White Paper

# Understanding the Diverse CAGT Landscape in Asia Pacific

*The APAC CAGT landscape, often perceived as uncertain, is primed for clinical research and market access success*

**MARIA ROSELLE LUCAS,** Medical Director, Head, Medical Oncology/Hematology, Asia, IQVIA APAC
**EDWIN GUMAFELIX,** Medical Director, Medical Oncology/Hematology, Asia, IQVIA APAC
**LARA DONATO,** Associate Medical Director, Medical Oncology/Hematology, Asia, IQVIA APAC
**KIM STRYDOM,** Medical Director, Therapeutic Strategy, Asia Pacific Therapeutic Strategy Group, IQVIA
**ANISH SULE,** Head, CSMS-COE India, IQVIA, India
**VAISHNAVI KRISHNAN,** Medical Science Liaison, CSMS Asia, IQVIA, India

# Table of contents

# Introduction

The last two decades have brought tremendous progress within the area of cell and gene therapy (CAGT) especially for the treatment of cancer. The broad field of CAGT holds promise for innovative cancer treatments across the world. Presently, there are over 1,000 global clinical trials underway with rapid expansion seen in China, Japan and Australia besides North America and Europe.

In order to better understand the potential of the Asia Pacific (APAC) region, IQVIA APAC conducted an advisory board involving key opinion leaders (KOLs) from 7 major markets including Australia, China, Japan, New Zealand, Singapore, South Korea and Taiwan. The advisory board brought key insights in several areas such as availability of centers, current clinical trial trends, the patient recruitment scenario and the regulatory landscape. The resulting discussion and knowledge from the KOLs supported the development of this whitepaper. Successes in clinical trial conduct and regulatory approval of CAR-T in Australia and China to date, indicate that the region holds a large potential for the future of CAGT.

According to the KOLs, there are no major challenges anticipated with respect to patient recruitment and trial conduct. As for the long-term follow-up to continue the safety observation in accordance with the US FDA requirements, the investigators are open to innovative solutions to manage this. These KOLs are also keen to give a better understanding on the current regulatory oversight in the region.

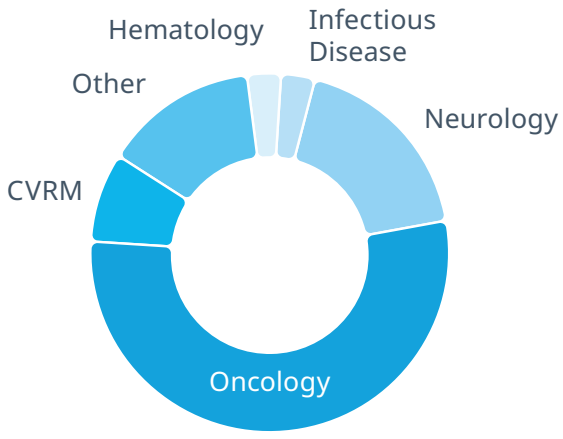
The last two decades have seen significant growth in cancer research with considerable advancements made in this field. This, in turn, led to innovative and novel approaches for managing cancer[1]. It has been suggested that cancers originate from a single malignant cell that has been genetically transformed by external influences such as environmental factors, chemical and physical factors and viruses[2].

Gene therapy delivers genetic material directly to the malignant cells or to effector-immune response cells to address DNA abnormalities within the cancer tissue itself, or to induce an immune response against the malignant cells. These therapies could result in the replacement of deleted or defective genes (tumor suppressor genes), suppression of cancer promoting oncogenes, or inhibition of the growth of the tumor and its vasculature[3,4]. As an upcoming field, it is useful to consider an overview of the current Cell and Gene Therapy (CAGT) landscape in selected markets in Asia Pacific (APAC). This whitepaper presents excerpts from an expert key opinion leader (KOL) advisory board, conducted virtually in November 2020.

## Market landscape and CAGT trials

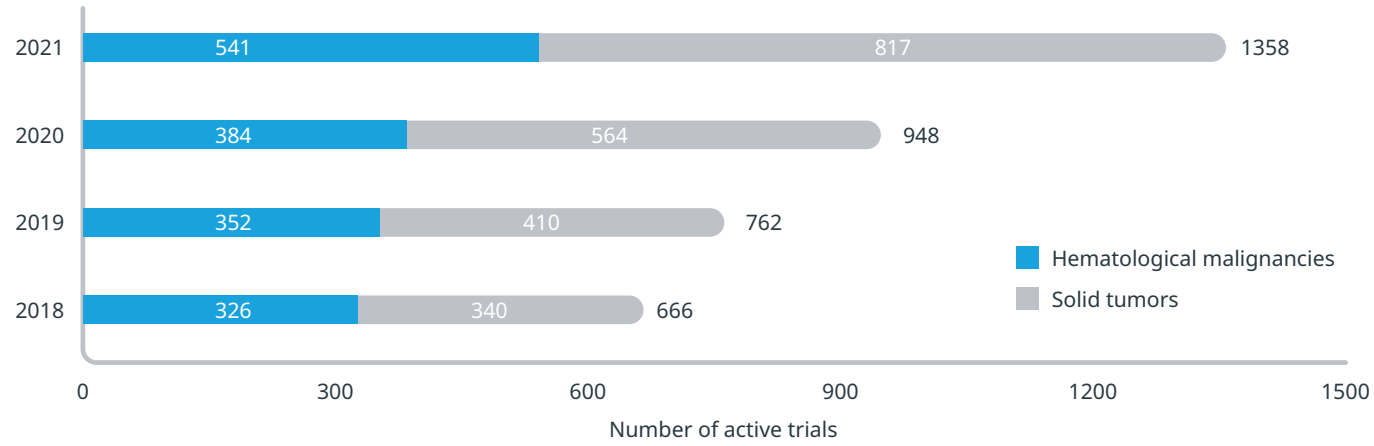
The therapeutic areas that apply CAGT most frequently are oncology, hematology, neurology, infectious diseases and cardiovascular diseases[5]. (*Figure 1*).

**Figure 1: Top common therapeutic areas using CAGT**




Source: IQVIA Analytics

**Figure 2: Comparison of active cell therapies in hematological malignancies and solid tumors indications during the past four years**




Source: IQVIA Analytics

Analysis has shown that the number and global distribution of CAGT trials have been consistently increasing [7]. (*Figure 2*)

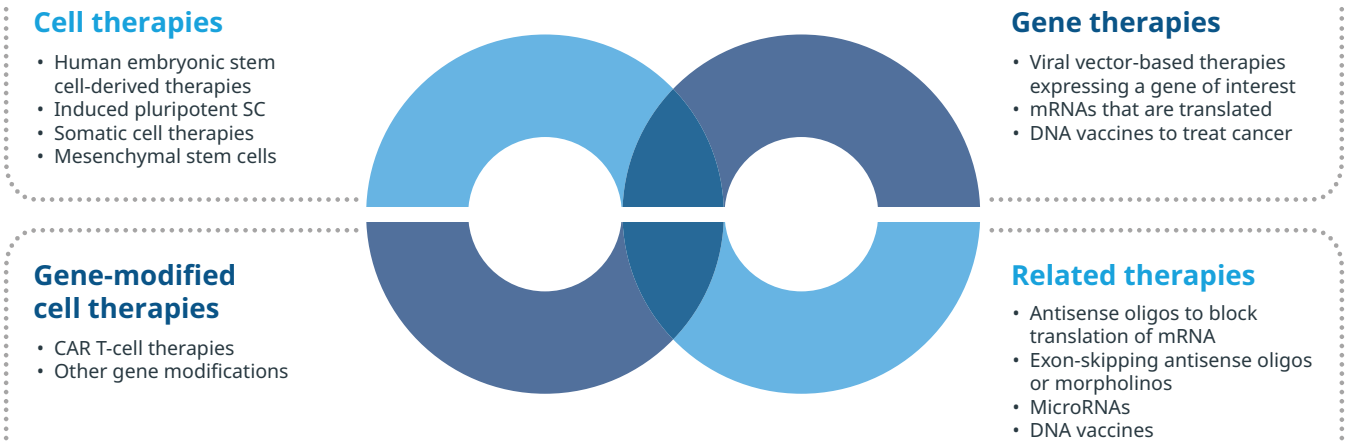
A classification of the types of CAGT is detailed in *Figure 3*. CAR-T cell therapy in particular, has taken the world by storm as a potentially curative cancer therapy in the treatment of selected hematological malignancies by targeting the CD-19 antigen. For solid tumors, the major challenge is the limited evidence of CAR-T to overcome existing issues in treating these types of cancers.

However, there is continuous interest in the identification of CAGT antigens that can effectively target solid tumors.

Globally, more than 1,000 clinical trials are enrolling patients for CAGT, and this is projected to double in the next five years. As seen from *Figure 4*, CAGT trials are quickly expanding across North America, Europe, China and Japan. Australia also has a growing footprint. On the other hand, other APAC markets remain largely underdeveloped in terms of the CAGT trial setting.

Some pharmaceutical companies may be less familiar with the regulatory pathways and requirements that currently exist in APAC, and IQVIA has identified a need to demonstrate the potential of CAGT trials in this region. We therefore gathered insights from CAGT regional experts in Australia, China, Japan, New Zealand, Singapore, South Korea and Taiwan.

**Figure 3: Types of CAGT[5]**




Source: IQVIA Analytics

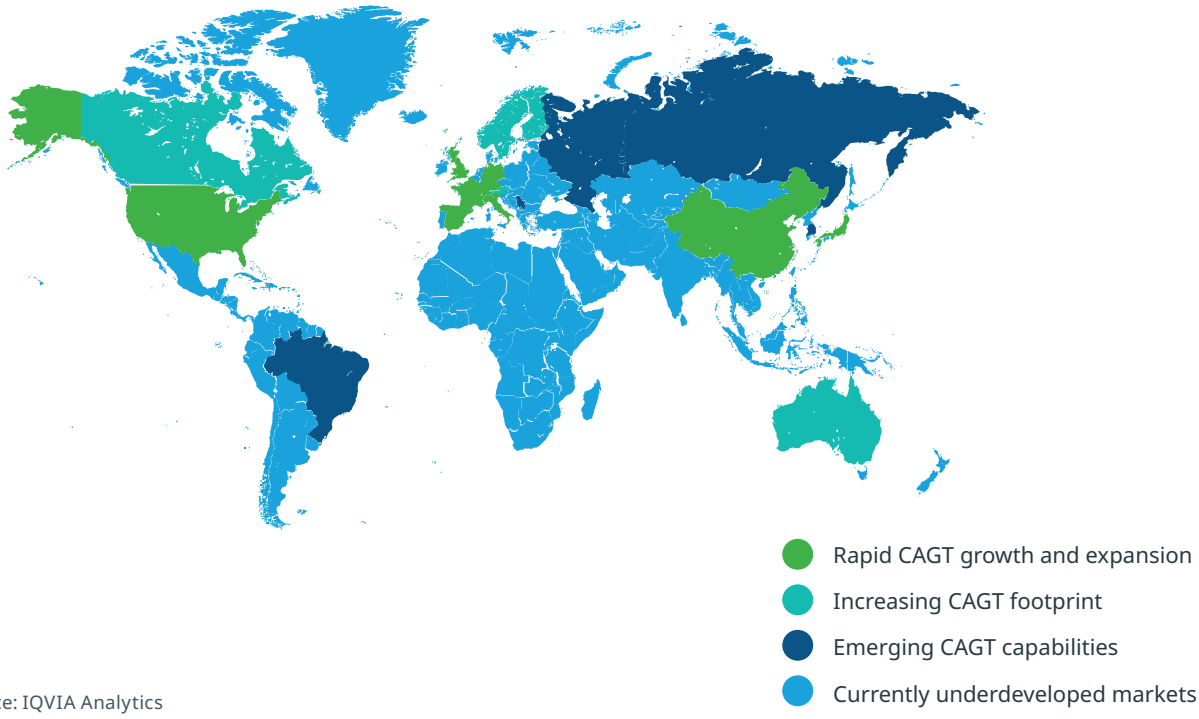
## Expert opinion on the Asia Pacific potential

The execution of clinical trials in CAGT, mostly represented in the region by CAR-T studies, is similar to the conduct of other clinical trials with respect to the basic principles. However, CAGT trials bring unique specificities, starting with specimen collection, which is critical for product manufacturing in CAR-T and other CAGT products.

A pre-test strategy is required and patients with absolute lymphocyte count (ALC) below 300 may be excluded from trial participation or collection may be tried again later.

By delving into the region-specific details, we now explore the overview of the CAGT landscape in each of these markets with a brief note on the regulatory challenges from a clinical trial perspective. The KOLs provided a summary of the regulatory requirements as seen in *Figure 5*.

**Figure 4: Global scenario of CAGT trials[5]**




Source: IQVIA Analytics

**Figure 5: Summary of regulatory requirements** [5]

| REGULATORY REGION | SUMMARY |
|---|---|
| AUSTRALIA | Extent of regulation depends on prior regulatory and ethics committee review and approval elsewhere. There are also government and institutional reviews for certain CAGT products. The processes are well-established and efficient. |
| CHINA | Local authority approval is required for IITs. There are local, though not nationwide, Good Manufacturing Practice (GMP) requirements. |
| JAPAN | Pharmaceuticals and Medical Devices Agency (PMDA) regulates CAGT clinical trials via 2 legislated Acts: Pharmaceutical and Medical Devices Act and the Act on the Safety of Regenerative Medicine. |
| NEW ZEALAND | Product review by Environmental Protection Authority (GMOs), clinical trial review by Gene Technology Advisory Committee and national ethics committee. Sites' readiness to handle CAGT products is audited by Medsafe. |
| SINGAPORE | Health Sciences Authority (HSA) regulatory authority engages KOLs regularly. The local Institutional Review Boards (IRBs) conducts ethical review of clinical trials. There are also international manufacturing accreditation standards, e.g. FACT and PIC/S. |
| SOUTH KOREA | Both IRB and Korean Food and Drug Administration (FDA) approval are required for clinical trial conduct. |
| TAIWAN | Requirement to adhere to Good Tissue Practice in addition to specific Cell Therapy Product regulations and Human Gene Therapy Product regulations. |

Note: IQVIA has a regulatory intelligence database with more complete details of regulatory requirements. The information in this table was sourced directly from the KOLs.

Source: IQVIA Analytics

## AUSTRALIA

In Australia, there are now 6 approved treatment centers that provide commercially available CAR-T cells in both adult and pediatric populations for diffuse large B-Cell lymphoma and pediatric acute lymphoblastic leukemia. There are also multiple sites that are conducting trials in association with either multinational pharmaceutical companies, smaller biotech firms or inhouse innovators.

> *"This definitely growing capacity contributed to the pivotal trials, we are seeing a very rapid ramp up of routine capacity to provide CAR-T."*

From a CAGT clinical trial perspective, Australia has seen an increasing competition for subject recruitment between sites, as well as for treatment with the locally available and registered drugs.

Patient recruitment can be streamlined by ensuring good working relationships between collaborators, seeking physician referrals and building patient referral networks. Industry sponsors have ensured more ease in trial patient recruitment by distributing clinical trial sites carefully among states and cities. Another recruitment optimization suggestion is the spreading of nationwide physician and patient awareness and improvement of public understanding of the clinical trial space.

Australia has well established national biohazard regulations for Genetically Modified Organisms (GMO), coupled with a very effective trial notification system. The Office of the Gene Technology Regulator (OGTR) aims to protect human health and safety and mitigate risks to the environment from GMOs.

Australia's established regulation, local knowledge and expertise ensures a strong ability to handle CAGT trials and products - setting a gold standard for the region.

### CHINA

China has undertaken numerous studies in cellular therapy in recent years. The first CAR-T cell therapy, Yescarta® is expected to be approved for subsets of patients with non-Hodgkins Lymphoma in the next few months.

Patient recruitment to lymphoma studies has not been a substantial issue in China as they have large lymphoma centers in the country. Dr. Ying, from one of these centers, added:

> *"We are working on CAR-T cells targeting CD-19 and CD-20 or combining CAR-T cells with novel agents like PD-1 antibodies or PD-L1 antibodies or PD-inhibitors. And, we are conducting clinical trials for CAR-T cells for different indications like Mantle cell lymphoma and follicular lymphoma and probably against the T-cell lymphoma."*

There are additional products (Kymriah® for relapsed/ refractory Acute Lymphoblastic Leukemia (ALL) and Non-Hodgkin's Lymphoma, Liso-cel® for third line DLBCL and Gamma-cel® for relapsed/ refractory B-ALL) in late-stage clinical trials.

A lack of Good Manufacturing Practice (GMP) accreditation at some hospitals can be perceived as a challenge, but with the appropriate process this can be overcome. Investigator Initiated Trials (IIT) require local health authority notification. All clinical trial products also have to undergo regulatory review for use as Investigational New Drug (IND).

### JAPAN

Clinical trials are ongoing in CAR-T cells directed against B-Cell Maturation Antigen (BCMA) in multiple myeloma or CD-19. There is also a domestic CAR-T that is being evaluated. Kymriah® is the only CAR-T cell therapy that is on the market and Yescarta® has been projected to enter the Japanese market in 2021. The number of academic and industry sponsors that are conducting CAR-T trials is increasing and should continue to increase in future. The current challenge for Japan is that a referral system for CAGT does not exist, limiting possible patient recruitment.

*The number of academic and industry sponsors that are conducting CAR-T trials is increasing and should continue to increase in future.*

### NEW ZEALAND

In New Zealand, CAGT therapies are limited to dendritic cell therapy, autologous and allogenic hematopoietic stem cell transplantation. There are currently no standard CAR-T cell therapies approved. However, a GMP facility operates in Malaghan Institute in Wellington for the manufacture of trial products for phase I/II investigator-initiated CAR-T cell- and dendritic cell therapies.

Besides this, there has been a phase I CAR-T trial in hematology. The absence of commercially available CAR-T cell therapies at present, opens up an opportunity for clinical trials in New Zealand.

*The absence of commercially available CAR-T cell therapies at present, opens up an opportunity for clinical trials in New Zealand.*

Clinical trial limitations are mainly due to lack of access to trial centers for patients in their vicinity. CAGT clinical trial regulation is managed via Medsafe (therapeutic

product regulator), the Environmental Protection Authority (EPA) l, the 'Gene Technology and Advisory Committee and Health and Safety legislation to address additional regulatory aspects regarding CAGT trials.

### SINGAPORE

In the Division of Medical Oncology at the National Cancer Centre Singapore, there have been a number of clinical trials of cancer vaccines using both dendritic cells and viral vector backbones. CAR-T trials have been conducted in the hematological indications of leukemia and lymphoma in the large academic centers viz., National Cancer Centre Singapore, Singapore General Hospital, KK Women's and Children's Hospital and National University Health System, Singapore.

There has been increasing activity in the last 5-10 years in cell- and immunotherapy areas. The launch of the new national clinical GMP facility as part of ACTRIS - Advanced Cell Therapy and Research Institute Singapore - located at the new National Cancer Centre Singapore will further accelerate cell therapy in Singapore.

*The launch of the new national clinical GMP facility as part of ACTRIS will further accelerate cell therapy in Singapore.*

Singapore hematologists are very familiar with CAR-T cell trials and that ensures minimal challenges with blood cancer patient recruitment. Additionally, International Pharmaceutical Inspection Co-operation Scheme (PIC/S) and Foundation for Accreditation of Cellular Therapy (FACT) guidelines must be trained and followed for Health Science Authority (HSA) audits.

### SOUTH KOREA

In South Korea, there are several ongoing investigator-initiated clinical trials and industry - sponsored clinical trials in CAGT, but at present CAR-T trials have not been conducted. South Korean sites conducting CAGT clinical trials require regulatory registration. A clinical trial with Kymriah®, a gene therapy, will commence in 2021. Dr. Kang (a leading Researcher from Seoul National University Hospital), puts forward:

*"Although we don't perform CAR-T trials yet, I see no problem over patient recruitment because we have already performed many clinical trials for many types of cancers, and with success."*

### TAIWAN

In Taiwan, autologous cell therapies are already approved whereas CAR-T or gene therapy have not yet been approved. In September 2018, the Taiwan-FDA approved six therapies, two of which are for malignancy indications. Autologous CD-34 peripheral blood stem cell transplantation and other autoimmune cell therapies are ongoing in hematological malignancies and solid tumors, respectively. This includes early stage to advanced stage solid tumors that have failed standard treatments.

*There is a well-established cancer registration system to support patients and there are no noticeable challenges with recruitment or trial conduct.*

Currently, there are two single-center trials for CAR-T in Taiwan. One is sponsored by a multinational company (phase-III in Taipei University) and the other is a phase-I open label dose-finding study supported by a local pharmaceutical company in Taipei General

Hospital. There is a well-established cancer registration system to support patients and there are no noticeable challenges with recruitment or trial conduct.

The following regulation and processes are in place: review of clinical cell therapy product for clinical trial application, cell therapy new product application, product donor eligibility determination guidelines and human gene therapy product clinical trial review guidelines.

## The future of CAGT for the Asia Pacific region

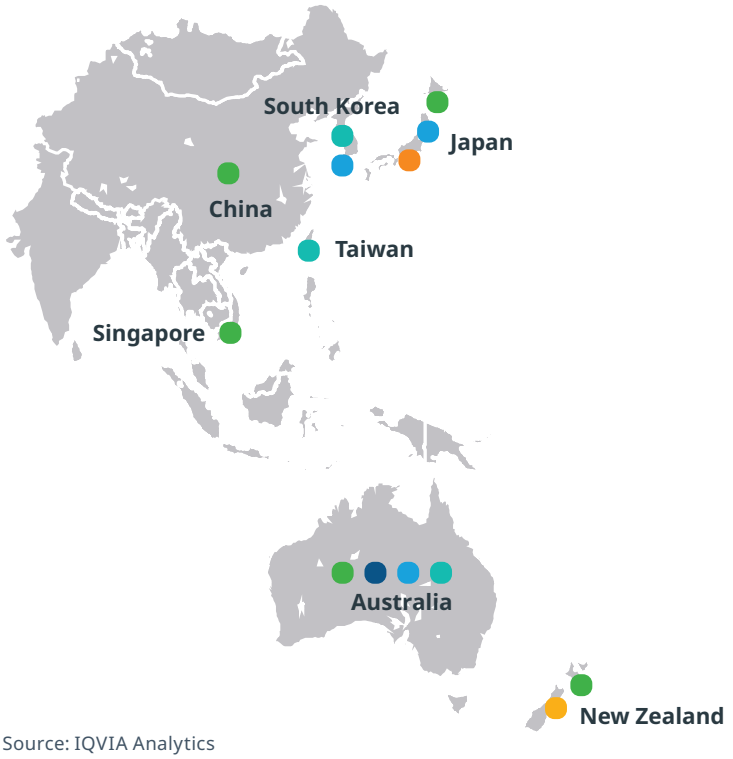
This overview aims to present expert views and data on the success that the APAC region has achieved so far in initiating CAGT trials. There have been significant achievements with CAGT trials in Australia and China, who remain at the forefront of the CAGT developments and processes in the region. This warrants further evaluation into how these efforts and successes can be replicated in other APAC markets. The country-wide distribution of key indications for ongoing CAGT trials is depicted in *Figure 7*.

Long-term safety follow-up of patients undergoing CAGT / CAR-T are presently in line with the US FDA's recommendations of 15 years. While they are aware of the complexities of such long-term patients' follow up, experts are open to investigate new solutions, such as registries, and are also looking forward to hearing about advances in recommendations globally.

If CAR-T cell therapy gains more popularity, there may be a need for development of region-specific guidelines such as safety management. The KOLs and IQVIA strongly believe that the APAC region is equipped and prepared to contribute to the increase in CAGT trial volume. Both IQVIA and the KOLs believe, the APAC region is well-placed to run CAGT trials successfully.

*The KOLs and IQVIA strongly believe that the APAC region is equipped and prepared to contribute to the increase in CAGT trial volume.*

**Figure 7: Country-wise distribution of key indications for ongoing CAGT trials [5]**




- Follicular lymphoma and mantle cell lymphoma
- Acute lymphocytic leukemia
- Diffuse large B Cell lymphoma
- Multiple myeloma
- Indolent B cell lymphomas
- Solid tumors

*Solid tumors include head and neck cancer, colon cancer, liver cancer, neuroblastoma, pancreatic cancer, prostate cancer, ovarian cancer, cervical cancer, breast cancer, lung cancer*

Source: IQVIA Analytics

# References


1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646–74.
2. Hong B, van den Heuvel AP, Prabhu VV, Zhang S, El-Deiry WS. Targeting tumor suppressor p53 for cancer therapy: strategies, challenges and opportunities. Curr Drug Targets 2014; 15: 80–9.
3. Pagliarini R, Shao W, Sellers WR. Oncogene addiction: pathways of therapeutic response, resistance, and road maps toward a cure. EMBO Rep 2015; 16:280–296.
4. Katoh M. Therapeutics targeting angiogenesis: genetics and epigenetics, extracellular miRNAs and signaling networks (Review). Int J Mol Med 2013; 32: 763–7.
5. Data used by MARS dashboard is used in most of the analysis, including market data purchased from Clarivate Analytics, sale data from CRM, and IQVIA involvement data.
6. IQVIA Whitepaper. Making the Move: Bringing Cell and Gene Therapy Development Programs to the United States. Available from: https://www.iqvia.com/library/white-papers/making-the-move-bringing-cell-and-gene-therapy-development-programs-to-the-us Accessed on: 25Jan2021.
7. Upadhaya S., et al. The Clinical Pipeline for Cancer Cell Therapies. Nature Reviews Drug Discovery, ISSN 1474-1784. 04 June 2021. doi: https://doi.org/10.1038/d41573-021-00100-z

# About the authors

**MARIA ROSELLE V. LUCAS, MD**
Medical Director, Head,
Medical Oncology/Hematology,
Asia, IQVIA APAC

Dr. Roselle Lucas serves as a scientific and medical expert in different clinical trials in both Oncology and Hematology. She provides medical support to investigative sites and project staff for protocol-related issues, in addition to providing guidance to the operations team on the medical and scientific aspects of assigned projects. She brings industry experience, having worked in Medical affairs. She earned her MD at St Luke's College of Medicine, Philippines.

**EDWIN GUMAFELIX, MD**
Medical Director,
Medical Oncology/Hematology,
Asia, IQVIA APAC

Dr. Edwin Gumafelix is a Therapeutic Medical Advisor of IQVIA-APAC Medical and Scientific services. He provides Medical Monitoring and Scientific oversight to various oncology trials conducted by IQVIA in the region. He has been involved in different Phase 1 to Phase IV clinical studies in hematology and oncology. Edwin is a board-certified medical oncologist and internal medicine specialist. He has over 10 years of clinical practice experience in the field of Internal Medicine and Oncology. He earned an MD at the University of the Philippines.

**LARA KRISTINA S. DONATO, MD**
Associate Medical Director,
Medical Oncology/Hematology,
Asia, IQVIA APAC

Dr. Lara Donato has had more than 10 years of experience in the health care setting in both the clinical field and industry. She has clinical experience in diagnosing and handling hematologic and oncologic diseases. She has served as a Medical and Scientific advisor in different phases of clinical trials across the Asia Pacific in different Hematologic and Oncologic indications such as AML, Non-Hodgkin's Lymphoma, CML, Multiple Myeloma, Prostate Cancer, Lung Cancer, Triple-Negative Breast Cancer, Giant Cell tumor of the bone and other solid tumors. She provides medical support to investigative site and project staff for protocol related issues as well as gives guidance to the operations team on the medical and scientific aspects of different projects. She has earned her MD at De La Salle University College of Medicine, Philippines

**KIM STRYDOM, M.D.**
Medical Director, Therapeutic Strategy, Asia Pacific Therapeutic Strategy Group, IQVIA

Dr. Kim Strydom is a medical director in the Asia Therapeutic Strategy department and serves in a local SME role for IQVIA's Cell And Gene Therapy Center of Excellence. Kim obtained her MBChB and Pharmacology Honours degrees in South Africa and worked in academic and clinical research before joining Quintiles (now IQVIA). Kim has extensive clinical trial industry experience as a CRA, Drug Safety physician, Pharmacovigilance lead and as a medical monitor in numerous therapeutic areas.

**ANISH SULE,**
Head, CSMS-COE India,
IQVIA, India

Anish has more than 16 years of experience in clinical and commercial through inception to culmination of product lifecycle. He has worked across Clinical trials Phase I to IV, Medical Writing, Medical Affairs, Patient Engagement, Pharmacovigilance and Management of patients. Anish has experience across various therapeutic areas including Oncology and Hematology and has been involved in Medical Writing of several clinical trial protocols. He has set-up Medical Writing and Communications team for CSMS-Asia. Anish has been a co-author for publication on 'Feasibility considerations that impact operational delivery strategy in highly competitive rheumatoid arthritis space in Asia'. He is a key author of 'Guidelines for management and prevention of ADRs associated with anti-tubercular drugs' which was released at South East Asia level by WHO in co-ordination with ICMR India.

Anish is leading Patient Engagement and Medical Solutions including Medical Writing and Communications for Asia Pacific region.

**VAISHNAVI KRISHNAN**
Medical Science Liaison,
CSMS Asia, IQVIA, India

Vaishnavi has had more than 6 years experience in medical writing and medical communications.
A medical professional by qualification, her experience spans medical content and strategy development for medical campaigns, whitepapers, newsletters, manuscript for publications, web-based articles, storyboard concept for medical videos and patient education material. She has written, strategized and reviewed content for several therapeutic areas that include ophthalmology, maternal and child health nutrition, general medicine and medical oncology.

She currently supports medical communications through extensive medical writing material for global clients and especially within the Asia Pacific region.

*The white paper is further supported by IQVIA team members: Alma Panganiban-Padrinao, MD, Head Medical TSSU; Mahesh Pandey, CS Emerging Market, Market Access Manager; Jerome Armellini, Senior Director, TSL; Manfred Seow, Therapeutic Strategy Director.*

# KOL Advisory board

We would like to thank the KOLs who took part in the advisory board, bringing their knowledge and insights on the CAGT landscape in APAC.

**DR. MICHAEL DICKINSON**
Australia

From Peter MacCallum Cancer Centre and a field of interest in lymphoma Dr. Dickinson has more than 10 years experience in CAGT and has conducted about 6 CAGT trials as the Principal Investigator, with all 6 ongoing.

**DR. NOBUHURU FUJII**
Japan

From Okayama University Hospital, Division of blood transfusion and a field of interest within hematopoietic stem cell transplantation. Dr. Fujii has more than 10 years experience in CAGT and has conducted about 5 CAGT trials with 2 ongoing.

**PROF. ZHITAO YING**
China

From Peking University Cancer Hospital, Department of Lymphoma and a field of interest in lymphoma. Dr. Ying has about 5-10 years experience in CAGT and has conducted about 6 CAGT trials, with about 3 ongoing.

**DR. ROBERT WEINKOVE**
New Zealand

From Capital & Coast District Health Board, Malaghan Institute of Medical Research and fields of interest in immunotherapy, B-cell lymphoma and CLL. Dr. Weinkove has about 3-5 years experience in CAGT and has conducted about 2 CAGT trials, with 1 ongoing presently.

**PROF. HAN CHONG TOH**
Singapore

From National Cancer Centre, National Cell Therapy Centre and a field of interest in cancer immunotherapy, cancer vaccines and T Cell therapy. Dr Toh has more than 10 years experience in CAGT and has conducted about 7 CAGT trials as the Principal Investigator, with 2 ongoing.

**DR. HYOUNG JIN KANG**
South Korea

From Seoul National University Hospital, Center for Cell and Gene Therapy and a field of interest in Pediatric hematology-oncology and CAGT. Dr. Kang has more than 10 years experience in CAGT and has conducted about 2 CAGT trials with 1 ongoing.

**DR. YEE CHAO**
Taiwan

From Taipei Veterans General Hospital and a field of interest in cell therapy. Dr. Chao has about 3-5 years experience in CAGT and has conducted 1 CAGT trial, with about 2 ongoing.

# Contributors

IQVIA APAC conducted an advisory board along with a pre-meeting questionnaire involving key opinion leaders (KOLs) from 7 key markets including Australia, China, Japan, New Zealand, Singapore, Taiwan and South Korea. We'd like to thank the KOLs who took the time to share their knowledge and support the development of this white paper.

# About IQVIA Asia Pacific

IQVIA (NYSE:IQV) is a leading global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry. IQVIA creates intelligent connections across all aspects of healthcare through its analytics, transformative technology, big data resources and extensive domain expertise. IQVIA Connected Intelligence™ delivers powerful insights with speed and agility — enabling customers to accelerate the clinical development and commercialization of innovative medical treatments that improve healthcare outcomes for patients. With approximately 70,000 employees, IQVIA conducts operations in more than 100 countries.

With regional headquarters in Singapore and offices in 15 countries, IQVIA Asia Pacific provides technology-enabled services and solutions to meet the growing and rapidly changing needs of clients, both local and multinational, operating in Asia Pacific. IQVIA is committed to advancing healthcare by offering evidence-based insights and deep domain expertise in thought leadership, with the aim of improving understanding and accelerating innovation within the healthcare ecosystem. To learn more, visit www.iqvia.com/locations/asia-pacific.

**CONTACT US**
iqvia.com/contactus

**LOCATION**
79 Anson Road #19-01
Singapore 079906
**iqvia.com**