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ASX: ALA

# Investor Presentation

Dr Michael Baker

February 2022

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# Arovella Therapeutics Highlights

## World Leading Partners

Arovella licenced its iNKT Cell Therapy Platform from Imperial College London and its DKK1 mAb/CAR from MD Anderson

## Allogeneic Platform, Two Targets

Arovella is developing off the shelf cell therapies for CD19 expressing lymphomas and DKK1 producing cancers

## Acquiring New Technologies

Arovella continues to focus on sourcing, evaluating and acquiring innovative technologies that align with key focus areas

## World Class Team

Arovella's leadership group has deep experience in drug development, particularly cell therapies

## Data Driven

Arovella uses data to drive decision making for its key assets and clinical indications

## Growth Potential

Arovella is the only ASX listed company working with an iNKT cell therapy platform and the only company worldwide with CAR technology targeting a DKK1 peptide

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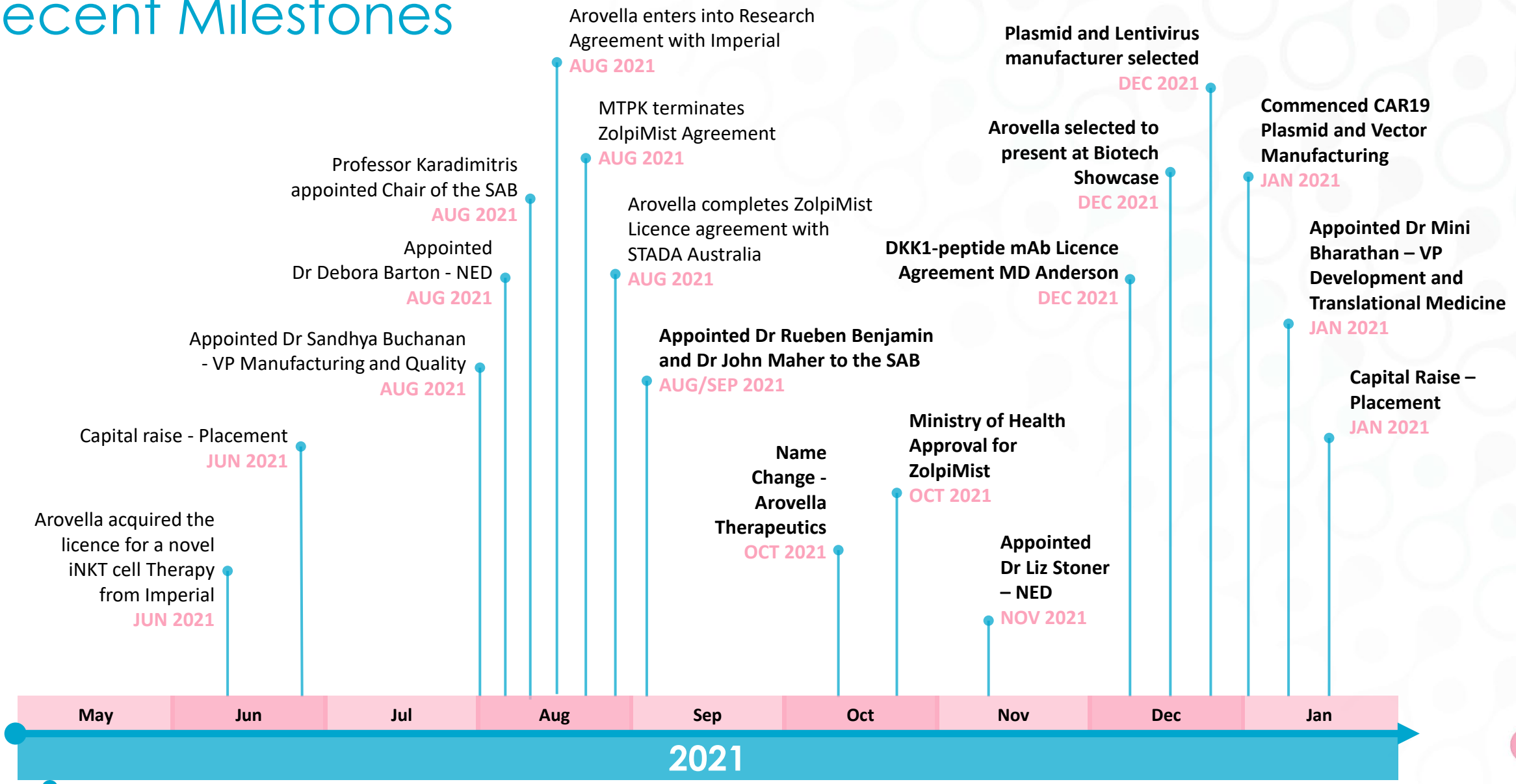
# Recent Milestones



# Arovella Company Overview

## Financial Snapshot

| ASX CODE | ALA |
|---|---|
| Market capitalisation[1] | $24 million |
| Enterprise value | $15 million |
| Shares on issue[1] | 601 million |
| 52-week low / high | $0.033 / $0.075 |
| Cash (30 December 2021) [2] | $8.8 million |

## Major Shareholders

| Shareholder | Ownership (%)[1] |
|---|---|
| MERCHANT FUNDS MANAGEMENT PTY LTD | 47,416,660 (7.89%) |
| MANN BEEF PTY LTD | 20,000,00 (3.33%) |
| UBS NOMINEES PTY LTD | 15,064,640 (2.51%) |
| ZERRIN INVESTMENTS PTY LTD | 14,625,227 (2.43%) |
| DYLIDE PTY LTD | 12,500,000 (2.08%) |


1. *As of 31 January 2022 and including shares issued from the Placement announced 24 January 2022*
2. *Includes the proceeds from the Placement but not the $1.5m from the underwritten SPP announced 24 January 2022*

# Arovella Board and Senior Leadership

## Paul Hopper

### CHAIRMAN

Over 25 years experience in the medical, healthcare & life sciences sectors. Focussed on start-up and rapid growth companies, he has served as either Founder, Chairman, non-executive director or CEO, of more than fifteen companies in the US, Australia and Asia. Mr Hopper has founded, or technology seeded, six companies on the ASX and Nasdaq.

## Dr. Michael Baker

### CEO & MANAGING DIRECTOR

Over 15 years experience in scientific research, drug development and venture investing sectors. He was an Investment Manager with the leading Australian life science fund, BioScience Managers. He also conducted due diligence to shortlist investment opportunities and played an active role in managing portfolio companies.

## Dr. Debora Barton

### DIRECTOR

Over 20 years of oncology experience, in academia, as a practicing physician and in the biotechnology / pharmaceutical industry. Served in key senior executive positions, including Carisma Therapeutics where Dr. Barton is currently the Chief Medical Officer, Iovance Biotherapeutics and Advanced Accelerator Applications, acquired by Novartis during Debora's tenure.

## Dr. Liz Stoner

### DIRECTOR

Dr. Stoner is a distinguished biopharma executive, who brings decades of international industry experience to her role, including senior roles in Clinical Development Operations at Merck Research Laboratories. Liz is an Executive Partner at MPM Capital, and she has held numerous leadership roles at MPM portfolio companies. Liz was previously an Assistant Professor of Paediatrics at Cornell University Medical College.

## Dr. Sandhya Buchanan

### VP MANUFACTURING & QUALITY

Dr Buchanan has more than 20 years' experience working in cell & gene therapy and vaccine development. Dr Buchanan was formerly at Atara Biotherapeutics as the chemistry manufacturing and control technical lead for autologous CAR-T programs and head of Viral Vector Development. Dr Buchanan has a PhD in Pharmaceutical Sciences from the University of Colorado Health Sciences Center

## David Simmonds

### DIRECTOR

David was a senior audit partner with Ernst & Young from 1989 to 2017. From 2008 to 2013, David led the Capital Markets desk in Australia with responsibility for overseeing or reviewing all Australian cross border fundraisings. David was a member of the Board of MS Research Australia.

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# Arovella Therapeutics Pipeline

## Cell Therapy

| | INDICATION | DISCOVERY | PRECLINICAL | PHASE 1 | PHASE2/3[1] | PARTNER |
|---|---|---|---|---|---|---|
| ALA-101 (CAR19-iNKT) | **CD19 expressing cancers** | CD19 Expressing Lymphoma | | | | |
| ALA-102 | **Not Disclosed** | ND | | | | |
| ALA-103 | **Not disclosed** | ND | | | | |
| ALA-104 (DKK1-CAR-iNKT) | **Multiple Myeloma** | Multiple Myeloma & Solid Tumours | | | | |

## OroMist

| | INDICATION | REFORMULATION | PRECLINICAL | CLINICAL | COMMERCIAL | PARTNER |
|---|---|---|---|---|---|---|
| ZolpiMist®[2] | **Short-term insomnia** | Short-term insomnia | | | | Teva[3] STADA[4] |
| ALA-001 (Sumatriptan) | **Migraine** | Migraine | | | | Strides |
| ALA-018 (Anagrelide) | **Solid tumours & thrombocytosis** | Solid Tumours | | | | |
| ALA-021 (Pharma grade Cannabis) | **DRE[5], melanoma, motion sickness** | Multiple | | | | Cann Pharma Australia |
| ALA-023 (Not disclosed) | **Not Disclosed** | ND | | | | Sanofi |

1. *Phase 3 trial may not be required if Phase 2 is a registrational trial*
2. *ZolpiMist has been approved by the Ministry of Health (Chile), TGA (Australia) and the FDA (US) and Arovella holds the rights to ZolpiMist outside of North America*
3. *Arovella is assisting TEVA with regulatory submission and commercialisation efforts*
4. *STADA have the license to commercialise ZolpiMist in Australia*
5. *DRE – Drug Resistant Epilepsy*

# Cell Therapy Commercial Activity

| Transactions | | |
|---|---|---|
| **Parties** | **Deal Type** | **Total Value** |
| Gilead / Kite | Acquisition | **US$11.9b** |
| Celgene / Juno | Acquisition | **US$9b** |
| Janssen / Fate | Partnership | **US$3b** |
| Kite / Shoreline Biosciences | Strategic Partnership | **US$2.3b** |
| Atara Bio / Bayer | Strategic Collaboration | **~US$670m** |
| Gilead / Cell Design Labs | Acquisition | **US$567m** |
| Caribou / Abbvie | Collaboration Agreement | **US$340m** |
| Moderna / Carisma Therapeutics | Research Deal | **US$45m**[1] |

| Significant Capital Raises | |
|---|---|
| **Company** | **Amount Raised** |
| Sana Biotech | **US$675m** |
| Lyell | **US$425m** |
| Legend Biotech | **US$424m** |
| Carsgen | **US$400m** |
| Instil Bio | **US$368m** |
| Century Therapeutics | **US$243m** |
| Gracell | **US$209m** |

- The global cell and gene therapy market is expected to reach US$12.9b by 2026[2]

1. *Milestone payments are included but have not been disclosed*
2. *https://www.globenewswire.com/news-release/2021/12/08/2348195/0/en/Global-Gene-and-Cell-Therapy-Market-Size-Points-22-3-CAGR-Projected-to-Reach-USD-12-9-Billion-by-2026-Facts-Factors.html*

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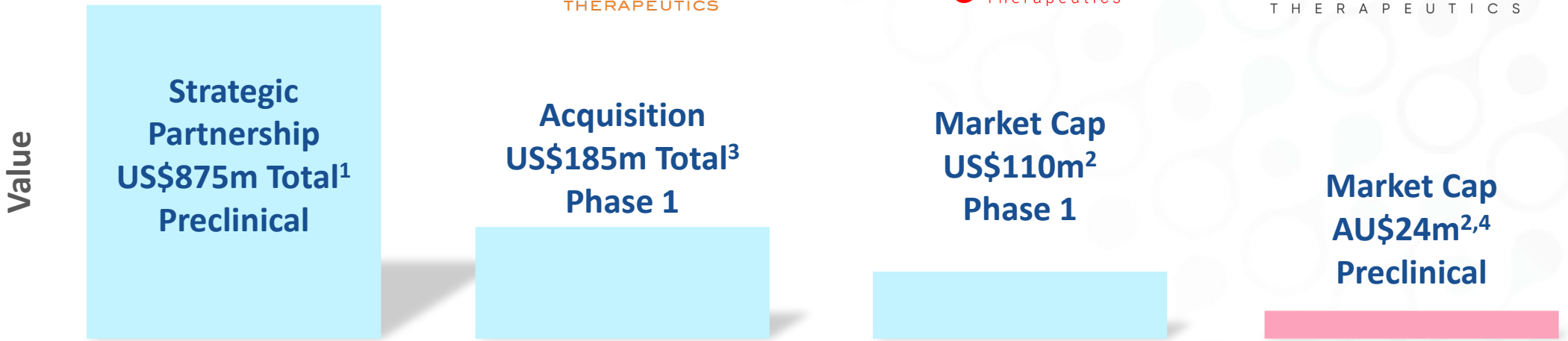
# Commercial Activity for iNKT Cell Therapies




**May 2021 –** Appia Bio raised US$52m in their Series A

**Aug 2021 –** Appia Bio entered into Strategic Partnership with Kite Pharma - US$875m deal value

**May 2021 –** Kuur Therapeutics was acquired by Athenex for US$70m upfront and US$115m milestone payments

**Oct 2021 –** MiNK Therapeutics listed on the Nasdaq raising US$40m, currently valued at US$110m[1]

**Jun 2021 –** Acquired the licence to its iNKT cell therapy platform from Imperial College London

**Dec 2021 –** Acquired the licence to the DKK1 technology from MD Anderson Cancer Center

**Jan 2022 -** Placement and SPP

1. https://www.gilead.com/news-and-press/press-room/press-releases/2021/8/kite-and-appia-bio-announce-collaboration-to-research-and-develop-allogeneic-cell-therapies-for-cancer
2. *As of 31 January 2022*
3. *https://ir.athenex.com/news-releases/news-release-details/athenex-acquire-kuur-therapeutics-expand-cell-therapy*
4. *Including shares issued from the Placement announced 24 January 2022*

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# iNKT Cell Therapy Platform

Imperial College London

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# Overview of CAR-iNKT Cell Therapy

**Blood Collection and Immune Cell Harvesting**

- Following blood collection from a healthy donor at a hospital or clinic, immune cells are collected

**Isolation and re-programming of immune cells**

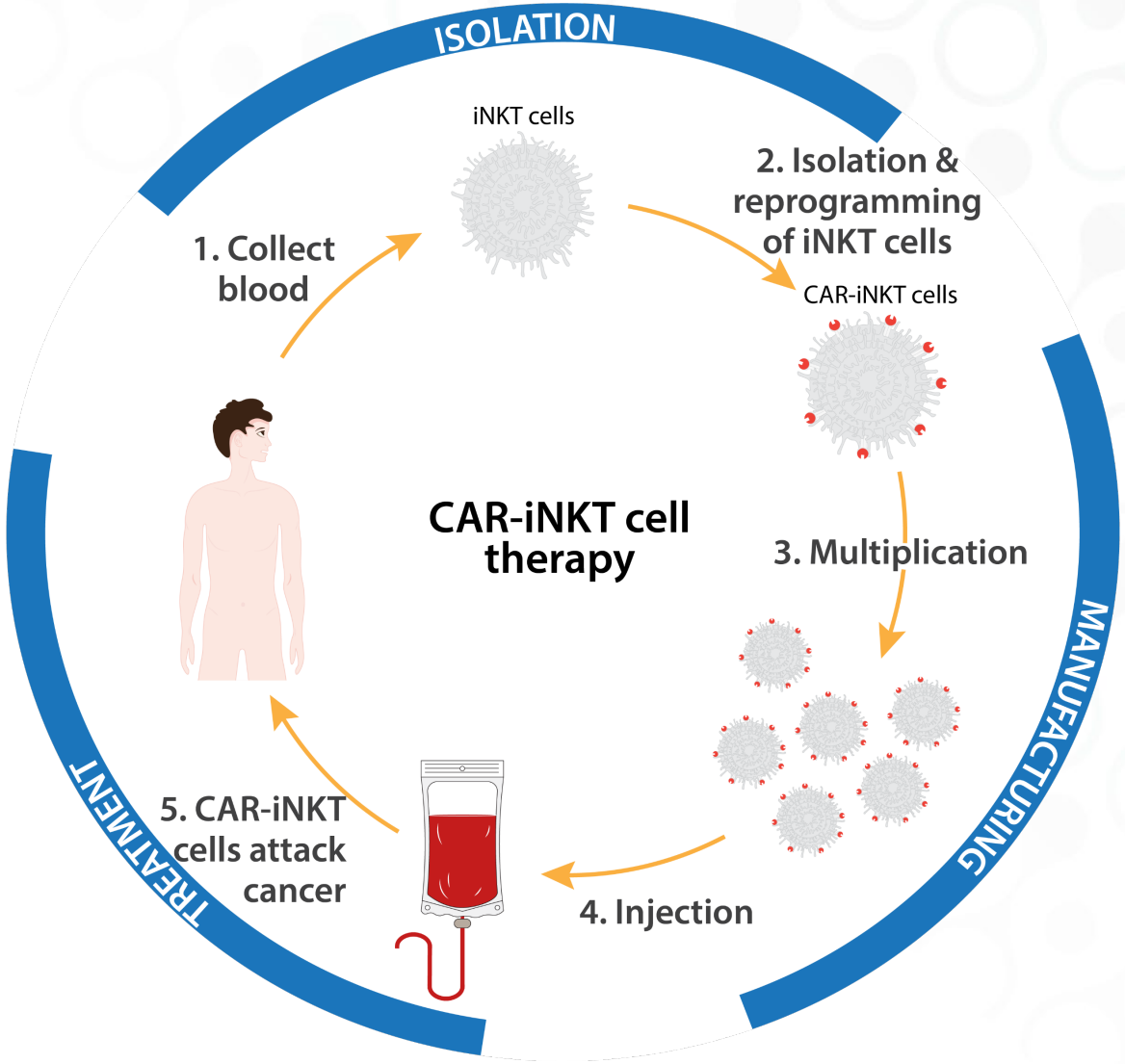
- Isolated iNKT cells are genetically re-programmed to produce a chimeric antigen receptor (CAR) that will attack specific markers on cancers

**Multiplication of cells**

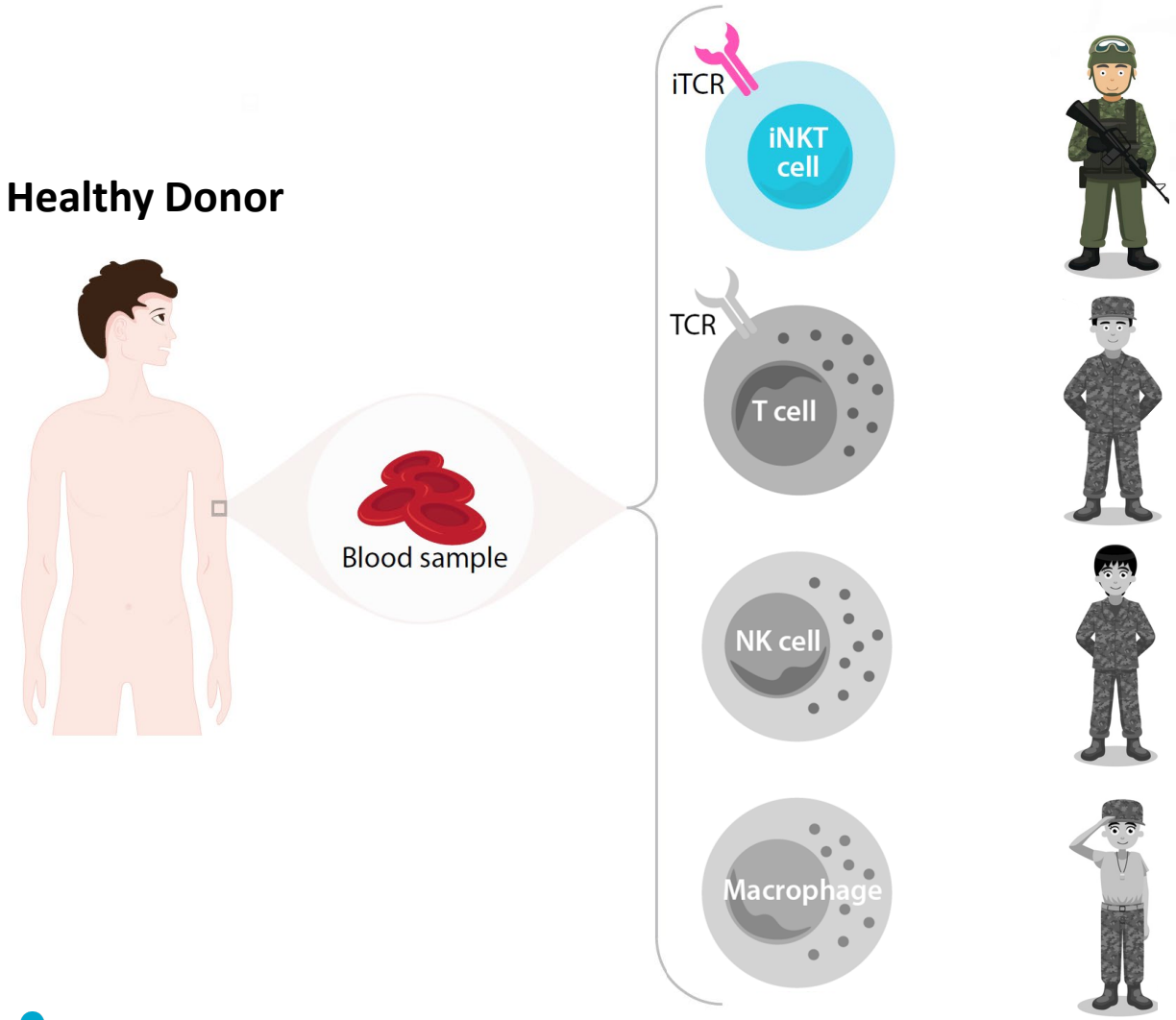
- The CAR-iNKT cells are grown up to sufficient numbers for patient treatment and stored frozen

**Cells are administered to the patient**

- When CAR-iNKT cells are required, they are thawed and administered, and they will find and kill the cancer cells



# Expand the Cell Therapy Revolution: iNKT Cells




## iNKT Cell Benefits

- They are one of the most potent, naturally occurring immune cells
- They bridge the innate and adaptive immune system
- They naturally target and kill cancer cells
- They activate other beneficial immune cells
- They can be used “off the shelf” as they suppress graft versus host disease (GVHD)
- They show significantly improved killing of CD1d producing cancers over T cells when combined with chimeric antigen receptors (CARs)

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# CAR-iNKT Cells are Engineered to Enhance Activity

| | APPROVED CAR-T CELLS | CAR-NK CELLS | CAR-iNKT CELLS |
|---|---|---|---|
| Subpopulation of T cells with NK cell properties | ✗ | ✗ | ✓ |
| Intrinsic anti-cancer receptor (dual targeting) | ✗ | ✗ | ✓ |
| Persistence | ✓ | TBD | TBD[1] |
| Minimal genetic engineering for off the shelf | ✗ | ✓ | ✓ |
| Naturally suppress GVHD | ✗ | ✗ | ✓ |
| Low risk of CRS or neurotoxicity | ✗ | ✓ | ✓ |
| Allogeneic, 'off-the-shelf' dosing | ✗ | ✓ | ✓ |

*CAR – Chimeric Antigen Receptor; iNKT – invariant Natural Killer T Cell; CRS – Cytokine Release Syndrome; TBD – To Be Determined*
*1. Spontaneous secondary remission observed in preclinical animal models*

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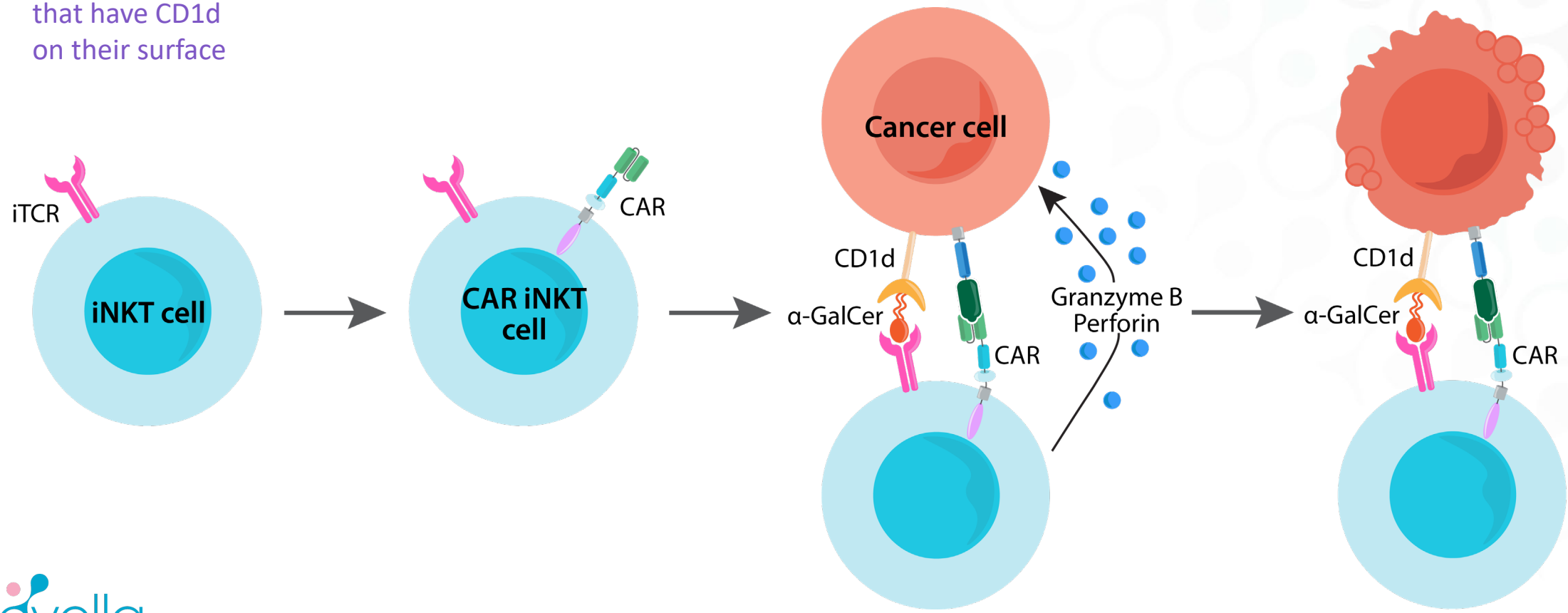
# How does the CAR-iNKT Cell Therapy Platform Work?

1. iNKT cells contain an iTCR that naturally assists to recognise and kill cancer cells that have CD1d on their surface
2. We introduce a chimeric antigen receptor (CAR) to target cancer cells, making them dual targeting
3. CAR-iNKT cells are activated after they attach to the cancer cells, releasing components to trigger cancer cell death
4. The cancer cell is killed, and other components are recruited to assist

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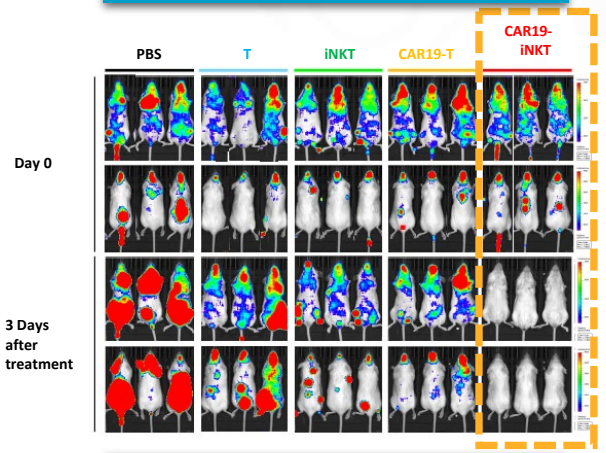
# ALA-101: CAR19-iNKT Cells to Treat Blood Cancers

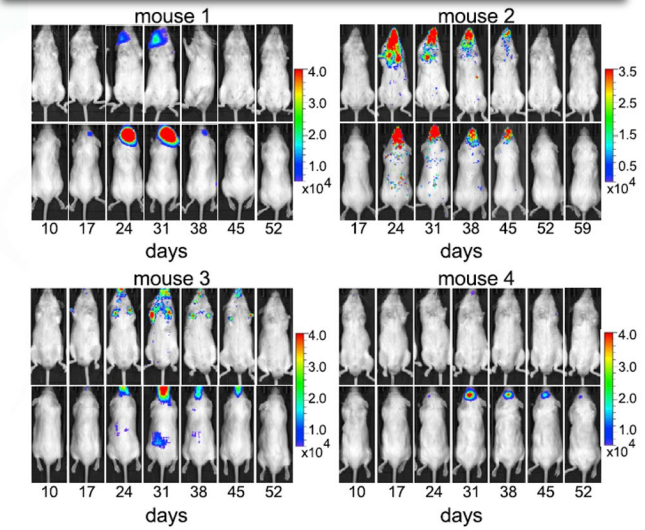
- ALA-101 is anticipated to be an effective, off-the-shelf cell therapy for the treatment of CD19 expressing cancers
- We have demonstrated robust activity against CD19 expressing cancers
- ALA-101 is more efficient at clearing tumour cells than conventional cell therapies when the cancers produce CD1d
- Our therapy results in better animal survival than conventional cell therapies
- Our data validates the use of iNKT cells as a treatment for CD19 expressing cancer types
- We commenced the manufacturing of the plasmid and lentivirus in Q1 2022

## CAR19-iNKT Outperforms Conventional Therapies

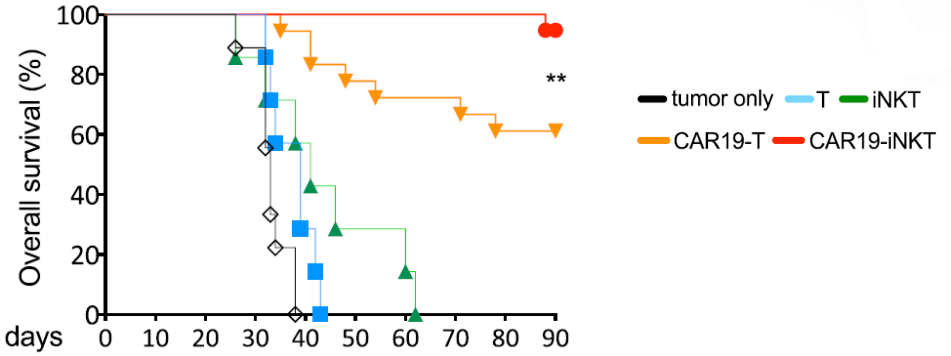
### *Faster Killing of Cancer Cells That Have CD1d*




### *Spontaneous Secondary Remission*




### *Increased Survival Over CAR-T Cells*





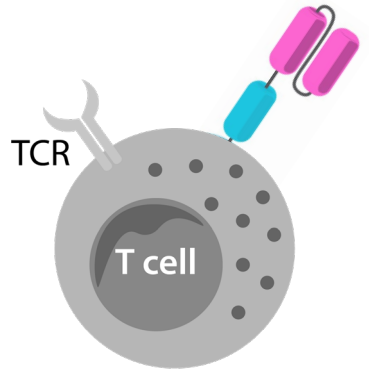

Rotolo *et al.*, Cancer Cell (2018)

# Pipeline Expansion
# ALA-104

# Development of DKK1-CAR to Date

- The DKK1 mAb was developed at MD Anderson and can be incorporated into a chimeric antigen receptor (CAR)
- The DKK1 peptide-targeting mAb has demonstrated activity against multiple myeloma and breast cancer
- The DKK1 peptide-targeting scFv has been incorporated into CAR-T cells, and has excellent activity against blood cancers and solid tumours (unpublished data)
- Arovella will combine the DKK1-CAR with its iNKT cell therapy platform and initially target multiple myeloma, where DKK1 is highly expressed

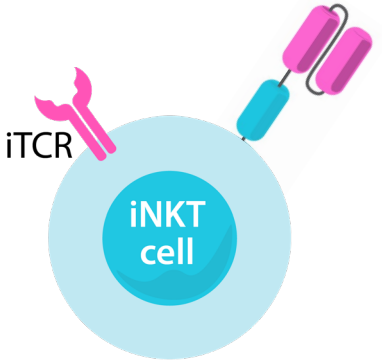
## Already Completed




**DKK1-CAR-T cells**

Multiple Myeloma ✓
Pancreatic Cancer ✓
Lung Cancer ✓
Breast Cancer ✓

## Arovella To Complete




**DKK1-CAR-iNKT cells**

Multiple Myeloma
Pancreatic Cancer
Lung Cancer
Breast Cancer

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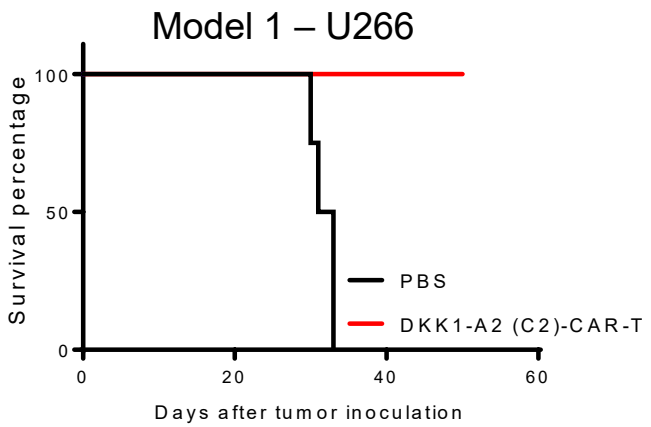
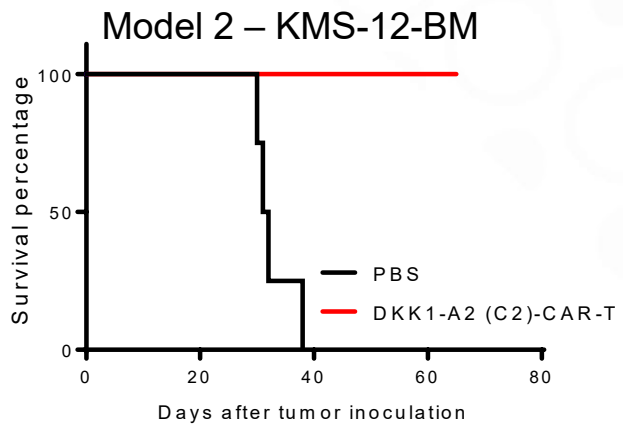
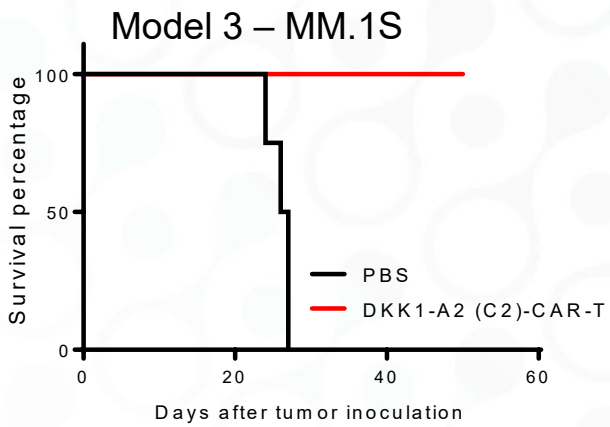
# DKK1-CAR-T Cell Activity in Multiple Myeloma

DKK1-CAR T cells were tested in three different animal models for multiple myeloma, displaying robust activity in all standard models




- All treated mice were alive at 50-60 days, while untreated mice succumbed to the cancer at 30-40 days
- Multiple myeloma cells also express CD1d, so including DKK1-CAR into iNKT cells will make them dual targeting
- DKK1-CAR-T cells also have activity in animal models for **lung**, **pancreatic** and **triple negative breast** cancer

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# DKK1-CAR-T Preclinical Safety

Prof Qing Yi at Houston Methodist has demonstrated:

- They only kill cells that have the DKK1 peptide presented in an HLA-A2 complex on their surface
- They do not kill healthy blood cells
- That the DKK1-CAR-T cells are considered safe using *in vivo* models
- The DKK1 mAb targeted only 1 out of 35 normal tissues tested (tonsil)

Arovella will confirm:

- That the DKK1 technology does not target or attack healthy cells
- The ability to combine DKK1-CAR with Arovella's iNKT cell therapy platform

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# The Inventor – Professor Qing Yi

Professor Qing Yi is a trained medical immunologist with over 25 years of experience. He is one of the leading investigators in the fields of tumor immunology and immunotherapy in multiple myeloma and other cancers. He has trained at the **Karolinska Institute**, **MD Anderson**, the **Cleveland Clinic** and is now at **Houston Methodist**.

Professor Yi is the Director for the Center for Translational Research in Hematological Malignancies and Associate Director for the Cancer Center Basic Research Programs, Cancer Center Houston Methodist.

Professor Yi has been awarded 9 R01 grants, 1 project and 1 core grant in the MD Anderson Myeloma SPORE (P50), 4 R01-type translational grants from the LLS, 4 Senior Researcher Awards from the MMRF, 2 K99/R00 grants, and numerous intramural and industry grants. Dr Yi was recruited to Houston Methodist through an Established Investigator Award from CPRIT with a total grant amount of ~$6 million.

Professor Yi and colleagues have published more than 160 peer-reviewed research articles, with 45 being in top-tier journals with an impact factor of greater than 10.

# DKK1's Role in Cancer

**2021**


Oncogene,
2021 Jul 01; 40(26)

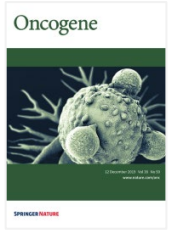
The dickkopf1 and FOXM1 positive feedback loop promotes tumor growth in Pancreatic and Esophageal Cancers

**2019**


Annals of translational medicine,
2019 Dec 21; 146(2)

Crosstalk of estrogen receptors and wnt/β-catenin signaling in Endometrial Cancer

**2019**




Oncogene,
2019 Dec 06; 38

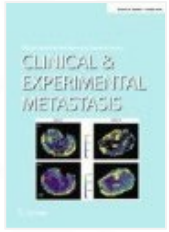
Dickkopf-1 contributes to Hepatocellular Carcinoma tumorigenesis by activating the Wnt/β-catenin signaling pathway

**2019**


American journal of cancer research,
2019 Feb 01; 9(2)

Dickkopf-1 (DKK1) promotes tumor growth via akt-phosphorylation and independently of wnt-axis in barrett's associated Esophageal Adenocarcinoma

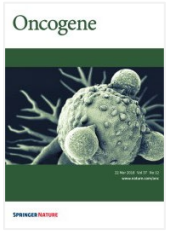
**2018**




Clinical & experimental medicine,
2018 Sep 2035(8)

Dickkopf-1 (Dkk1) protein expression in Breast Cancer with special reference to Bone Metastases

**2018**




Oncogene,
2018 Mar 18; 37(26)

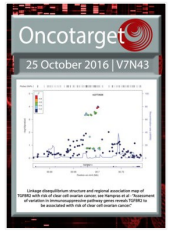
Activation of the dickkopf1-CKAP4 pathway is associated with poor prognosis of Esophageal Cancer and anti-CKAP4 antibody may be a new therapeutic drug

**2017**


Cell cycle,
2017 Jul 27; 16(17)

The role of dickkopf-1 as a potential prognostic marker in Pancreatic ductal adenocarcinoma

**2016**




Oncotarget,
2016 Sep 06; 7(43)

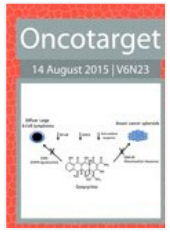
Dickkopf-1 expression is associated with tumorigenity and lymphatic metastasis in human hilar Cholangiocarcinoma

**2016**


Journal of cellular and molecular medicine,
2016 May 31; 20(9)

Dickkopf-1-promoted vasculogenic mimicry in Non-small Cell Lung Cancer is associated with EMT and development of a cancer stem-like cell phenotype

**2015**




Oncotarget,
2015 Jun 19; 6(23)

Serum dickkopf-1 is a novel serological biomarker for the diagnosis and prognosis of Pancreatic Cancer

- DKK1 is overproduced in a number of cancer types, including pancreatic, oesophageal, hepatocellular, breast, lung cancer and multiple myeloma
- Overexpression of DKK1 can indicate poor overall survival and shorter disease-free survival[1]
- DKK1 has recently emerged as a potential biomarker of cancer progression and prognosis for several types of malignancies[2]
- There is growing evidence that DKK1 plays an essential role in cancer progression[2]

*1. Zhu et al., 2021*

*2. Chu et al., 2021*

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# Robust Intellectual Property

- **Patent life until 2039**
- As the first DKK1-CAR product, it has a robust patent position
- Title: Monoclonal Antibodies Against MHC-Bound Human Dickkopf-1 Peptides and Uses Thereof
- Applicant: Board of Regents, The University of Texas System
- Patent applications have been filed in the US, Europe, Canada, China, and Australia
- Favorable Search Report


**(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)**

**(19) World Intellectual Property Organization**
International Bureau

**(43) International Publication Date**
**06 August 2020 (06.08.2020)**

WIPO | PCT

**(10) International Publication Number**
**WO 2020/160532 A1**

**(51) International Patent Classification:**
*A61K 39/395* (2006.01) *A61P 35/00* (2006.01)
*C07K 16/28* (2006.01) *C07K 14/705* (2006.01)

**(21) International Application Number:**
PCT/US2020/0 16364

**(22) International Filing Date:**
03 February 2020 (03.02.2020)

(25) **Filing Language:** English

(26) **Publication Language:** English

**(30) Priority Data:**
62/800,007 01 February 2019 (01.02.2019) US

**(71) Applicant: BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 210 West 7th St., Austin, TX 78701 (US).

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**(81) Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

**(84) Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

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# CAR-iNKT Cell Therapy Development


- Acquire the license to additional CARs/Technologies complementary to the iNKT cell therapy platform
- Dose first patient in Phase 1 clinical trial for CD19 producing cancers
- FDA IND clearance for CAR19-iNKT program
- Complete GMP manufacturing of CAR19-iNKT cells for phase 1 clinical trial
- Define Manufacturing strategy for DKK1-CAR-iNKT cells
- Demonstrate activity of DKK1-CAR-iNKT cells in models for multiple myeloma, and potentially solid tumours
- Confirm Safety and Specificity of the DKK1-CAR and combine with the iNKT cell platform
- Select GMP manufacturer to produce CAR19-iNKT cells
- Recruit cell therapy translation and development expert ✓
- Select GMP manufacturer for plasmid and lentivirus for CAR19 ✓
- Acquire the license to another complementary CAR ✓
- Recruit cell therapy manufacturing expert – Dr. Sandhya Buchanan ✓
- Enter into Research Agreement with Imperial College London ✓

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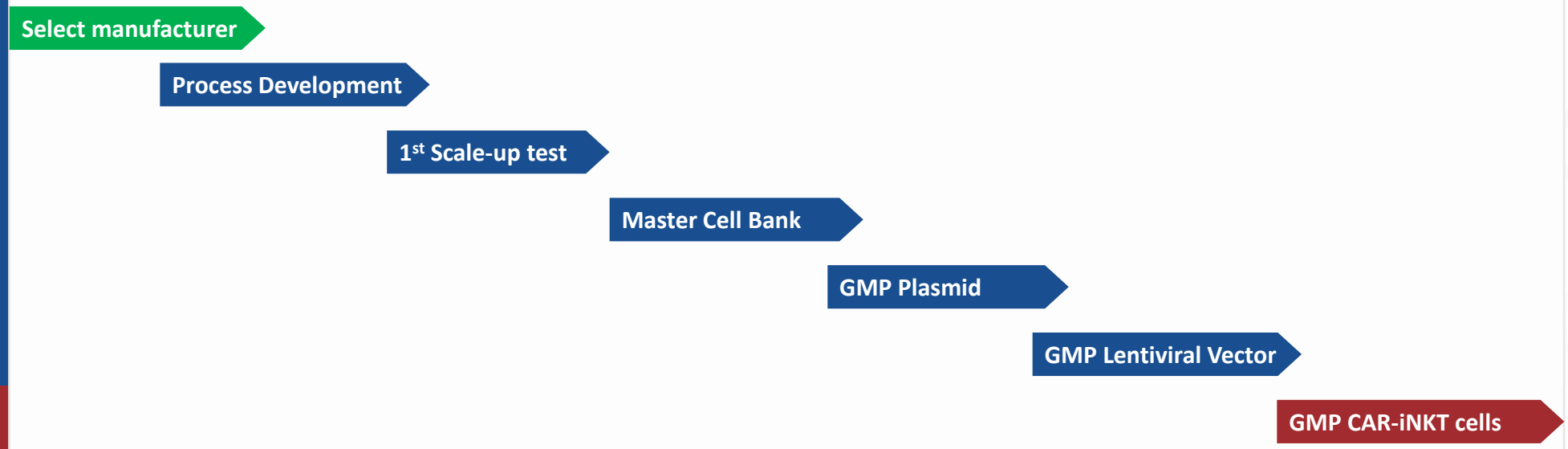
# CAR-iNKT Cell Manufacturing Pathway

**Key Components**

- Plasmid DNA encoding the CAR
- Lentiviral vector to deliver the CAR
- iNKT cells to produce the CAR (final product)

**Prepare plasmid and Lentiviral vector for the CAR**

**Use the GMP Lentiviral Vector to prepare CAR-iNKT cells[1]**




1. *Does not depict the development work for the CAR-iNKT cells, which will be performed in parallel*

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# Thank You

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CEO & Managing Director

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# Appendices

# Cancer Continues to be a Major Health Issue

Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer)) occurred in 2020[1]

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020[2]

The global cancer biologics market should reach $143.0 billion by 2026 from $77.5 billion in 2021 at a (CAGR) of 13.0%[3]

1. https://pubmed.ncbi.nlm.nih.gov/33538338/
2. https://www.who.int/news-room/fact-sheets/detail/cancer
3. https://www.businesswire.com/news/home/20211004005398/en/Global-Market-for-Biological-Therapies-for-Cancer-2021-2026---ResearchAndMarkets.com

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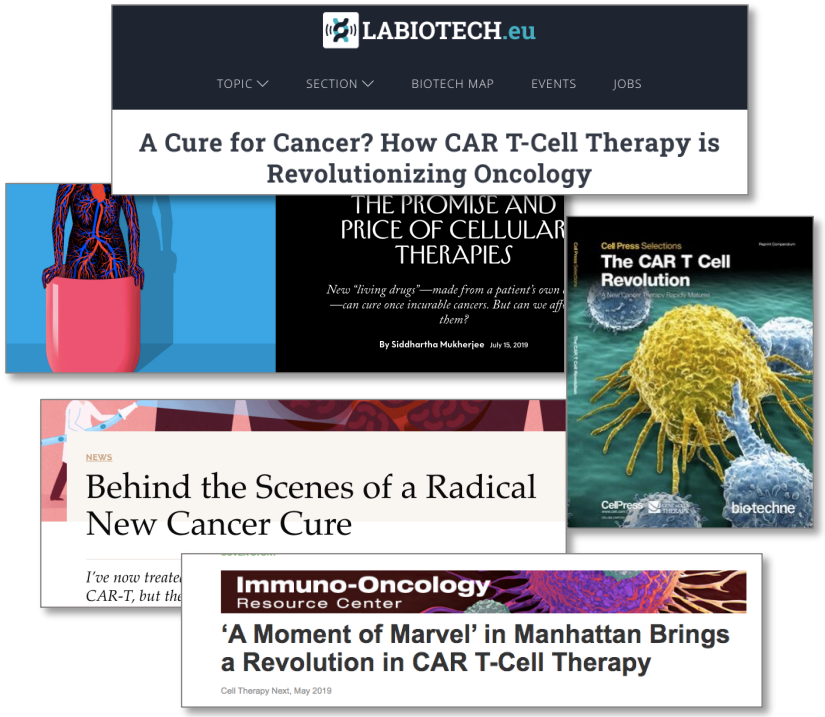
# Chimeric Antigen Receptor (CAR) Cell Therapy Revolution

## CAR-T Revolution

Due to their impressive cure rates, CAR-T cell therapies have revolutionised the treatment of cancer. As of October 2021, there are five approved CAR-T products to treat a number of haematological malignancies




| Product | Approval Year | 2020 Revenue |
|---|---|---|
| KYMRIAH® (tisagenlecleucel) Suspension for IV infusion | 2017 | US$474m[1] |
| YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion | 2017 | US$563m[2] |
| TECARTUS™ (brexucabtagene autoleucel) Suspension for IV infusion | 2020 | US$44m[2] |
| Breyanzi® (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION | 2021 | NA |
| Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION | 2021 | NA |

1. https://www.businesswire.com/news/home/20210204006011/en/Gilead-Sciences-Announces-Fourth-Quarter-and-Full-Year-2020-Financial-Results
2. https://www.novartis.com/sites/www.novartis.com/files/q4-2020-investor-presentation.pdf

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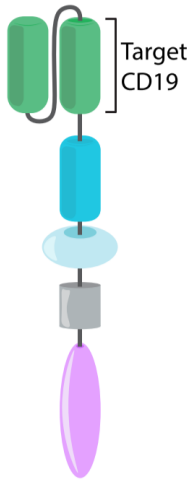
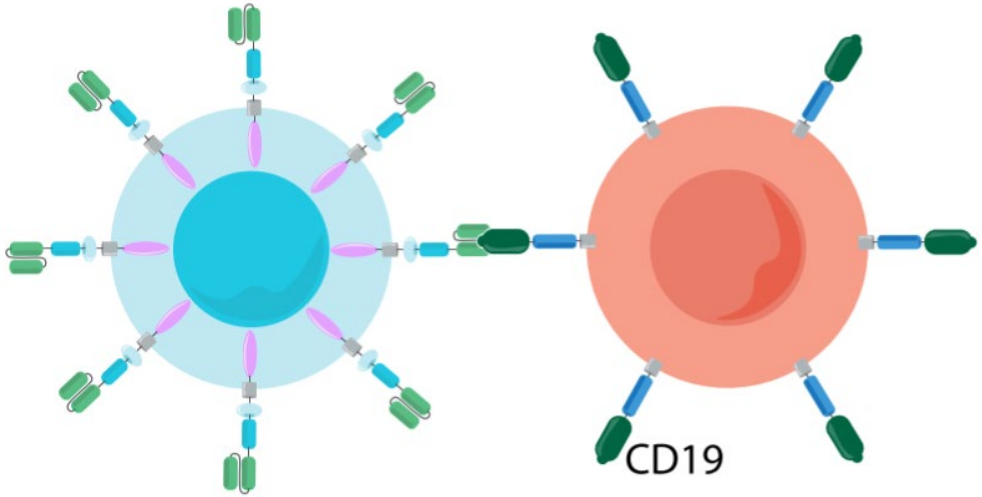
# What are Chimeric Antigen Receptors (CARs)?

**Immune Cell**

**CD19-CAR**




**CAR-Producing Cell**




**Cancer Cell**

Specific immune cells for the therapy are collected from a patient or a healthy volunteer

The immune cells are genetically re-programmed with a CAR, supercharging them to seek out and destroy specific cancer cells

Once administered to the cancer patient, the CAR-producing cells can seek out and destroy the cancer cells

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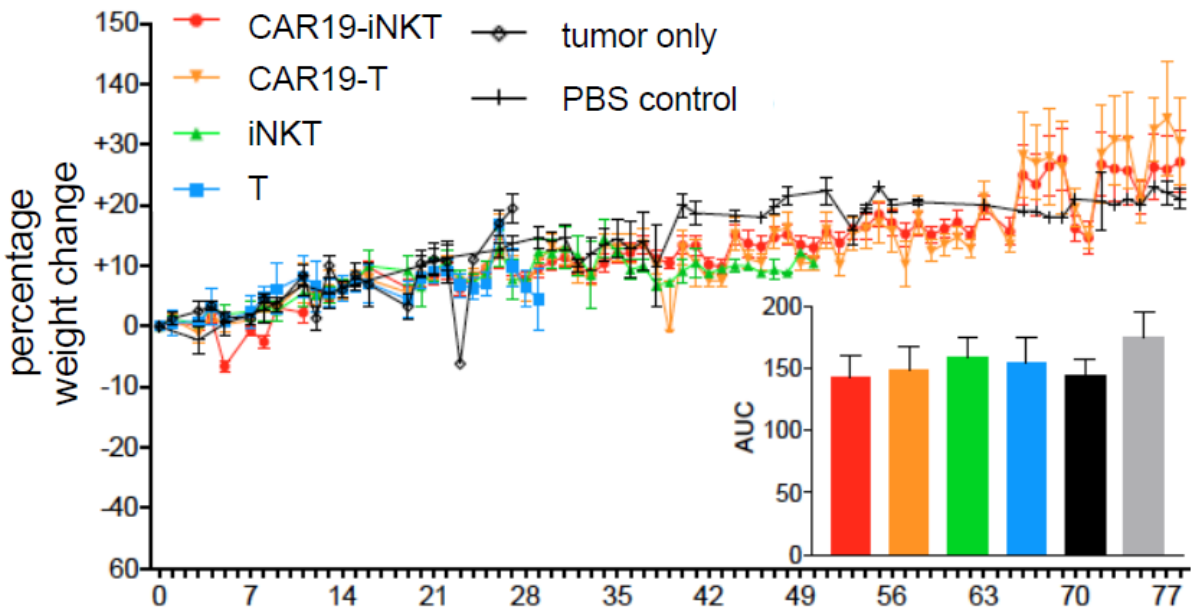
# Preclinical *In Vivo* Safety Evaluation of CAR19-iNKT cells

## CAR19-iNKT cells do not elicit adverse effects in preclinical mouse tumour models

- No body weight loss
- Data in mouse models did not show off-target effects
- No histological changes in normal tissues
- Beside the profound anti-lymphoma effect of CAR19-iNKT cells, there was no evidence of negative pathology findings, clinically or as determined by extensive histopathological analysis

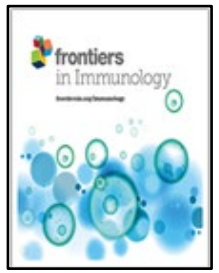
Mice Body Weight




Rotolo *et al.*, Cancer Cell (2018)

# iNKT Cells Protect Against Graft Versus Host Disease

**2017**




*Front Immunol*
*2017 July 31;8:900*

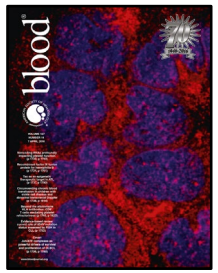
Invariant Natural Killer T Cells As Suppressors of Graft-versus-Host Disease in Allogeneic Hematopoietic Stem Cell Transplantation

**2017**


*Leukemia*
*2017 Apr;31(4):903-912*

Pre-transplant donor $CD4^-$ invariant NKT cell expansion capacity predicts the occurrence of acute graft-versus-host disease

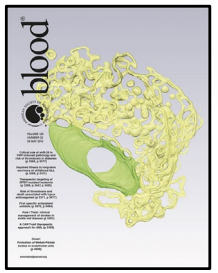
**2016**




*Blood*
*2016 Apr 7;127(14):1828-35*

Larger number of invariant natural killer T cells in PBSC allografts correlates with improved GVHD-free and progression-free survival

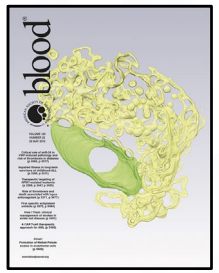
**2015**




*Blood*
*2015 May 28;125(22):3374-3375*

A party of three: iNKT cells in GVHD prevention

**2015**




*Blood*
*2015 May 28;125(22):3491-3500*

Third-party $CD4^+$ invariant natural killer T cells protect from murine GVHD lethality

**2014**


*Blood*
*2014 Nov 20;124(22):3320-3328*

$CD4^+$ invariant natural killer T cells protect from murine GVHD lethality through expansion of donor $CD4^+CD25^+FoxP3^+$ regulatory T cells

**2012**


*Blood*
*2012 May 24;119(21):5030-6*

Graft invariant natural killer T-cell dose predicts risk of acute graft-versus-host disease in allogeneic hematopoietic stem cell transplantation

**2011**


*Blood*
*2011 Mar 17;117(11):3220-3229*

Low doses of natural killer T cells provide protection from acute graft-versus-host disease via an IL-4–dependent mechanism

**2010**


*Transfusion*
*2010 Feb;50(2):407-17*

Adoptive therapy by transfusing expanded donor murine natural killer T cells can suppress acute graft-versus-host disease in allogeneic bone marrow transplantation

**2008**


*J Immunol.*
*2008 Sep 1;181(5):3268-76*

Human Invariant NKT Cells Display Alloreactivity Instructed by Invariant TCR-CD1d Interaction and Killer Ig Receptors

- Conventional CAR-T cell therapies are limited to autologous products due to the potential for acute graft versus host disease (GVHD)
- Allogeneic CAR-T cell products require additional genetic engineering
- Invariant Natural Killer T (iNKT) cells have been shown to intrinsically protect against GVHD
- Arovella's CAR-iNKT cell therapies will be developed as allogeneic products, requiring minimal genetic engineering

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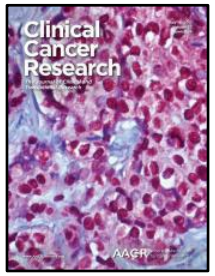
# Use of iNKT Cells in Clinical Trials

**2020**


[Nat Med](#)
*2020* Nov;26(11):1686-1690.
Anti-GD2 CAR-NKT cells in patients with relapsed or refractory neuroblastoma: an interim analysis

**2017**

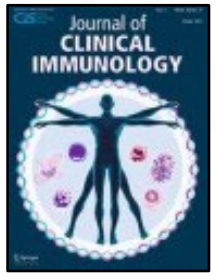



[Clin Cancer Res](#).
*2017 Jul 15;23(14):3510-3519*
Adoptive Transfer of Invariant NKT Cells as Immunotherapy for Advanced Melanoma: A Phase I Clinical Trial

**2013**


[Blood](#)
*2013 Jan 17;121(3):423-430*
Clinical regressions and broad immune activation following combination therapy targeting human NKT cells in myeloma

**2012**




[J Clin Immunol.](#)
*2012 Apr 26;32(5):1071-81*
Accumulation of Activated Invariant Natural Killer T Cells in the tumour Microenvironment after α-Galactosylceramide-Pulsed Antigen Presenting Cells

**2011**


[Clin Cancer Res.](#)
*2011 Aug 1; 17(15):5140-51*
Comparison of Clinical and Immunological Effects of Intravenous and Intradermal Administration of α-GalactosylCeramide (KRN7000)-Pulsed Dendritic Cells

**2009**


[J Immunol.](#)
*2009 Feb 15;182(4):2492-501*
A Phase I-II Study of α-Galactosylceramide-Pulsed IL-2/GM-CSF-Cultured PBMCs in Patients with Advanced and Recurrent NSCLC

**2008**


[Cancer Immunol Immunother.](#)
*2008 Mar;57(3):337-45*
Phase I study of α-galactosylceramide-pulsed antigen presenting cells administration to the nasal submucosa in unresectable or recurrent HNC

**2006**


[Clin Cancer Res](#).
*2006 Oct 15;12(20 Pt 1):6079-86*
A Phase I Study of *In vitro* Expanded Natural Killer T Cells in Patients with Advanced and Recurrent Non–Small Cell Lung Cancer

**2005**


[J Exp Med.](#)
*2005 May 2;201(9):1503-17*
Sustained expansion of NKT cells and antigen-specific T cells after injection of α-galactosyl-ceramide loaded mature dendritic cells in cancer patients

**2005**


[Clin Cancer Res](#).
*2005 Mar 1;11(5):1910-17*
A Phase I Study of α-Galactosylceramide (KRN7000)–Pulsed Dendritic Cells in Patients with Advanced and Recurrent NSCLC

- iNKT cells, in the presence and absence of CARs, have been used in numerous clinical trials against a range of tumour types, including blood cancers and solid tumours
- Efficacy data is encouraging in both solid tumour and haematological malignancies
- The side effect profile is encouraging with low risk of neurotoxicity and cytokine release syndrome with no evidence of GVHD for allogeneic iNKT cell products

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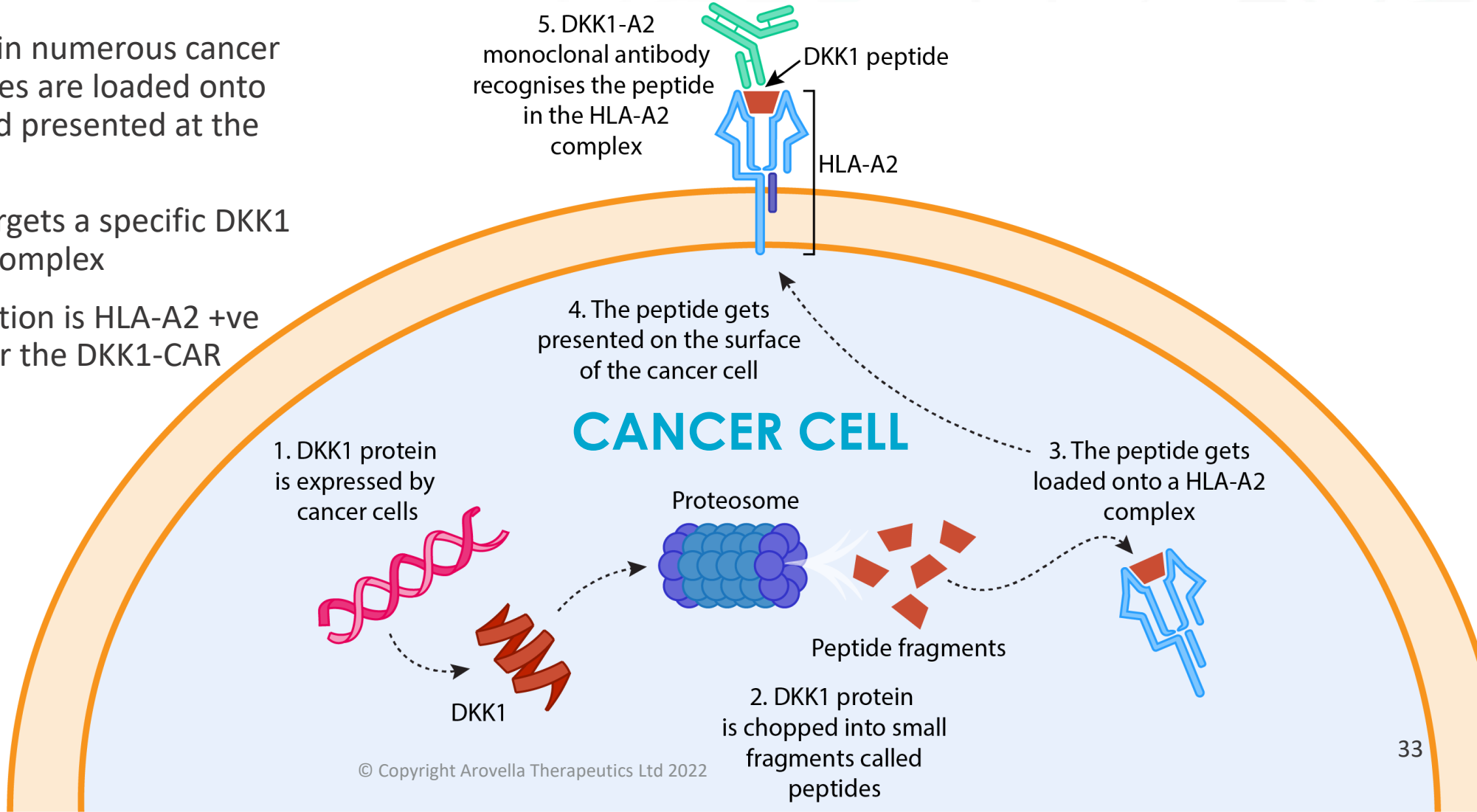
# A Novel Cancer Target – DKK1 (ALA-104)

- DKK1 is a secreted protein that functions as a negative regulator of the Wnt signaling pathway
- DKK1 is overproduced in numerous cancer types and DKK1 peptides are loaded onto immune complexes and presented at the surface of cancer cells
- Our DKK1 mAb/CAR targets a specific DKK1 peptide in an HLA-A2 complex
- ~40-50% of the population is HLA-A2 +ve meaning the market for the DKK1-CAR could be quite large



# Understanding Immunology and Cell Therapy

- **Antigen =** Any substance that induces the immune system to produce antibodies against it is called an antigen. Any foreign invaders, such as pathogens (bacteria and viruses), chemicals, toxins, and pollens, can be antigens.
- **CAR** = Chimeric Antigen Receptor can be introduced into immune cells to target cancer cells.
- **CAR-T** = Chimeric Antigen Receptor T Cell.
- **iNKT** = invariant Natural Killer T cells are components of the immune system that seek and destroy foreign or abnormal cells.
- **TCR** = T Cell Receptors are group of proteins found on immune cells that recognise fragments of antigens as peptides bound to MHC complexes.
- **CD1d** = Cluster of differentiation 1, which is expressed on some immune cells and cancer cells.
- **CD19 =** Cluster of Differentiation 19 is a protein that is expressed in a B cells and many cancer cell types.
- **Cell Therapy =** The use of intact cells to lessen or cure a disease. Cells may be from the patient (autologous) or from a healthy donor (allogenic).
- **Immuno-oncology** = The use of the immune system to treat cancer.
- **Invariant =** Never changing.
- **In vitro =** Work completed in a test tube or outside of an animal.
- **In vivo =** work completed using an organism (i.e. mouse, human).
- **Lymphomas =** Lymphoma is a cancer of the lymphatic system, which is part of the body's germ-fighting network.
- **Novel =** Of new or unusual kind.
- **Platform =** A systematic method to leverage prior knowledge for a given new therapy.

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# Committed to helping people live longer and healthier lives

**Patient-Centric**
It starts with the end in mind. In our case, it is our patients.
At Arovella, we are invested in making a positive difference in helping patients live longer and healthier lives. Creating a brighter future for people is our driving force.

**Data-driven and Milestone Focused**
Behind all life-changing therapies is excellent, ground-breaking science. We utilise data to shape our decisions to enable us to reach our set milestones

**Accountable, Honest and We Act With Integrity**
Our mission of helping patients focuses us. We hold ourselves to account for our actions. We strive to do what is right for all of our stakeholders.

**We Are Persistent and Never Give Up**
Drug development is a challenging arena. We are committed to our mission of helping patients, and we will continue to push each other through positive and challenging times in the pursuit of developing life-changing therapeutics.