of CGTs. While it undoubtedly comes with its fair share of challenges and uncertainties, the opportunities it presents are monumental, and its potential rewards are nothing short of transformative.

CONFERENCE HIGHLIGHTS

Cell therapy manufacturing



Introduction of the quality by design (QbD)-based approach to determine the critical quality attribute (CQA) of cell product

Presented by Prof Shin Kawamata, CEO, Cyto-Facto Inc, Kobe, Japan

Cyto-Facto is a public sector/academic-originated contract manufacturing organisation/contract development manufacturing organisation (CMO/CDMO). Based in Kobe, it leverages the use of a leading QbD-based cell manufacturing system with several cutting-edge capabilities. Specifically, in addition to being a closed-loop, automated culture/intelligent cell processing system, its QbD-based cell manufacturing system is also equipped with a real-time vision tool and in-process medium analysis capabilities. The system is also capable of enabling automated sampling for offline quality control (QC), as well as preparing batch data for mesenchymal stem cell (MSC) and iPSC/embryonic stem cell (ESC) manufacturing processes.

In addition to this system, Cyto-Facto also leverages several other tools and technologies in support of its QbD manufacturing approach. These include, for example, a cloud-type cell manufacturing control system known as AMPGCT4.0, as well as efforts to advance reverse translational research through the creation of linkages between manufacturing data and clinical data.

Making hope – Cell therapy with dual site strategy

Presented by Isaac Chow, Chief Business Officer, Biosyngen

Founded in 2016, Biosyngen is a cell therapy company focused on developing treatments for solid tumours. The company is currently in its Series B+ financing round, and deploys the use of a dual site strategy– its operations are based in Singapore and Guangzhou, China – to better position itself for global coverage. In particular, its presence in Guangzhou has enabled it to increase speed of execution by tapping into the vast local clinical network, even as its intellectual property and scientific know-how are developed and managed in Singapore.

Earlier in June 2023, Biosyngen and the Guangzhou Development District also announced the joint development of the China-Singapore Technology Innovation and Translational Medicine Centre for Tumour (TMC) to accelerate the process of bringing life-saving treatments from bench to bedside. Under this arrangement, promising products nearing the end of their pre-clinical studies can be incubated, funded, and supported by the TMC.

Viral vector manufacturing for cell therapy products

Presented by Dr Lucas Chan, Scientific Founder & Chief Scientific Officer, CellVec

In the context of CAR T therapies, retroviruses and lentiviruses are the two most common forms of gene transfer vectors, but there are now hundreds of clinical studies on retroviruses, lentiviruses, adenoviruses and AAV. Thanks to these extensive clinical studies, viral vector manufacturing has a good clinical safety profile – for example, there is now an understanding of how we can control a vector's multiplicity of infection (MOI) dosing to reduce the risk of insertional mutagenesis – as well as well-defined regulatory and commercialisation pathways.

Nevertheless, several challenges continue to remain roadblocks in viral vector manufacturing. These include, for example, difficulties in achieving consistently high titre and yield; lack of scalability; a complex and unstable transient manufacturing process in the case of lentiviral vectors; and lack of a viral vector-based downstream purification process. Further considerations also include the lack of CGT-focused analytical technologies for the analysis of manufacturing impulse controls and end-product quality, as well as long QC testing lead times.

New methods enabling rapid adventitious agent detection for cell therapy manufacturing

Presented by Dr Rohan Williams, Principal Investigator, Singapore-MIT Alliance for Research and Technology (SMART)

The Critical Analytics for Manufacturing Personalised Medicine (CAMP) Interdisciplinary Research Group (IRG) – part of the SMART program – is primarily focused on conducting research in two areas: developing CQAs for efficacy and safety, as well as developing and evaluating process analytic technologies (PATs).

The CAMP IRG has primarily focused its research on three major contamination detection methods: firstly, sample preparation techniques designed to enrich or filter specific biotic entities; secondly, the targeted detection of pre-defined species of bacteria or viruses; and thirdly, untargeted approaches to detect signatures of contamination or specific entities enabled by their particular techniques, including, for example, metagenomics.

Regulatory considerations on product manufacturing and characterisation

Presented by Dr Ong Lee Lee, Regulatory Consultant, Advanced Therapy Products Branch, Medicinal Product Pre-Market Cluster, Health Products Regulation Group, HAS

Relative to conventional chemical and biologic products, cell, tissue and gene therapy products (CTGTP) are structurally more intricate and much larger. At the same time, CTGTP batch sizes are also usually small – one batch might comprise just a single dose, especially in the case of autologous products – and might only remain stable for a few hours at room temperature.

In addition, donor cells tend to be accompanied by high variability, and the release of some CTGTP for administration might even precede the availability of all QC tests. Manufacturing failures also have a much more significant and direct impact on CTGTP than conventional products, particularly for autologous products, where there are no alternative batches to fall back on.

Taken together, these challenges mean that it may be necessary to begin considering manufacturing issues from as early as the donor phase. For example, if cell tissues are being sourced from related donors, there is the need to not only conduct rigorous donor screening and testing, but also determine the volume of cells required to ensure that there are adequate starting materials for the manufacturing process. Furthermore, an efficient and reliable logistics network is required to ensure the seamless delivery of CTGTP from manufacturing sites to the patient, and support varying transportation and storage requirements for fresh and cryopreserved products.

Innovative microfluidics for CGT applications

*Presented by Dr Shireen Goh, Lead Scientist, Bioprocessing Technology Institute (BTI), A*STAR*

Studies have revealed that the quality of vector harvests from perfusion cultures can be adversely affected by contamination from cellular debris originating from dead cells within the bioreactor. Conventional alternating tangential flow (ATF) filtration used in biomanufacturing are also not ideal solutions to this problem due to the entrapment of lentiviruses in the membrane filter.

To address this challenge, a microfluidic, non-membrane-based, clog-free filter was developed. Its innovative design uses channels that are significantly larger than cells to eliminate the entrapment issue commonly seen in membrane filters. Known as uFiltr8, the filter works by homogeneously distributing cells across a spiral channel; as the cells move through the channel, they move from side to side, facilitating filtration. Plans are currently underway to commercialise this innovation through the creation of a spin-off company.

Advances in liver cancer therapy using our first-in-class TCR T therapy

Presented by Dr Lu-En Wai, Director of Research & Development, Lion TCR

LioCyx-M is the first global treatment for hepatitis B virus (HBV)-hepatocellular carcinoma (HCC) leveraging mRNA-encoded HBV-specific TCR T-cell technology. It is designed with an mRNA electroporation technology that enables multiple infusions to be manufactured in a single batch, and has a predictable and manageable safety profile. As a precision medicine approach, it does not require lymphodepletion; furthermore, as it relies on a natural cytokine release, there is no T-cell over-activation and exhaustion.

Currently, two manufacturing sites have been established to support the global clinical trial operations and commercialisation of LioCyx-M. In view of the novelty of the treatment and its efficacy in Phase 1 trials, the US Food and Drug Administration (FDA) has granted Lion TCR dual designations – namely, the Fast Track Designation for the accelerated approval and priority review for HCC, and the Orphan Drug Designation for waiver of new drug application fee and seven years of market exclusivity.

Manufacturing mesenchymal stromal cells-small extracellular vesicles (MSC-sEVs) for clinical testing

*Presented by Dr Lim Sai Kiang, Research Director, IMCB, A*STAR & Founder, Paracrine Therapeutics*

According to current scientific consensus, therapeutic MSC EVs refer to small EVs – specifically those between 50 and 200 nm in size – which are also known as MSC-sEVs. In elucidating the mechanism of action for MSCs, there are two critical considerations.

Firstly, there are the possible modes of EV activity and their interactions with target cells; secondly, there is the site of the EV activity and their proximity to target cells. While endocytosis and fusion are the two mechanisms of action that often come to mind, studies have shown that these are not very effective and may in fact be rare events requiring specialised proteins.

Rather, another mechanism, which has been termed modifying extracellular environment of target cells (MEET) is the preferred construct. Under the EV-MEET mechanism, EVs located outside the target cell can either interact directly with receptors on the target cell membrane, or enzymatically modify other substances so that the end-product can interact with the receptors or be incorporated into the target cell membrane.

DELOITTE'S PERSPECTIVE

Strategies to optimise the CGT value chain

CGTs present a unique set of opportunities and challenges that demand a new approach to the pharmaceutical value chain. Unlike traditional pharmaceutical products such as pills and biologics, CGT products require end-to-end involvement from pharmaceutical companies throughout the entire journey, from pre-treatment diagnostics to post-treatment follow-ups.

As highlighted by multiple speakers during the conference, one significant obstacle in the journey from scientific innovation to commercialisation in the field of CGTs is the inherently unpredictable and fluctuating nature of the production process. To ensure that they are prepared to cope with any sudden and unforeseen circumstances in their value chains, CGT players must therefore learn to embrace the unexpected along five key dimensions (see Figure 2):

1. Protocol and process standardisation

Protocol and process standardisation is essential to ensuring safety and consistent product quality. This no doubt applies to all manufacturing processes, but it is an aspect that is much more acute in the context of CGT, given its highly personalised nature and necessity for closed-loop value chains with batch monitoring and tracking. To ensure that CGT products meet stringent demands of quality, safety, and regulatory compliance, all standardisation efforts must also be closely tied to industry standards and Good Manufacturing Practices (GxP) regulatory frameworks.

2. Monitoring and traceability

A robust monitoring and traceability system is a critical pre-requisite to ensure the safety and reliability of CGT processes, and should comprise the following:

- **Chain of identity (COI):** COI is a critical component of the monitoring system that uses unique identifiers to trace products from donor to recipient across all phases of the entire patient journey, including collection, manufacturing, treatment, and ongoing monitoring. Such a comprehensive tracking approach ensures that the origin and history of each product are transparent and verifiable at all points in the value chain.

- **Chain of custody (COC):** COC complements COI by tracking the product's journey in detail. It records staff actions, storage conditions, location, date, and time at each stage of the value chain. This level of granularity is especially important for CGTs, where there is direct patient involvement, as it provides a complete record of how the therapy has been handled and managed throughout its lifecycle[3].

3. Resilience and flexibility

To build resilience against unexpected circumstances, it is necessary to conduct a detailed mapping of the entire value chain to identify dependencies and risks. In addition, flexibility also needs to be built into processes and decision-making to enable adaptation in the face of rapidly evolving situations. Examples of possible actions to take include standardising risk mitigation procedures and conducting stakeholder cross-training.

3. "Realising the promise of cell and gene therapies in Asia Pacific". Deloitte. 2023.

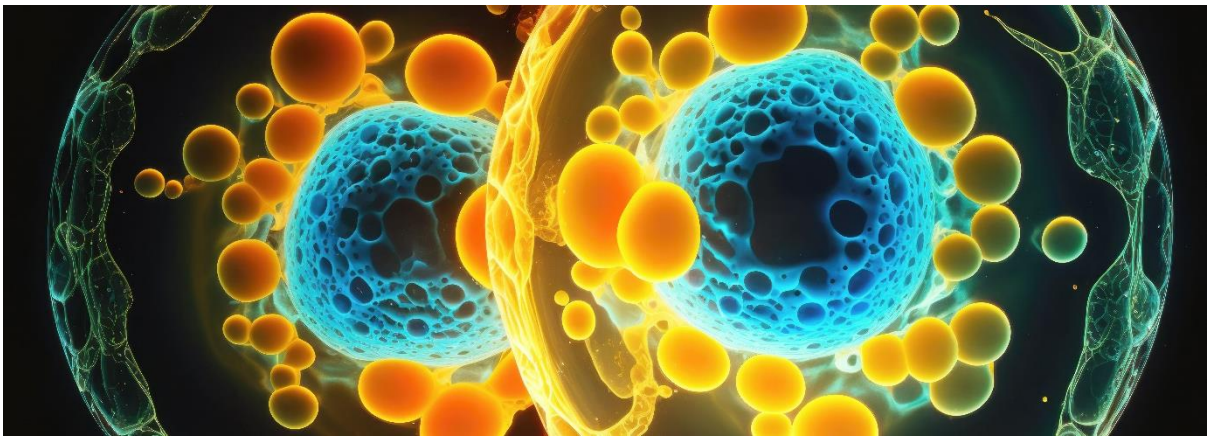
4. **Business continuity management**
   To achieve effective business continuity management, it is crucial to plan for contingencies – particularly high-impact, high-probability scenarios – in collaboration with all stakeholders. Clear guiding principles must be established for issue escalation, and alternative arrangements for transportation and logistics should be put in place where possible.

5. **Patient-centricity**
   As a first step towards greater patient-centricity, "voice of the customer" assessments should be conducted to obtain stakeholder input from patients, physicians, and hospitals on the CGT patient journey. These inputs can then be used to inform the development of a comprehensive approach to enhance therapy adoption, enhance patient well-being, and increase trust in the health care system – all while minimising disruption to existing processes.

Figure 2: Five dimensions to consider in optimising the CGT value chain

CONFERENCE HIGHLIGHTS

Keynote lectures



From innovation to dissemination: Globalising the revolution in advanced CGTs

Presented by Prof Bruce Levine, Immediate Past President, International Society for Cell and Gene Therapy & Barbara and Edward Netter Professor, University of Pennsylvania

Currently, ongoing research to improve T-cell potency in solid tumours is focused on the use of several levers, such as activators, cytokines, metabolism/transcriptional regulation, and gene knockouts (KOs). These efforts have, in turn, yielded more than 10 next-generation CARs, including but not limited to T-cells redirected for antigen-unrestricted cytokine-initiated killing (TRUCKs), universal CARs, self-driving CARs, armoured CARs, and tandem CARs.

In terms of manufacturing improvements, the current focus is also on making faster, better, and cheaper CARs– for example, by reducing *ex vivo* culture periods to improve the antileukemic activity of CAR T-cells. Current trials are experimenting with three-day, two-day, and even 24-hour manufacturing periods, and the results have shown that the *in vivo* expansions of these short CARs are comparable to that of conventional CARs that take between nine and 10 days to manufacture.

CAR cells are also now moving beyond oncology to other domains, such as human immunodeficiency virus (HIV), autoimmunity and tolerance, heart failure and fibrosis, and ageing – and even beyond T-cells to CAR natural killer (NK)/invariant NK (iNK) cells, CAR macrophages, CAR in blood stem cells, and CARs derived from induced pluripotent stem cells (iPSCs).

The difficulties in choosing an appropriate AAV serotype for clinical trials: What AAV biology is teaching us

Presented by Prof Mark A Kay, Dennis Farrey Family Professor of Paediatrics & Professor of Genetics, Stanford University

Wild type AAV has two genes: Replication (Rep), and Capsid (Cap). The former is involved in replicating newly synthesised DNA, while the latter is involved in encapsidating and packaging the newly synthesised single-stranded genomes. In the context of gene therapy, the Rep and Cap genes are removed, and a new therapeutic gene cassette is inserted into the AAV vector.

AAV2 (isolated from humans) was the early prototype vector. Later, a recombinant AAV (rAAV) was developed for trials with mice and dogs with haemophilia B. This work eventually led to the first clinical trial in which AAV2 was systemically delivered into humans; however, unlike what was witnessed in the earlier animal models, there was a lack of persistence due to a loss of the vector genomes.

In addition, there was an asymptomatic elevation in liver enzymes or transaminitis, which is an indication that there had been a mild level of liver injury. Subsequent studies later revealed that the AAV2 had induced a cellular cytotoxic T lymphocyte (CTL) response that was directed against the capsid proteins, with the uncapsidation of the capsid leading to an immune response that eliminated the transduced cells.

OVERVIEW

Evolution of the CGT research landscape

CGTs are poised for a transformative expansion, with the number of approved therapies projected to increase significantly over the next few years. Current clinical trials are primarily focused on blood cancers and rare genetic diseases, but are rapidly broadening to include various non-communicable conditions and solid tumour cancers.

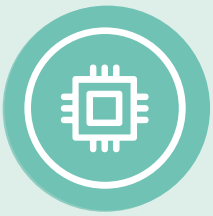
Other focus therapeutic areas also include cardiovascular diseases, immunology, dermatology, neurology, infectious disease epidemiology, and musculoskeletal disorders.

The evolution of CGT can be categorised into three distinct phases[4]:

- Basic Research Phase (1909-1973), which laid the foundation for gene therapy through crucial discoveries in genetics
- Early Age of Clinical Trials (1989-2003), which marked the commencement of gene therapy trials addressing conditions such as severe combined immunodeficiency (SCID) and melanoma; however, the emergence of several challenges led to a certain degree of caution
- Phase from Bust to Boom (2003-2022), which saw a resurgence in gene therapy, with regulatory approvals for various products; ground-breaking technologies such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 promise accelerated advancements in the field, heralding an era of rapid gene therapy development

Over the next decade, CGTs can be expected to move beyond exploratory experiments to become mainstream medical treatments. Nevertheless, these treatments, while promising, come with substantial costs: CGTs are amongst the world's most expensive treatments, with costs that can go as high as US$3 million[5]. This poses significant challenges to health care systems in terms of accessibility and affordability, and will necessitate a re-examination of health care policies and reimbursement strategies.

4. Fatemeh Arabi, Vahid Mansouri & Naser Ahmadbeigi. "Gene therapy clinical trials, where do we go? An overview". Biomedicine & Pharmacotherapy, Volume 153. 2022.
5. "Multi-million-dollar therapies may alter payment models". Deloitte. 2022.



DELOITTE'S PERSPECTIVE

Leveraging artificial intelligence (AI) in CGT R&D

It would not be an understatement to say that the CGT R&D process is a highly complex and multi-faceted one that is fraught with challenges. The good news, however, is that the emergence of new AI technologies could potentially provide CGT stakeholders with innovative solutions to overcome some of their most pressing issues.

Key use cases for AI include:

1. **Accelerating the experimental process**
   Traditional target discovery and drug development processes require years of efforts; however, with AI, the wet-lab experimental process, including target identification, lead identification, optimisation, and outcome prediction, can be expedited through rapid data analysis, virtual screening, and predictive modelling. In addition, by enhancing the *in silico* data analysis process with AI, CGT stakeholders can also benefit from more efficient analysis of complex biological data that will enable them to better identify patterns and predict drug-target interactions for more rapid decision-making.

2. **Integrating diverse sources of data**
   One of the significant advantages of AI is its ability to integrate data from diverse sources. R&D data can come from various patients, cell types, and hardware platforms, and AI can analyse all of this disparate data to identify trends and extract valuable insights that are applicable across different therapeutic approaches. This capability enables stakeholders to make real-time protocol adjustments to streamline the development process and achieve cost savings.

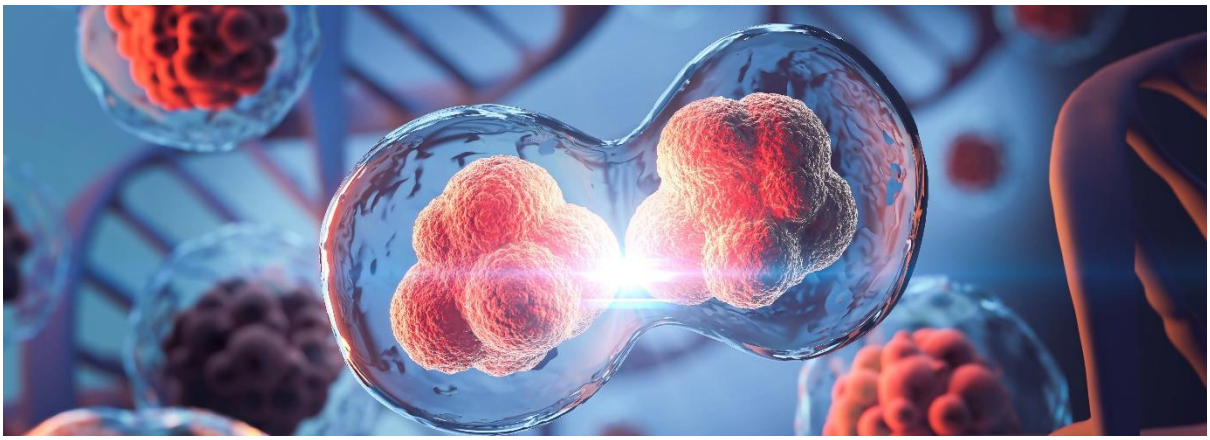
3. **Designing gene constructs**
   AI algorithms can assist with the design of gene therapy constructs by optimising gene sequences for efficient expression and safety. This is particularly important in the context of CGTs, where the design of vectors and gene editing tools is critical.

4. **Boosting patient success rates**
   Through predictive modelling and the meticulous interrogation of the relationship between human-relevant biomarkers and *in vitro* phenotypes post-treatment, an AI-driven patient selection process can help to increase the quantifiability and predictability of therapeutic outcomes in clinical trials. This advanced approach allows for the targeted recruitment of patient populations with higher likelihoods of responding positively to the treatment, which can ultimately help to boost the success rates of Phase II and III clinical trials.

To harness the full potential of AI in CGT, close collaboration between subject matter specialists in cell biology, process engineering, software development, and AI is required. Despite its inherent complexities, AI is poised to play a pivotal role in enabling the efficient development of CGTs and ensuring its widespread availability.

CONFERENCE HIGHLIGHTS

Recent developments in regenerative medicine



T-MSC, a lab-born pre-cell drug for autoimmune disease and beyond

Presented by Prof Xu Ren-He, Distinguished Professor, University of Macau & President, Macau Society for Stem Cell Research

Derived from human embryonic stem cells (hESCs) that have differentiated into trophoblasts, trophoblast-derived mesenchymal stem cells (T-MSCs) have demonstrated both preventative and therapeutic effects in the treatment of multiple sclerosis in mice. Capable of crossing the inflamed blood-brain barrier (BBB), T-MSC spheroids were also shown to be able to treat multiple sclerosis and achieve a successful reduction of brain injury in monkeys.

Relative to bone marrow mesenchymal stem cells (BM-MSCs), T-MSCs demonstrated more remarkable and consistent efficacy, and have been able to elicit a stronger immunomodulatory response. Unlike somatic MSCs, T-MSCs have since been approved by the US FDA for clinical trials, and the first-ever such trial is currently underway to evaluate its safety and potential efficacy.

Stem cell fate engineering and expanded pluripotent state

*Presented by Prof Jonathan Loh Yuin-Han, Deputy Executive Director (Research & Development), IMCB, A*STAR; Professor (Adj), National University of Singapore (NUS) & President, Stem Cell Society Singapore (SCSS)*

Cell reprogramming is a powerful tool for us to overcome certain deficiencies. For example, in the treatment of dyskeratosis congenita (DC), reprogrammed DC cells overcame a critical limitation in telomerase RNA component (TERC) levels to restore telomere maintenance and control. However, donor cell type can play a role in influencing the epigenome and differentiation potential of human iPSCs – which suggests some evidence of an epigenomic memory.

Recent research conducted on single-cell profiling and the dynamic rewiring of the epigenome during reprogramming have revealed certain expressions of surface markers in early to intermediate reprogrammed cells that differentiate them from their parent cells. The findings from this research, in turn, led to the development of a model for human cell reprogramming.

Allogenic mitochondrial transplantation as a novel therapy for mitochondrial DNA disorders

*Presented by Dr Ng Shi Yan, Principal Investigator, IMCB, A*STAR*

Given that mitochondria are the energy powerhouses of cells, any mutations in mitochondrial DNA (mtDNA) could potentially lead to serious disorders. Two examples of such mitochondrial disorders are the mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome that affects multiple organ systems. For these disorders, mitotherapy – or the transplantation of engineered mitochondria – could be used to enable the delivery of healthy mtDNA and provide additional metabolic support for tissue repair.

As autologous mitotherapy would not be suitable for patients with mitochondrial mutation, allogenic mitotherapy has been the focus for mtDNA disorders. Briefly, allogenic mitotherapy entails the derivation of healthy mitochondria from a small pool of pre-screened donors for mitochondrial transplantation, with genetically pristine mitochondria then used to treat the mtDNA disorders and provide acute metabolic rescue. The mitochondria can also be engineered to provide tissue-specificity, without sacrificing host tissues in the process.

Regenerative medicine for the eye

Presented by Prof Jodhbir Singh Mehta, Deputy Chief Executive Officer (Research), Singapore National Eye Centre

In ophthalmology, regenerative therapies are mostly targeted either at the retina or the cornea. For the retina, cell-based therapies primarily rely on two approaches: the use of a carrier, or the use of suspension cultures. At the Duke-NUS Medical School, an innovative method has been developed to induce photoreceptor progenitor differentiation using a laminate-based technique as an alternative to retinal organoids. Of note is also the fact that the process does not use fetal progenitor cells; instead, GMP-approved hESC lines are used.

In terms of treatments targeted at the cornea, the discovery of rho-kinase (ROCK) inhibitors had been a pivotal moment for ophthalmology, as they enable cell proliferation by reducing negative feedback mechanisms. ROCK inhibitors also demonstrate a cell-specific effect, and different tissues across the body show varying expressions of these inhibitors.

Cellular therapy for cardiomyopathy

Presented by Asst Prof Lynn Yap, Lee Kong Chian School of Medicine

Cell therapies have a history of more than 20 years in heart diseases. Early studies leveraging MSCs or cardiospheres sourced from adult stem cells did not lead to successful trials; as a result, the current focus has shifted towards allogeneic stem cell sources, such as iPSC, ESCs, and human pluripotent stem cell (hPSC)-derived cardiomyocytes. It must be noted, however, that one possible side effect of cardiomyocyte transplantation is cardiac arrhythmia.

Under a laminin-based approach developed by the Duke-NUS Medical School, cardiovascular progenitors are injected directly into the heart where they work to promote neovascularisation. A patented protocol has since been developed to utilise laminin-521 and laminin-221 in the differentiation of progenitor cells. A teratoma assay in which the cells were injected into nude mice was later conducted, and the cells have since been verified as safe for future preclinical stages.

Human iPSC-derived islet cells: The next frontier for regenerative medicine in diabetes

*Presented by Dr Natasha Hui Jin Ng, Senior Research Fellow, IMCB, A*STAR; Co-founder, BetaLife & Advisor, Biotech Connection Singapore*

One form of curative treatment for Type 1 diabetes (T1D) is human islet transplant therapy. However, this therapy cannot be the mainstay treatment for diabetes treatment for two reasons. Firstly, this is because the therapy requires patients to undergo immunosuppression; and secondly, there is a lack of sufficient donor islets. The advent of stem cell-derived pancreatic cell transplantation is therefore considered to be a revolution in this field as it will enable us to overcome some of these constraints.

Nevertheless, three challenges will need to be addressed in the use of human iPSC-derived islet cells. Firstly, there are safety concerns relating to the tumorigenic potential of residual iPSCs, presence of partially differentiated or immature cells, and immunogenicity of the transplanted cells. Secondly, there are efficacy concerns relating to the purity of the transplanted cells, variation in differentiation capacity across cell lines, as well as ability to translate *in vitro*/pre-clinical potency data into *in vivo* response and improve graft survival in an *in vivo* environment.

Finally, there are manufacturability concerns relating to the definition of standards and quality control (QC) parameters for human iPSC master cell banks (MCB) and working cell banks (WCB) for cell stocks, differences in scale-up considerations between autologous and allogeneic cell manufacturing processes, as well as whether native or encapsulated cells are being transplanted, as the former would require immunosuppression and therefore render certain patients ineligible.

From epithelial stem cells to cultured skin grafts: Enhancing clinical relevance in an evolving landscape of cell therapy

Presented by A/Prof Alvin Chua, Assistant Director (Transplant Research), Singapore General Hospital (SGH)

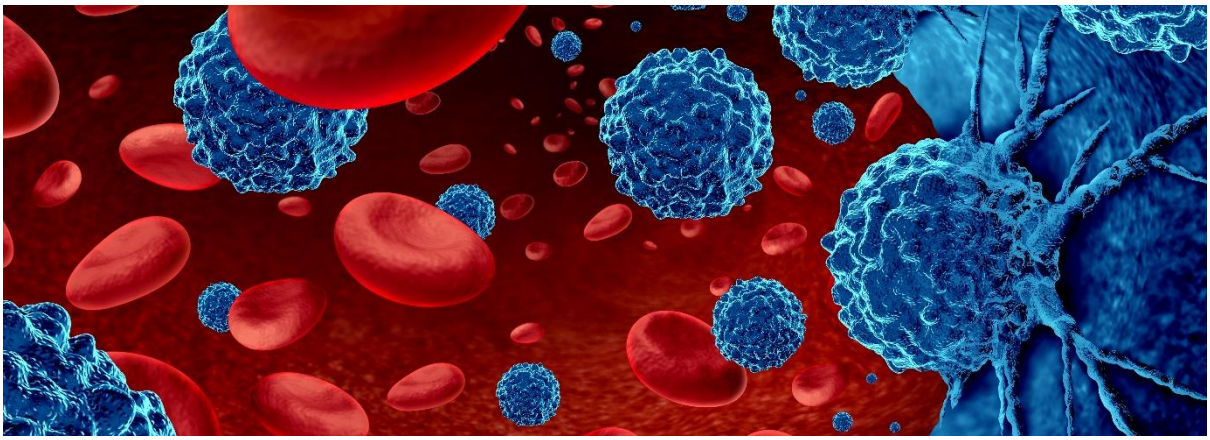
In the case of acute skin injuries, such as deep thermal burns, the conventional approach is to transplant a piece of healthy split-thickness skin graft from a donor onto the wounded area to replace the necrotic burn tissue. However, in instances where the injury is too extensive, a cultured epithelial autograft (CEA) approach is utilised instead.

On the back of several positive pre-clinical results, preparations had been made to develop a laminin-based CEA at a GMP manufacturing facility for Phase 1 clinical trials. This effort, however, was met with many challenges. In particular, there had been a full withdrawal and discontinuation of a key keratinocyte growth medium by the sole supplier; in addition, a few non-GMP reagents had also been flagged.

The key lesson from this experience is that there is a need to gain complete control of the entire cell culture system, including its protocol and critical reagents. It is also crucial to engage multiple suppliers to mitigate disruptions, and all components should be of GMP-grade from the get-go.

CONFERENCE HIGHLIGHTS

Cellular immunotherapy for haematological malignancies and solid tumours



Current and future perspective on CAR T therapy in multiple myeloma (MM)

Presented by Dr Chandramouli Nagarajan, Senior Consultant, SGH

With the introduction of CAR T therapies, patients who were previously undergoing palliation or the recycling of conventional chemotherapy drugs now have another option. In the case of refractory MM, the B-cell maturation antigen (BCMA) has been identified as one of the most promising new therapeutic targets – not only because of its exclusive presence in B cells and plasma cells, but also because it is intricately woven in the survival and development of plasma cells. Nevertheless, the use of anti-BCMA CAR T therapies still appears to be limited; while they exhibit short-term efficacy, many patients still go on to suffer relapses.

There are three main reasons behind CAR T resistance: lack of persistence of CAR T-cells due to CAR design, culture conditions, or the functionality/phenotype input of T-cells; antigen escape, and reduced functionality due to the immunosuppressive microenvironment. To overcome these challenges, possible solutions could include, but are not limited to, optimising CAR design and culture, considering the use of dual-targeting, pooled, sequential, or armoured CAR T, and leveraging the use of PD-1/PD-L1 blockades, immunomodulatory agents (IMiDs)/CRBN E3 ligase modulators (CELMoDs), and CD38-targeted mAbs.

TIM-3 CAR for acute myeloma leukaemia (AML)

*Presented by Dr Wang Cheng-I, Senior Principal Investigator, Singapore Immunology Network (SIgN), A*STAR*

Approximately 85-90% of AML patients achieve remission, but half of them eventually relapse – and relapse almost always leads to death. The reason behind this relapse is the inadvertent selection of increasingly more chemo-resistant leukaemia stem cells (LSCs) with greater aggressiveness following multiple rounds of chemotherapy treatments. Furthermore, it has been challenging to identify markers on LSCs; while CD33 and CD38 are possibilities, they are also present in other immune cells and are not unique to LSCs.

Based on a literature review of prior work conducted by a group of Japan-based researchers, it was discovered that TIM-3 had been identified as a potential marker for AML. More specifically, TIM-3 had been expressed in most AML types, except M3, and was expressed on LSCs at high levels in AML patients. Furthermore, TIM-3 is absent in haematopoietic stem and progenitor cells (HSPCs) and most non-haematopoietic tissues. Of particular interest is also the fact that TIM-3 is not simply a marker, but is also involved in driving the self-renewal of LSCs through a TIM-3/Gal9 autocrine stimulatory loop.

In view of this finding, work was done to repurpose a TIM-3 antibody – which had initially been developed as a checkpoint blockade for immunotherapy – into an anti-TIM-3 CAR T treatment. Ongoing work is now being done to engineer a dual-targeting CAR to broaden the coverage of LSCs.

Myeloid cells in cancer immunotherapy

Presented by Dr Christopher Garris, Asst Prof, Harvard Medical School

Given the anti-tumour properties of interleukin 12 (IL-12) and the fact that IL-12 is a key phenotype for tumour rejection in myeloid cells, the logical question is how we can maximise its production. To this end, a combination therapy known as cyclodextrin-adjuvant nanoparticle dual immunotherapy (CANDI) had been developed. Results from the use of CANDI found potent synergy in the combination of cellular inhibitor of apoptosis (cIAP) with a small molecule toll-like receptor (TLR) agonist, which resulted in the synergistic induction of IL-12 within macrophages.

Further studies conducted on mice with glioblastoma also observed a therapeutic response following the treatment with CANDI within a five to seven-day period. It was later also found that the use of a triple combination CANDI – that is, with the further addition of a Janus kinase (JAK) inhibitor, ruxolitinib – to be effective at enhancing the number of IL-12-producing cells. This was a surprising finding, because ruxolitinib is typically used as an immune suppressant rather than an immune potentiator.

Cytokine-induced killer (CIK) cells in haematological malignancies

Presented by Dr Linn Yeh Ching, Senior Consultant, Department of Haematology, SGH

CIK cells are non-major histocompatibility complex (MHC) restricted, which means that they kill autologous and allogeneic targets to a comparable degree. Their mechanism for target recognition can be either TCR-dependent or TCR-independent, and other receptors such as NKG2D and DNAM-1 are also involved in cytotoxicity. Of note is also the fact that the CD3+CD56+ cells are more terminally differentiated than the CD3+CD56- subset, and demonstrate lower proliferation and higher cytotoxicity due to their higher granzyme content.

Clinical data has since demonstrated the feasibility and safety of allogeneic CIK cells, whose efficacy may be superior to donor lymphocyte infusion (DLI) in prophylactic settings (with predicted high relapse risk) or pre-emptive settings (with positive minimal residual disease (MRD) or mixed chimerism). However, CIK appears to be less effective against overt relapse without the use of concomitant therapy.

Leveraging natural killer (NK) cell therapeutics in nasopharyngeal cancer (NPC)

Presented by Prof Lim Chwee Ming, Senior Consultant, Department of Otolaryngology-Head and Neck Surgery, SGH

Based on the results of a study with a 21-day expansion protocol, it was found that the expanded NK cells enriched with the CD16 phenotype were highly capable of killing NPC cells. Subsequent studies conducted with an animal model also found an additive tumour suppression effect in combining NK cells with cisplatin; however, this additive effect of NK cells was more pronounced in smaller tumours.

Research is currently ongoing to extend these findings in a Phase 1 to Phase 2 clinical trial that will leverage healthy donors' allogeneic NK cells in the treatment. Other strategies being considered to enhance NK cell therapies also include the addition of NK cell engager to redirect NK cells towards the tumour; CAR-NK cell development; as well as combinational therapy with chemotherapy.

Is there a role for cellular therapy in hepatocellular carcinoma (HCC)?

Presented by Dr Yong Wei Peng, Associate Director (Research), Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore

Several differences between the two forms of cellular therapies – CAR therapies and TCR therapies – are worth noting. Specifically, unlike CAR therapies, TCR therapies require a human leukocyte antigen (HLA) presentation in order to function. This presents both advantages and disadvantages: while not every patient will possess an HLA presentation and therefore qualify for a TCR therapy, TCR therapies are highly efficient and do not require the antigen to be present on the surface of the cell.

In the context of HCC, ongoing CAR T trials are predominantly focused on surface markers such as GPC3, which is a heparan sulphate proteoglycan (HSPG) that is often overexpressed in these malignancies. On the other hand, ongoing trials on TCR T therapies are primarily focused on alpha-fetoprotein (AFP) directed TCR T and hepatitis B virus (HBV)-associated peptide directed TCR T.

TCR therapy for solid tumours

*Presented by Dr Li Qi-Jing, Research Director, SIgN and IMCB, A*STAR*

Following success at cloning specific Epstein-Barr virus (EBV)-associated components, a clinical trial was conducted on TCR T therapies for NPC in humans. However, the outcomes were not as stellar as hoped, with patients exhibiting only brief and moderate responses. To understand the reasons behind this, biopsies were performed on the tumour and non-tumour sites. As it turned out, the answer was fairly straightforward: if the tumour microenvironment was 'hot', a slightly better response was observed.

However, because the TCR T did not elicit much change in the tumour microenvironment, it was decided that a stronger TCR T was required. One approach was to induce the T-cells to secrete anti-PD1 antibodies within the tumour microenvironment. This proved to be successful at achieving a more prolonged and sustainable partial response. Ultimately, the key takeaway is that by leveraging the capabilities of T-cells for tumour-targeting and protein production, we can harness them as drug platforms to design rational combinatory therapeutic strategies.

Investigating the metabolic tumour microenvironment of HPV-driven cancers

*Presented by A/Prof John Edward Connolly, Research Director, IMCB, A*STAR & Chief Scientific Officer, Parker Institute for Cancer Immunotherapy*

RNA sequencing studies have revealed that HPV-positive tumours display a unique metabolic signature that is oxidative in nature. Specifically, it is characterised by high hexokinase levels, an oxidative pentose phosphate pathway, and a high glycolysis signature. Non-HPV-associated head and neck cancers did not display this metabolic characteristic; furthermore, when the data were compared across the entire dataset in The Cancer Genome Atlas (TCGA) program, it was found that only HPV-positive tumours exhibited this unique metabolic signature.

By examining the same rate-limiting enzymes identified by the RNA sequencing studies at the single-cell level, it became possible to develop an understanding of the carbon flux of their pathways. This consequently led to the development of the MET-FLOW platform for the single-cell analysis of antibodies – and with it, the identification of dynamic metabolic reprogramming insights within the tumour microenvironment.

Tumour-infiltrating lymphocytes (TILs)

Presented by Prof N Gopalakrishna Iyer, Head & Senior Consultant, Division of Surgery & Surgical Oncology, NCCS

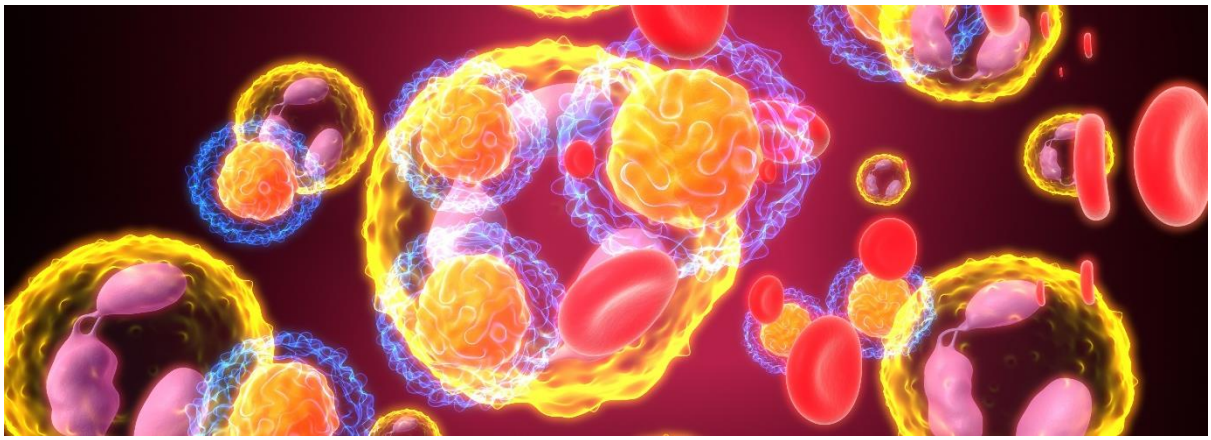
While CARs are often the focus of cell therapy, TILs are also one important domain in the immunology of head and neck squamous cell carcinoma (HNSCC). Based on deep profiling of HNSCC tumours, it was found that there was a higher proportion of exhausted, tumour-engaged T-cells within the primary tumour than in the metastatic site – a finding that suggests the primary tumour as a good source for the harvesting of TILs.

While there is no clear answer yet as to the ideal time to harvest TILs, it has been found that patients who had been treated with immune checkpoint blockade therapies and had undergone prior radiotherapy or cytotoxic treatments tend to have better responses to the PD1-blockade therapy.

Looking ahead, key challenges in preparing TILs for adoptive cell transfer/therapy lie in converting the cells to GMP grade and addressing logistics issues relating to feeder cells and irradiation. Further research is also required on the feasibility of a pre-treatment diagnostic test for efficacy – for example, one that uses tumour fragments to predict efficacy in an individual patient before infusion.

CONFERENCE HIGHLIGHTS

Next-generation CGTs for paediatrics



The role of molecular diagnostics in CRISPR-based genomic therapies

Presented by Dr Petros Giannikopoulos, Director, Innovative Genomics Institute (IGI) Clinical Laboratory

The challenge of clinical diagnostics lies in possessing both an understanding of the clinically important molecular data and the technical capability required to measure the relevant biomarkers. This conundrum also presents itself in the context of CRISPR-based genomic therapies, where the specifics of what should be measured remain unclear due to limited longitudinal clinical data; however, this may be changing as data collection is now ramping up.

As a background, CRISPR is a bacterial immune system that has been adapted for different purposes. In recent years, we have seen a proliferation of CRISPR editing approaches. These include, for example, stochastic indels, protospacer adjacent motif (PAM)-distal transition point mutations, PAM-proximal point mutations, as well as small insertions, small deletions, and large insertions.

Multiple-targeting CAR T-cell therapies

Presented by Prof Leung Wing Hang, Head of Department of Paediatrics and Adolescent Medicine, University of Hong Kong; and Director, Children's Blood and Cancer Centre, KK Women's and Children's Hospital (KKH)

All commercial CAR T products in the current market are single-targeting, but these come with high relapse rates. Specific to CD19 CAR T therapies, current results in the US have also revealed that only a minority or 36% of patients are cured with a single CD19 CAR T. To reduce CD19 antigen escape, multiple targeting therapies are therefore required.

Current multiple-targeting strategies include co-infusion, co-transduction, bicistronic vectors, and tandem CARs. Recent clinical data from the co-infusion of a CD19 CAR T and CD22 CAR T for childhood B-cell acute lymphoblastic leukaemia (B-ALL) – for which manufacturing was conducted in seven days without leukapheresis – revealed high success rates both in cell production and complete remission.

However, it must be acknowledged that a CD19 and CD20 tandem CAR may not be the best approach in a paediatric context, given that CD20 antigens are low or absent in childhood cases. In the context of childhood B-ALL, research is ongoing to examine the alternative approach of using a CD19 and CD22 tandem CAR instead.

CRISPR-based gene therapy for haemoglobinopathies

Presented by Prof Rupert Handgretinger, Children's University Hospital, Tübingen, Germany

Before the introduction of CRISPR-based approaches, the lentiviral vector-based approach had been the dominant approach to gene editing. In the US, the lentiviral vector-based approach ZYNTEGLO® (betibeglogene autotemcel) has been approved for use, following the release of the studies showing that patients with β-Thalassemia had a reduced dependence on red blood cell (RBC) transfusions following an autologous infusion of CD34+ cells which had been edited to correct the β-globin mutation.

On the other hand, more recent CRISPR/Cas9-based gene editing approaches focus on the disruption of γ-globin repressors, with the objective of increasing foetal haemoglobin (HbF) expression. In a pivotal Phase 3 trial of exagamglogene autotemcel (exa-cel) involving participants with transfusion-dependent thalassemia (TDT) and sickle cell disease (SCD), the BCL11A gene was disrupted using CRISPR/Cas9 and electroporation. This was followed by haematopoietic stem cell transplantation (HSCT) for both TDT and SCD.

The promising results from recent trials also suggest the possibility of moving towards the innovative, point-of-care manufacturing of gene-modified stem cells, where automated GMP-compatible CRISPR/Cas9 editing of cells can be conducted for the clinical treatment of β-haemoglobinopathies by the patient's bedside.

OVERVIEW

The rise of T-MSCs and iPSCs in regenerative medicine

Dedicated to the development of innovative approaches for the repair, replacement, or regeneration of damaged or diseased tissues and organs within the human body, the field of regenerative medicine deploys a range of different strategies within its toolkit to transplant or introduce materials, living cells, and biological molecules. As highlighted over the course of this conference, regenerative medicine plays an important role in addressing many areas in the escalating global health care challenge.

One key area where regenerative medicine has been making significant strides is the domain of autoimmune diseases, which affect approximately 10% of the global population, with a higher prevalence among women (13%) than men (7%)[6]. Recent research has also shed light on the increased risk of autoimmune diseases in patients recovering from COVID-19[7]. Adding to the complexity of autoimmune and rheumatological diseases is also their high mortality rates, which can be as high as 37.5%[8].

In this regard, the therapeutic potential of MSCs has gained prominence for their efficacy across various autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. What sets them apart, particularly in the context of CGT, is their adaptability for personalised treatment approaches. Trophoblast-derived mesenchymal stem cells (T-MSCs), a subset of MSCs, hold the potential to be harnessed as a personalised therapy for autoimmune diseases. Factors such as age, sex, and the biological source of the donor can be considered, offering tailored solutions that align with the unique needs of each patient.

Another notable development is the emergence of iPSCs as pivotal assets in the realm of regenerative medicine, particularly in tackling neurologic diseases. These cells possess several distinct advantages. They retain the genetic makeup of their donor, offering a valuable tool for modelling neurologic diseases like Parkinson's, Alzheimer's, and spinal cord injuries. Unlike MSCs, which have limitations in terms of quantity and differentiation potential, iPSCs can differentiate into a wide range of cell types using established protocols. Furthermore, iPSCs address ethical concerns associated with embryonic cells and have the potential to reduce the cost of clinical trials while minimising immunorejection rates, making them a promising avenue for future regenerative therapies.

6. Nathalie Conrad *et al.* "Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK". The Lancet, Volume 401. 2023.
7. Renin Chang *et al.* "Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study". The Lancet, Volume 56. 2023.
8. Maria Teresa Ospina & Alexander Sanchez. "Factors associated with mortality in patients with autoimmune diseases admitted to the intensive care unit in Bogota, Colombia". Frontiers in Immunology, Volume 8. 2017.

OVERVIEW

The revolution in the treatment of solid tumours

Cancer is the second leading cause of death worldwide. In 2020, there were approximately 18.1 million new cases of cancer globally, leading to an estimated 10 million deaths[9]. Additionally, the economic burden of cancer care is a growing concern – the global costs of cancers from 2020 to 2050 is estimated to come in at staggering US$25.2 trillion[10].

Notably, the economic impact of cancer is not uniformly distributed across countries: high-income nations tend to experience higher economic costs due to their more expensive health care systems and higher prevalence of cancer-related risk factors, such as smoking and obesity.

In the treatment of cancers, CAR T-cell therapies have made significant strides for advanced relapsed/refractory (R/R) blood cancers; however, their progress in the treatment of solid tumours is confronted with substantial challenges. Solid tumours often present physical barriers and an immunosuppressive microenvironment that hinders CAR T-cells' ability to reach and kill tumour cells, and this tends to be further complicated by tumour heterogeneity. Nevertheless, researchers are actively exploring strategies to overcome these obstacles, including the development of "armoured" CAR T-cells capable of navigating the hostile tumour microenvironment by secreting specific cytokines and molecules.

TCR T-cell therapy is also emerging as a compelling avenue for the treatment of solid tumours. The primary reason behind its rise has to do with the nature of tumour antigens, which often have the highest specificity within cancer cells and are derived intracellularly, making them accessible to TCRs but not CARs. Although TCR T therapies have yet to receive clinical approval, several clinical trials on solid tumours have demonstrated their promising potential.

9. "Worldwide cancer statistics". Cancer Research UK. Accessed September 2023.
10. Simiao Chen *et al*. "Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050". JAMA Oncology, 9(4):465–472. 2023.

OVERVIEW

Leveraging CGTs to target paediatric diseases

Globally, an estimated 869,000 children (aged 5 to 9 years) and young adolescents (aged 10 to 14 years) died in 2020 – representing a mortality rate of 7 per 1000 children – with Sub-Saharan Africa and Southeast Asia exhibiting the highest regional mortality rates for both groups[11]. Many of these unfortunate fatalities were due to a range of severe conditions, including genetic and haematological disorders such as sickle cell disease (SCD) and anaemia.

Globally, an estimated 869,000 children (aged 5 to 9 years) and young adolescents (aged 10 to 14 years) died in 2020 – representing a mortality rate of 7 per 1000 children – with Sub-Saharan Africa and Southeast Asia exhibiting the highest regional mortality rates for both groups[11]. Many of these unfortunate fatalities were due to a range of severe conditions, including genetic and haematological disorders such as sickle cell disease (SCD) and anaemia.

Within the realm of paediatric health, one particularly challenging facet is the prevalence of paediatric genetic diseases (PGDs), which pose a significant health care challenge as they impact approximately 2% to 3% of all live births globally. Although each PGD may individually affect fewer than 1 in 2,000 individuals, the cumulative burden is substantial, impacting over 350 million children worldwide[12].

In light of these alarming statistics and the potential of advanced therapies like CGT, it becomes clear that addressing paediatric diseases is not solely about numbers; it is about improving the lives of countless children and their families while also alleviating the strain on health care systems and resources.

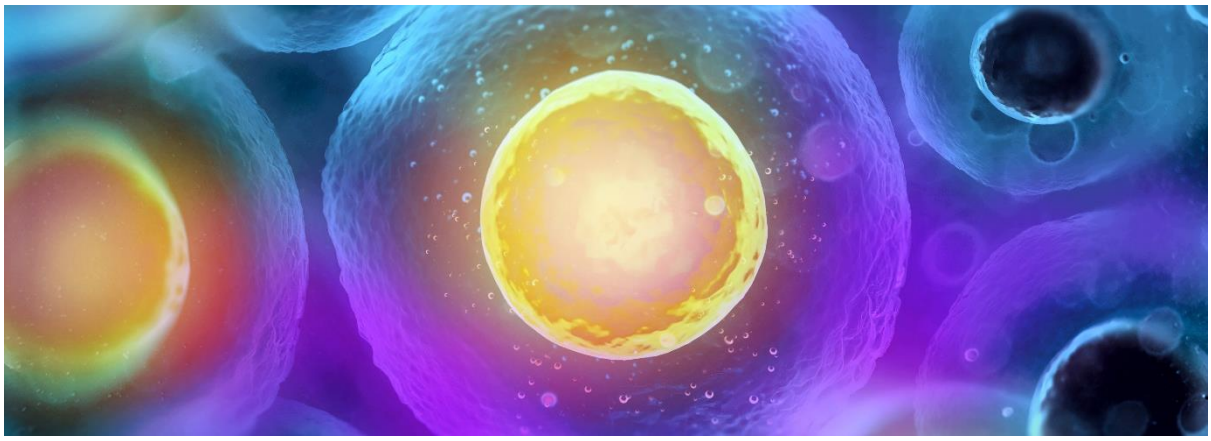
CGTs have gained momentum in addressing rare PGDs due to their potential to target monogenic disorders. Recent advances in genomic technologies have significantly enhanced our understanding of PGDs at the molecular level, enabling diagnoses in 25% to 50% of previously undiagnosed patients[13].

This shift from seeking diagnoses to exploring treatment options has opened up exciting opportunities for CGTs, which have shown remarkable success in treating rare paediatric diseases due to their potential to target monogenic disorders. Despite challenges such as small patient populations and logistical complexities, CGTs hold great promise, exemplified by advancements in the treatment of conditions such as haemophilia.

11. "Older children and young adolescent mortality (5 to 14 years)". World Health Organisation. Accessed September 2023.
12. Ai Ling Koh *et al.* "Therapeutics in paediatric genetic diseases: current and future landscape". Singapore Medical Journal, 64(1): 7–16. 2023.
13. Ibid.

CONFERENCE HIGHLIGHTS

Funding and financing considerations



Supporting advanced medicines innovation in the UK

Presented by Prof Chris Molloy, Chief Executive Officer, Medicines Discovery Catapult, UK

Advanced therapy medicinal products (ATMPs) challenge almost every existing health care model built in an era of small molecule medicines and biologics in four different aspects: R&D; regulatory and approval; delivery and manufacturing models; as well as pricing, affordability, and payment. This picture is made even more complex when we consider the interactions between each of these aspects. For example, R&D innovations, such as 'off the shelf' cells and in-body CRISPR, could help to reduce costs and increase affordability; however, they could also add to the regulatory burden.

Fundamentally, the key issue underlying affordability lies in the question of what a cure for an individual really is worth to a nation. Calculating the true costs and benefits of this will require the development of new frontier economics. Nevertheless, the good news is that we are already witnessing the development of several new approaches. In the UK, for example, the Highly Specialised Technologies Programme (HSTP) conducts the cost-effectiveness analysis for ultra-rare diseases by projecting over a longer time span and technological innovativeness beyond health benefits.

Innovative financing in biomedical research

Presented by Mr Quintus Lim, Associate Director, Policy & Programs, Milken Institute

There are four main reasons why we need innovative financing mechanisms for biomedical research. Firstly, on the back of the subsiding hype for biotech, funding levels are receding. Secondly, a significant proportion of funding rounds remain in their early stages – about half of them are only in Series A, which translates empirically to the pre-clinical to Phase 2 stages.

Thirdly, in the Singapore context, only about 8% of venture investors have invested in the biotech sector, and of this group of investors, only three in 10 are repeat investors. Given that repeat investors are an important source of smart capital with deep understanding of target markets and the experience to guide innovation towards commercialisation, driving repeat investment activity should be a key focus for Singapore.

Finally, there is also the issue of scaling. On a global level, the median accumulated funding raised by a biotech before its Series A funding round is about US$700,000. But there was a stark difference between biotech players who raised funds above the median, and those who raised funds below the median: the group whose funding was below the median took about two years longer to get to their Series A funding round. Overcoming this time gap– sometimes referred to as the "valley of death" – is therefore crucial.

Possible alternative capital sources for the biomedical sector could include family offices – globally, nearly 50% of family offices have expressed an interest in investing in gene therapies, and Singapore has witnessed the establishment of 700 new family offices in recent years – and philanthropic foundations with long investment timelines and whose investment strategies are insulated from shareholder and public pressure.

Considerations for financing of advanced therapies in Singapore and the region

Presented by Dr Ho Wen Qi, Director of Investments and New Ventures, ClavystBio

When preparing to engage with investors, particularly in the context of securing early-stage funding, CGT players should consider their technology along five key dimensions. First, they should consider how differentiated their technology is relative to other CGT products, and how their approach to the given indication differs in comparison to other modalities, such as small molecules and antibodies.

Second, manufacturing time and costs are key. Integrating methods and technologies to reduce costs while ensuring regulatory compliance can be one way to develop a compelling narrative for investors. Many CGT players have been able to successfully achieve this by leveraging GMP manufacturing facilities run by leading academic institutions to shorten manufacturing turnaround times and reduce costs.

Third, CGT players must formulate a robust clinical plan with clear endpoints and achievable timelines. In addition, the early identification of key opinion leaders (KOLs) is also vital to disseminating clinical results and informing the development of the clinical strategy.

Fourth, CGT players will need to develop a clear regulatory and reimbursement path. It is important that the CGT players align themselves with their respective regulatory bodies to accelerate pathways and reduce timelines, and remain open to the use of innovative reimbursement schemes.

Finally, CGT players should focus on obtaining investors possessing not only financial capital, but also a longterm view on investments. As CGTs have a long path to take from bench to bedside, it is important that their investors are in it for the long haul. Ideally, these investors should also develop productive relationships with the founders, and be able to provide advice on commercial matters, as well as inputs and guidance throughout the discovery and clinical development process.

DELOITTE'S PERSPECTIVE

Navigating the financial hurdles of CGTs

As compared to conventional pills or targeted therapies, CGTs are costly, complex, and high-risk endeavours. This not only renders them exceptionally expensive, but also poses financial challenges for payers and patients alike.

The underlying cause of the high prices of CGTs can be traced back to their extensive R&D expenses, high costs of delivering personalised treatments, high level of manufacturing intricacy, and landscape of escalating costs driven by emerging technologies. To navigate these financial hurdles, a fundamental re-evaluation of traditional commercialisation models, including pricing and contracting strategies is needed[14]. Key questions to consider include:

- **Payment responsibility:** Who should shoulder the burden of funding CGTs?
- **Risk ownership:** Who should assume the risks associated with CGTs, including their potential side effects and uncertainties surrounding the durability of treatment benefits?
- **Management of unexpected complications:** How do we address the intricacies and issues that could arise during CGTs in the event of unexpected complications?

The current state of reimbursement often falls short of covering the full spectrum of costs associated with CGTs. To address these challenges, stakeholders within the CGT ecosystem are actively exploring innovative financial models and strategies in several key areas:

1. **Value-based contracts (VBCs)**
   Some CGT manufacturers are contemplating anchoring payments to longer-term outcomes. However, the adoption of VBCs is confronted by resistance from many payers due to the complexity of reimbursement mechanisms and the need for substantial investments in technology infrastructure to track clinical outcomes over time. Furthermore, the limited number of approved therapies targeting small patient populations may mean that the costs of implementation could outweigh its benefits.

2. **Alternative financing mechanisms**
   Stakeholders are exploring the use of alternative financing models that allow beneficiaries to receive gene therapies with minimal cost-sharing. Collaborative initiatives like the performance-based annuity approach are being developed to determine payments based on patient responses to therapy over time. This approach entails an initial payment, with the total cost varying based on individual patient responses over time, to more effectively align the therapy's cost with its real-world performance.

3. **Regulatory and reimbursement strategy**
   Establishing clear regulatory and reimbursement pathways is paramount, and collaborative engagement with regulatory bodies can help to expedite approvals and reduce timelines. Additionally, a willingness to embrace innovative reimbursement schemes can also go a long way in enhancing the financial viability of CGTs. For instance, the National Medical Products Administration (NMPA) in China has implemented an accelerated approval process for innovative therapies, including CGTs. This streamlined process allows for faster review and approval of therapies to address unmet medical needs.

Driven by the imperative to deliver transformative therapies to patients in need, the funding and financing landscape is evolving rapidly to address the complex challenges posed by the high costs of CGTs. Collaborative efforts between manufacturers and payers will be instrumental in paving the way towards more innovative payment models to ensure the accessibility, affordability, and long-term sustainability of CGT treatments. Through pilot programs and data sharing, stakeholders can fine-tune these models to align with real-world patient outcomes and the dynamic landscape of CGTs.

14. "Distributions and supply chain models in the cell and gene therapy landscape". Deloitte. 2021.

CONFERENCE HIGHLIGHTS

Lunch Symposia

Lunch Symposium by Novartis

Learning from clinical practice: The role of CAR T in the treatment of follicular lymphoma (FL)

Presented by Dr Jason Butler, Clinical Haematologist, Royal Brisbane and Women's Hospital and the Sunshine Coast University Hospital

In recent years, much effort has been invested in investigating the risk factors for adverse outcomes in CAR T treatments for FL. These include, for example, clinical or patient-based factors, imaging-based factors such as those relating to positron emission tomography (PET) scans, tumour-based factors, and treatment-based factors. What is becoming clear, however, is that patients with high metabolic tumour volume tend to be the ones with worse outcomes.

Notable studies in this space include the ELARA study conducted on patients with R/R FL, where tisagenlecleucel (tisa-cel) was found to be a safe and effective treatment. It must be caveated, however, that adverse events and cytokine release syndrome (CRS) were observed in a number of patients, and about one-quarter of patients required a new line of therapy due to disease progression.

In the ZUMA-5 study leveraging axicabtagene ciloleucel (axi-cel) in the treatment of R/R indolent non-Hodgkin lymphoma, a relatively higher signal for efficacy was observed than in the ELARA study. However, CRS rates were also higher, and a significantly higher level of neurotoxicity was observed. Interestingly, CRS and neurotoxicity incidences were highly correlated with CAR T expansion: patients who displayed the best CAR T responses also experienced more adverse CRS and neurotoxicity events.

Lunch Symposium by Agilent

Exploration of factors affecting CAR T-cell engraftment and function through multiomic approaches

Presented by Assoc Prof Michael C. Milone, Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania

To understand the complex biology of CAR T-cell engraftment and function in MM, multiomic approaches, or approaches that integrate transcriptomics and metabolomics, have been deployed. While larger trials with clinically used CAR T-cells are needed, recent developments in this domain have revealed the different mechanisms, particularly multiple amino acid metabolism pathways, that differentiate between responders and non-responders of anti-BCMA CAR T (CART-BCMA) – which suggest the possibility of modulating CAR T-cell engraftment through metabolic manipulation in the future.

Briefly, in transcriptomics, single-cell RNA sequencing (scRNA-seq) was used to analyse cell-to-cell communication (CCC) in CAR T products. Pathway analysis indicated the prominence of certain transcription factors linked to MHC class II genes and some associated with cell "stemness". In addition, a majority of genes were associated with interferon response, with a decrease observed in inflammatory signals.

The study also underscored the presence of transcriptional stem cells in the myeloma microenvironment. One intriguing aspect is TCR diversity in myeloma, especially in its immune responses to tumour antigens like SOX2, a stem cell transcription factor. Observations suggest that immune responses to SOX2 could delay myeloma progression, and TCR responses might be crucial in determining the duration of response.

Metabolomics, on the other hand, entails the use of two approaches: untargeted metabolomics for discovery and hypothesis-generating; and targeted metabolomics for validation and quantification. Metabolomics studies are particularly challenging to conduct, as their method development and validation processes tend to be subject to high levels of variation and errors that can creep in at any step from sample storage to extraction, sampling, chromatography, ionisation, and mass spectrometry.

Lunch Symposium by Gilead Kite

CAR T-cell therapy for large B-cell lymphoma (LBCL): Where are we now

Presented by Dr Ran Reshef, Assoc Prof of Medicine, Columbia University Irving Medical Centre

Briefly, the process of CAR T for LBCL entails collecting T-cells from the patient's blood through leukapheresis and genetically modifying these T-cells to express the antigen-specific CAR and expanding them in the lab. The patient may also receive a conditioning regimen, which could include chemotherapy, before the expanded and modified CAR T-cells are infused into their bloodstream. Once inside the body, the CAR T-cells locate and bind to the cancer cells expressing the target antigen. Upon binding to the cancer cells, the CAR T-cells become activated and initiate a strong immune response against the cancer cells, leading to their destruction.

Pivotal trials in LBCL include ZUMA-1, JULIET, and TRANSCEND, which have collectively demonstrated CAR T's effectiveness and potential for treatment of the disease; however, these trials vary significantly by design and the treatments involved had been developed with different patient groups and endpoints in mind.

Lunch Symposium by Miltenyi Biotec

Upscaling of CAR T manufacturing: Challenges and potential solutions

Presented by Dr Ulf Bethke, Executive Expert Cell and Gene Therapy Asia Pacific, Miltenyi Biotec

Risk assessment strategies are key to successful manufacturing processes, as they define the testing procedures and acceptance criteria for raw materials. In addition, quality agreement procedures will also need to be established to evaluate suppliers' declarations on issues relating to international pharmacopoeia specifications, processing under GMP or non-GMP conditions, and incoming control tests for identity, content, stability, microbial, fungal, phage, and contamination.

Another factor affecting raw material quality is the variability of the starting material– which, in this case, refers to individual patient cells. To address this issue, it may be necessary to define the starting cells with the use of specific markers, and leverage cell separation technologies to generate reproducible starting material.

Other concerns also include the short shelf life of cells and their sensitivity to freezing and thawing, which can in turn be mitigated through improved dry ice and liquid nitrogen storage facilities in logistics and transportation, as well as the development of point-of-care manufacturing models and other decentralised manufacturing solutions.

CONFERENCE HIGHLIGHTS

Sponsored talks

Sponsored talk by BD Biosciences

Flow forward to advance cell therapy from bench to bedside

Presented by Keefe Chee, Segment Marketing Lead, Life Sciences, BD Biosciences Singapore

Developed by BD Biosciences, the BD FACSymphony™ cell analyser series is designed to support researchers in investigating the correlations between CAR T phenotype and function. On the other hand, the BD Rhapsody™ Single-Cell Analysis System can be used to enable high-throughput capture of multiomic information from single cells, as it provides an unprecedented depth of surface protein cell analysis in conjunction with the transcriptome.

Sponsored talk by Charles River Laboratories

Cell bank production and characterisation: Past and present with considerations for the future

Presented by Brian Fry, Senior Director, Cell Therapy CDMO, Charles River Laboratories

Long-term cell storage entails several considerations. Apart from the fact that the MCB and WCB need to be stored under defined and documented considerations, it may also be worthwhile to consider storing the cell materials at geographically separate locations to mitigate risks of catastrophic events.

A robust inventory management strategy will also need to be developed to support the documentation, transfer, shipping, and use of each vial of material. Further considerations also include those relating to process scaling, such as cell growth and viability under MCB and WCB conditions, as well as media formulation and stability.

Sponsored talk by Lonza

Bringing CGT to commercialisation

Presented by Dr Sacha Khong, Head of Manufacturing, Science & Technologies, Cell & Gene Technologies, Lonza Bioscience Singapore – CGT Tuas Singapore

Lonza is currently focused on supporting its customers with their new product introduction and lifecycle processes. This covers several aspects, including de-risking product introduction by performing robust fit assessments; standardising lifecycle workstreams; and establishing follow-through processes from capability assessment to commercial production.

Lonza's proprietary solutions include MODATM, a track and trace system developed to digitalise shop-floor traceability and enable open parallel processing. Lonza also possesses expertise in allogeneic manufacturing and storage processes, as well as QC testing.

Sponsored talk by Cytiva

Unleashing the power of viral vectors: Advancements in process development, manufacturing, and enabling tools

Presented by Dr Peiqing Zhang, Strategic Technology Partnership Leader – Genomic Medicine APAC, Cytiva

To increase the accessibility of viral vector-based gene therapies, there is a need to rethink the associated process development, manufacturing, and enabling tools. Strategies to consider could include upstream processing (USP) to support the optimisation of cell lines and plasmids and achieve better stabilisation, as well as downstream processing (DSP) to optimise the therapy process without affecting patient recovery rates.

In both USP and DSP, process intensification – and its accompanying business levers, such as cost of production, footprint reduction, manufacturing flexibility, time to market, time in facility, scalability, and ease of use– can be used as a tool to enhance process efficiencies. Briefly, process intensification seeks to minimise seven key areas of waste relating to transportation, inventory, motion, waiting, overproduction, overprocessing, and defects (TIMWOOD). In the context of gene therapy, process intensification can help to enhance the efficiency, scalability, and productivity of viral vector production, and lead to broader accessibility of these advanced medical treatments.

Sponsored talk by Beckman Coulter

Flow cytometry research tools for the era of immune therapies

Presented by Ms Toh Xue Yun, Regional Product Manager, Beckman Coulter Life Sciences

The ONE Study has been an important benchmark for clinical trials using flow cytometry as a form of standardisation. Beckman Coulter had played a role in the ONE Study by assisting with laboratory and panel designs, as well as leveraging its reagents expertise to manufacture the panels that were in the immune profiling process.

Beckman Coulter's AQUIOS CL flow cytometer enables the provision of 24/7 flow cytometry, and is capable of increasing productivity with its high throughput performance while minimising the risk of user errors and exposure to potentially biohazardous material such as open blood tubes. In addition, Beckman Coulter's CellMek SPS system can also help to address bottlenecks in sample preparation and data management, and enable the end-to-end automation of routine flow cytometry without the need for manual intervention.

Sponsored talk by Gilead Kite

CAR T-cell therapy: Shifting the treatment paradigm in R/R large B-cell lymphoma (LBCL)

Presented by Dr Ran Reshef, Assoc Prof of Medicine, Columbia University Irving Medical Centre

For nearly 30 years, treatment for patients with R/R LBCL in the second-line curative setting has been salvage chemotherapy, with a subsequent high-dose therapy followed by autologous stem cell transplant (HDT-ASCT). Nevertheless, the overall prognosis remains poor. With the advent of CAR T-cell therapies, however, the treatment paradigm for R/R LBCL is rapidly shifting.

In one trial conducted on ZUMA-7 for transplant-eligible patients, it was found that the administration of axi-cel resulted in a statistically significant improvement in event-free survival (EFS) and overall survival (OS) rates as compared to the standard chemotherapy for R/R LBCL patients. Another trial conducted on axi-cel also found that it could achieve favourable outcomes in R/R LBCL patients who have progressed after prior therapies, while a trial conducted on tisa-cel revealed clinically meaningful and durable responses in R/R LBCL patients with limited treatment options.

In addition, two single-arm trials – known as ALYCANTE and PILOT – have since provided valuable data on the feasibility and effectiveness of alternative treatment approaches for transplant-ineligible patients, shedding light on the potential of alternative treatment options for this patient population.

Sponsored talk by Miltenyi Biotec

Therapeutic T-cell manufacturing platform for continuous innovation

Presented by Dr Grigory Efimov, Senior Scientific Director of Immuno/T Cell Therapy, Miltenyi Biotec

Amongst the key challenges confronting the manufacturing of T-cell therapies is the difficulty in achieving scalability and reproducibility of robust, precise, and consistent processes to ensure the quality, safety, and efficacy of the final product. Furthermore, current manufacturing processes for many treatments continue to be labour-intensive and comprise multi-step procedures, which could increase the risks of errors, contamination, and variability.

In this context, a T-cell transduction application (TCTf) with fully automated and closed formulation and filling capabilities could be useful in supporting the entire workflow for T-cell transduction – from cell separation and activation to genetic modification and cell expansion. The CliniMACS Prodigy® platform by Miltenyi Biotec enables the automation of all cell processing steps to ensure a highly reproducible and standardised manufacturing process.

Sponsored talk by Singleron

Single cell analysis for improving cell therapies from target discovery to clinical biomarkers

Presented by Dr Jonathan Scolnick, General Manager, Singleron Biotechnologies

Singleron offers end-to-end services for single cell analysis. Backed by the use of machine learning (ML) technologies, its solutions help to support the identification of potential new therapeutic targets and provide insight into the activity and functionality of CAR T-cells.

Amongst its key technologies is the single cell omics preparation entity (SCOPE)-chip technology, which captures single cells by partitioning them into hundreds of thousands of microwells on the chip following the Poisson distribution. Other key focus areas also include leveraging patient data and ML to make advanced predictions of patient responses to CAR T therapies.

Sponsored talk by ThermoFisher

Enhancing non-viral gene editing and processing of NK cells

Presented by Dr Premkumar Jayaraman, Strategic Technology Partnership & Applications Leader, CGT, Asia Pacific & Japan, Thermo Fisher Scientific

Thermo Fisher's Gibco™ CTS™ NK-Xpander™ Medium enables the robust expansion of enriched human NK (hNK) cells from human peripheral blood mononuclear cells (hPBMCs) obtained from qualified donors. It is capable of producing high yields without the need for feeder cells, and the expanded hNK cells are able to maintain their CD56+/CD16+/CD3- surface marker expression and demonstrate cytolytic capabilities.

The Gibco CTS NK-Xpander Medium is also manufactured without cytokines and growth factors to allow flexibility with regards to the intended applications. The medium does not include human or animal-derived components; however, supplementation with human AB (hAB) serum is recommended for best results.

Sponsored talk by Novartis

Post CAR T complications

Presented by Dr Michaela Seng, Senior Consultant, KKH

Common toxicities associated with CAR T therapies include insertional oncogenesis; immune effector cell-associated neurotoxicity syndrome (ICANS) causing confusion, delirium, aphasia, and seizures; on-target, off-tumour toxicity; anaphylaxis or allergies, particularly those associated with immune responses to mouse-derived or recombinant proteins; as well as CRS and its range of side effects including fever, fatigue, hypotension, nausea, and capillary leak syndrome.

In addition, there is also the immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), which is a rare and life-threatening condition that can lead to severe inflammation and organ damage. Caused by an excessive immune response, IEC-HS typically involves the overactivation of macrophages and T-cells, which can lead to the destruction of blood cells and other tissues.

Sponsored talk by Agilent

Real-time measurement of immune cell cytotoxicity and metabolic fitness and persistence: Robust potency assays meeting the demands of cell therapy discovery, process development and QC/release criteria

Presented by Dr Federica Tomay, Cell Analysis Field Application Scientist South Asia Pacific, Agilent CrossLab Group, Agilent Technologies, Inc.

Potency is a significant critical quality attribute and pivotal release criteria within the realm of pharmaceutical and biopharmaceutical products. In line with US FDA guidelines, potency evaluations entail the comprehensive analysis of a whole host of different attributes that aims to achieve a level of congruence closely mirroring clinical outcomes.

To analyse these complex and multifaceted attributes, advanced technological solutions, such as Agilent's xCELLigence Real Time Cell Analysis technology, are required. By virtue of its adherence to US FDA guidelines, xCELLigence is capable of seamlessly integrating into the potency assessment process, and provides real-time, label-free monitoring and analysis for researchers and practitioners to evaluate potency.

DELOITTE'S PERSPECTIVE

Towards greater industry-academia collaboration

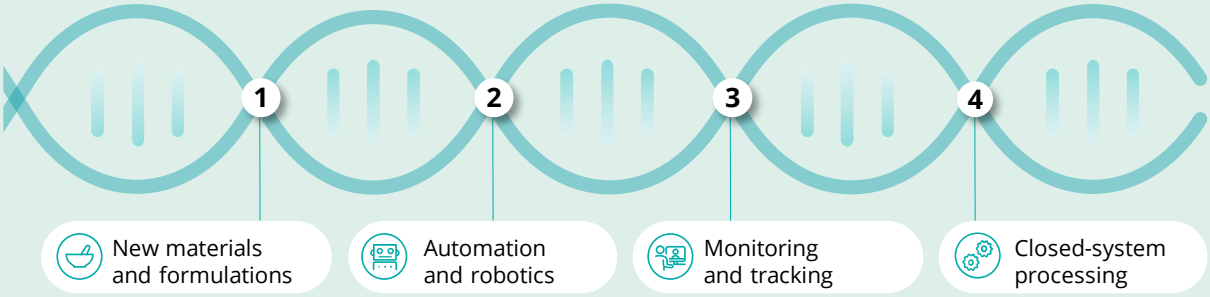
Pharmaceutical companies stand at the forefront of ground-breaking therapies, and their success fundamentally hinges on innovation. In this regard, it is critical to acknowledge that several pioneering advancements in the realm of CGT had in fact been originated, initiated, and validated by academic institutions.

As the landscape of medical research continues to evolve, we are observing a growing call for greater collaboration between the pharmaceutical industry and academia – particularly at an earlier stage of product development. If successful, such partnerships could potentially reduce the attrition of promising therapies in later, more costly human trials, while enabling the more efficient allocation of resources towards endeavours that exhibit the most potential.

Indeed, by joining forces with academic labs, pharmaceutical companies stand to benefit from the access not only to a vast pool of specialised knowledge and cutting-edge research techniques, but also the fresh perspectives of emerging scientists. Taken together, these synergetic and symbiotic relationships could help to unlock advances in the delivery of therapies for different areas, and enhance the therapies' overall effectiveness to ultimately benefit patients and the health care industry as a whole.

One area in which greater collaboration between pharmaceutical companies and academic labs could be especially meaningful is the domain of manufacturing innovation. By bringing together the collective expertise and resources of both sectors – for example, in the development of new materials and formulations, automation and robotics, monitoring and tracking technologies, and closed-system processing (see Figure 3) – industry-academia collaborations could enable novel technologies and manufacturing processes to be developed at a much earlier stage of product development for enhanced downstream efficiencies.

Figure 3: High potential opportunities for collaboration between pharmaceutical companies and academic labs



By working together to develop cost-effective manufacturing methods and scalable production techniques, pharmaceutical companies and academic labs could also help to increase the affordability and accessibility of CGT therapies for a broader patient population. In doing so, they can play a pivotal role in enabling society to address the critical issues of access and equity in health care – not least by ensuring that these innovative therapies reach those who need them most, regardless of economic or geographic constraints.

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