ASX Release

4 April 2023

AROVELLA iNKT CELL PLATFORM

EXPLANATORY WEBINAR PRESENTATION

- **Explanatory webinar to be held 11AM AEST today**
- **Describing cell therapy and iNKT cell basics and the advantages of Arovella's CAR-iNKT cell platform**

MELBOURNE, AUSTRALIA 4 March 2023: Arovella Therapeutics Ltd (ASX: ALA) wishes to remind investors of its webinar scheduled for today at 11:00 AM (AEST). A copy of the presentation to be delivered in the webinar is attached.

The webinar will be an opportunity to hear the impressive preclinical data for the iNKT platform and how Arovella's manufacturing process is truly differentiated and addresses critical challenges for cell therapies. Arovella's Senior VP of Development and Translational Medicine, Dr Mini Bharathan, will present alongside CEO and MD, Dr Michael Baker.

Shareholders, investors and other interested parties are invited to register and attend via the following link. Further details on how to attend will be provided by email following registration.

https://us02web.zoom.us/webinar/register/WN_q97UwBO3RTqQpaPwwzPSvw

A recording of the webinar will be made available via the Company's website and social media channels following the event.

Questions can be submitted during the webinar or sent in advance to investor@arovella.com.

Release authorised by the Managing Director and Chief Executive Officer of Arovella Therapeutics Limited.

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ASX:ALA

ALA-101: An Allogeneic iNKT Cell Cancer Therapy

Explanatory Webinar

4 April 2023

Dr. Michael Baker

CEO & MANAGING DIRECTOR

University of Cologne

THE UNIVERSITY OF MELBOURNE | MELBOURNE BUSINESS SCHOOL

BioScience Managers

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Arovella Therapeutics Highlights

Allogeneic iNKT Cell Platform

Arovella is developing off-the-shelf invariant Natural Killer T (iNKT) cell therapies for CD19 expressing lymphomas and solid tumours, and DKK1 producing cancers

Data Driven

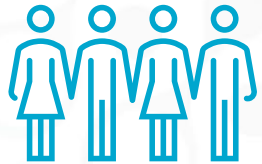
Arovella uses data to drive decision making for its key assets and clinical indications

World Leading Partners

Arovella's technologies are licensed from **Imperial College London** and **MD Anderson Cancer Center.** Arovella has an ongoing collaboration with **Imugene**

Strategic Acquisitions

Arovella is focused on acquiring innovative technologies that strengthen its cell therapy platform and align with its focus areas



Strong Leadership Group

Arovella's leadership team and its Board have proven experience in drug development, particularly cell therapies

Unique Value Proposition

Arovella is among few companies globally developing an iNKT cell therapy platform, and the only company developing a CAR targeting a DKK1-peptide

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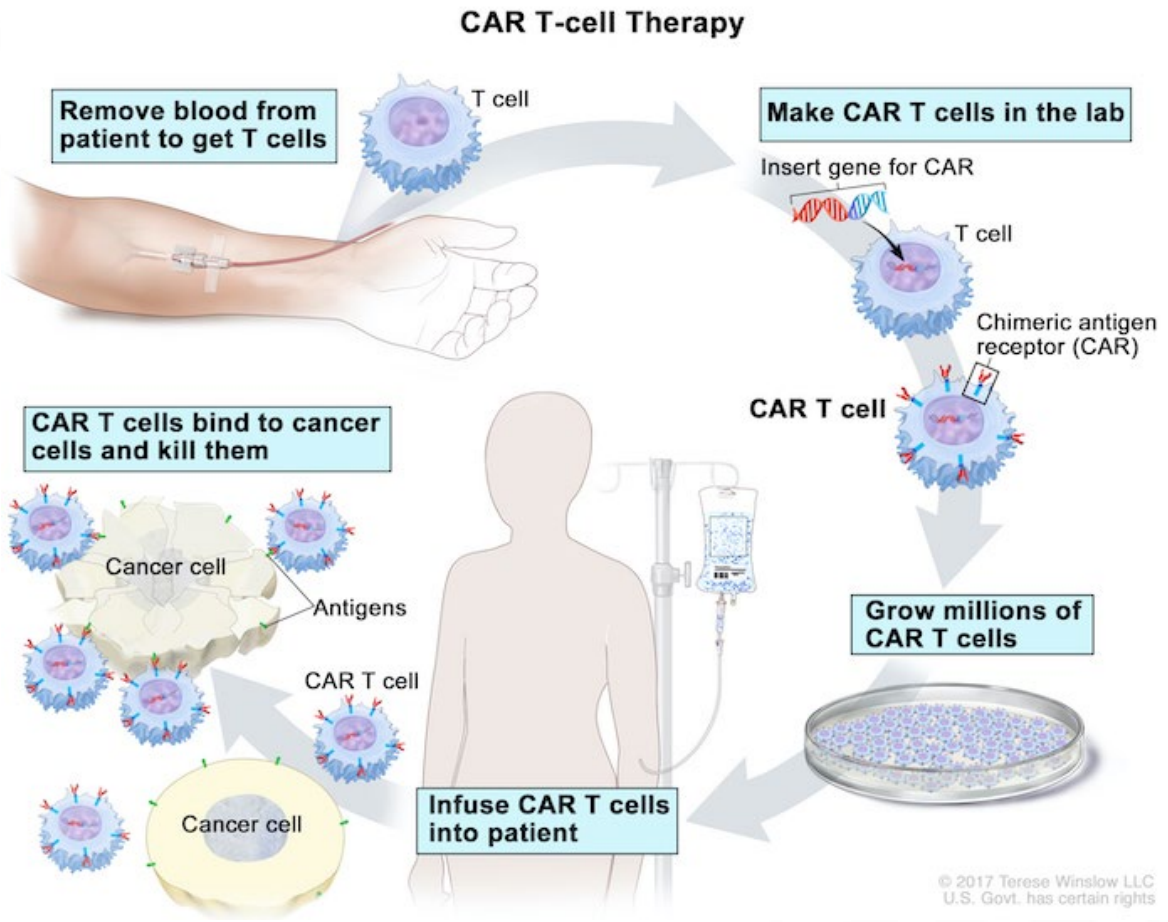
What are "CAR-T Cells"?

- T cells are a common type of immune cell that fight infections and can help fight cancer
- To generate autologous CAR-T cells, T cells are taken from a patient with blood cancer and 'reprogrammed' to produce a Chimeric Antigen Receptor (CAR)
  - The CAR is able to specifically recognise cancer cells through a target antigen
- CAR-T cells are administered to the patient to find and kill the tumour cells
  - Once the CAR binds to a tumour cell, the CAR-T cell is activated to kill the tumour cell

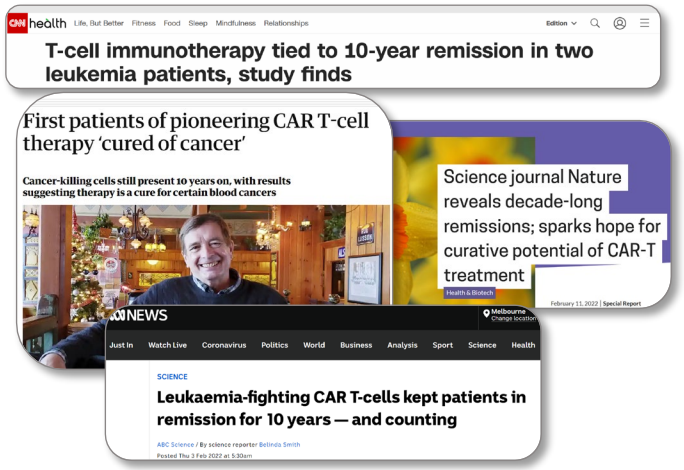


https://www.ohsu.edu/sites/default/files/2021-04/CAR%20TcellTherapy7-700px.jpg

Cell Therapy Has Revolutionized Blood Cancer Treatment

- CAR-T cells have demonstrated ability to **cure** haematological cancers and have generated strong sales
- The Cell Therapy market is expected to reach $12.3 billion by 2030[1]

February 2022



May 2022

Product	Approval Year	2022 Revenue
YESCARTA® (axicabtagene ciloleucel)	2017	US$1160m[2]
KYMRIAH® (tisagenlecleucel)	2017	US$536m[3]
Abecma® (idecabtagene vicleucel)	2021	US$388m[4]

1. https://www.businesswire.com/news/home/20221214005817/en/Global-Cell-Therapy-Technologies-Market-to-Reach-12.27-Billion-by-2030-at-a-14.5-CAGR---ResearchAndMarkets.com
2. https://s29.q4cdn.com/585078350/files/doc_financials/2022/q4/GILD-Q4-FY22-Earnings-Press-Release-2-February-2023.pdf
3. https://www.novartis.com/sites/novartis_com/files/q4-2022-media-release-en.pdf
4. https://bioprocessintl.com/bioprocess-insider/therapeutic-class/bms-sees-car-t-sales-rocket-in-line-with-increased-capacity/#:~:text=For%20the%20full%20year%202022,%2487%20million%20the%20year%20prior.

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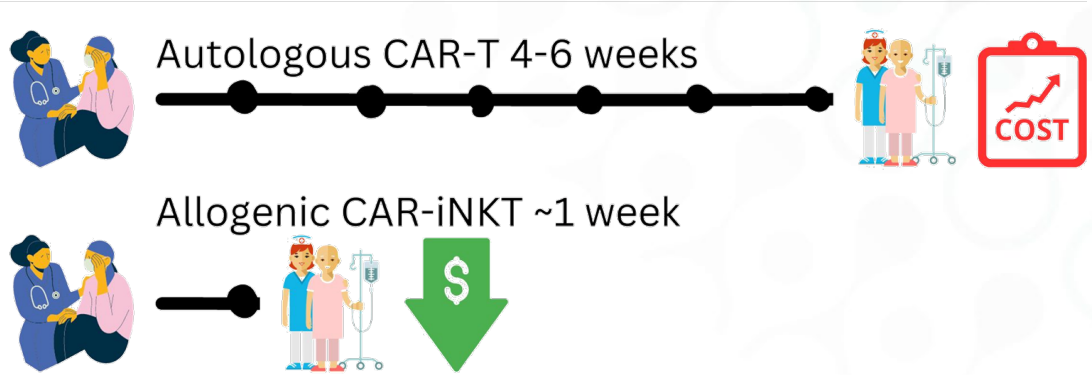
But…Manufacturing and Logistics Pose Major Challenges

- **T cells must originate from the patient to be treated** so each manufacturing batch is patient-specific
  - **High manufacturing and supply chain costs** lead to high drug costs (>$500k per patient)
  - Starting material (T cells) can be compromised due to disease, **reducing efficacy**
  - Limited number of centres able to collect cells and manufacture the therapy so **not all eligible patients can be treated**

- **Manufacturing CAR-T takes 4-6 weeks** for each patient
  - Patients with aggressive disease sometimes **die while waiting for treatment**
  - **Manufacturing run failures can occur**, further increasing the time to treatment (and cost)

Arovella's allogeneic CAR-iNKT cell platform has the potential to address the manufacturing and logistics challenges of CAR-T cells and the potential for improved efficacy



Advantages of iNKT Cells

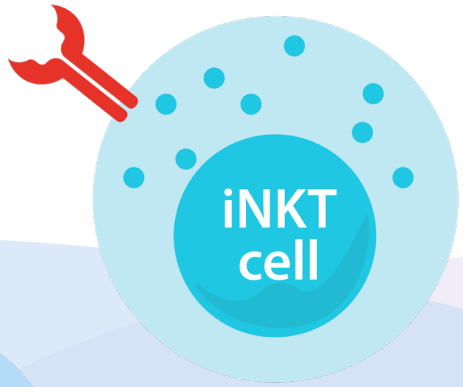
Cells from a healthy donor can be used to treat patients (no GvHD)

Naturally target tumour cells through invariant TCR (CD1d); **dual targeting with CAR**

Directly kill tumour cells via T-cell and NK-cell-like mechanisms

iNKT cells

subpopulation of T cells with properties of NK cells



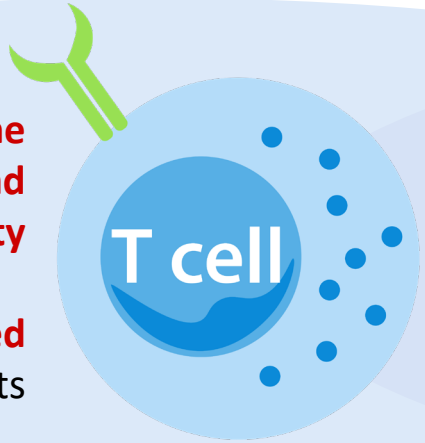
Modify the tumour microenvironment and **kill cells that promote tumour growth**

Infiltrate tumours and once activated, secrete signaling molecules to **activate other immune cells** to kill tumour cells

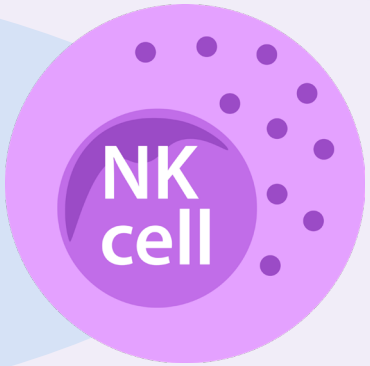
ADAPTIVE IMMUNITY

Can cause **severe cytokine release syndrome and neurotoxicity**

Complex gene editing required for allogeneic products



INNATE IMMUNITY



Limited persistence in an allogeneic setting

Limited durability of response

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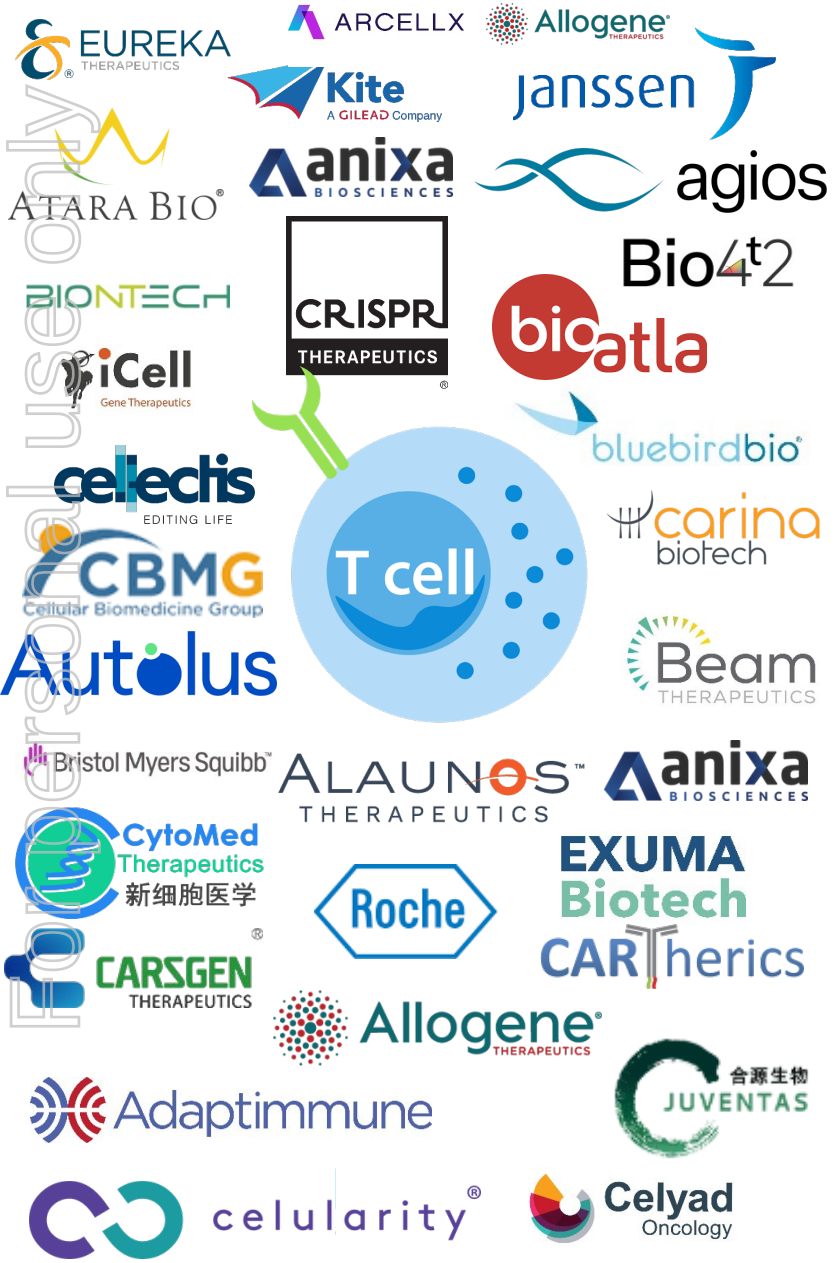
The Potential of CAR-iNKT Cells is Untapped



Dr. Mini Bharathan

SENIOR VP DEVELOPMENT & TRANSLATIONAL MEDICINE

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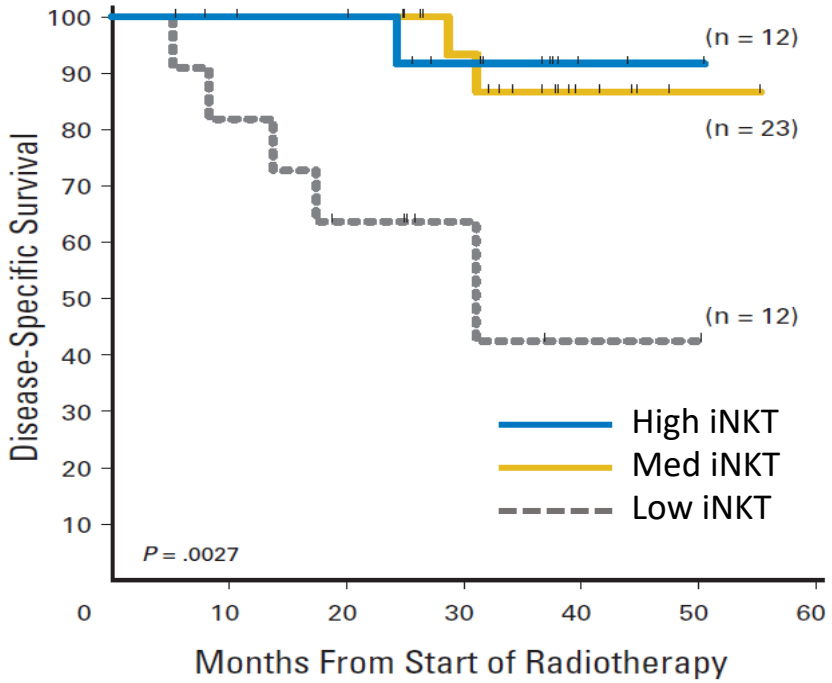
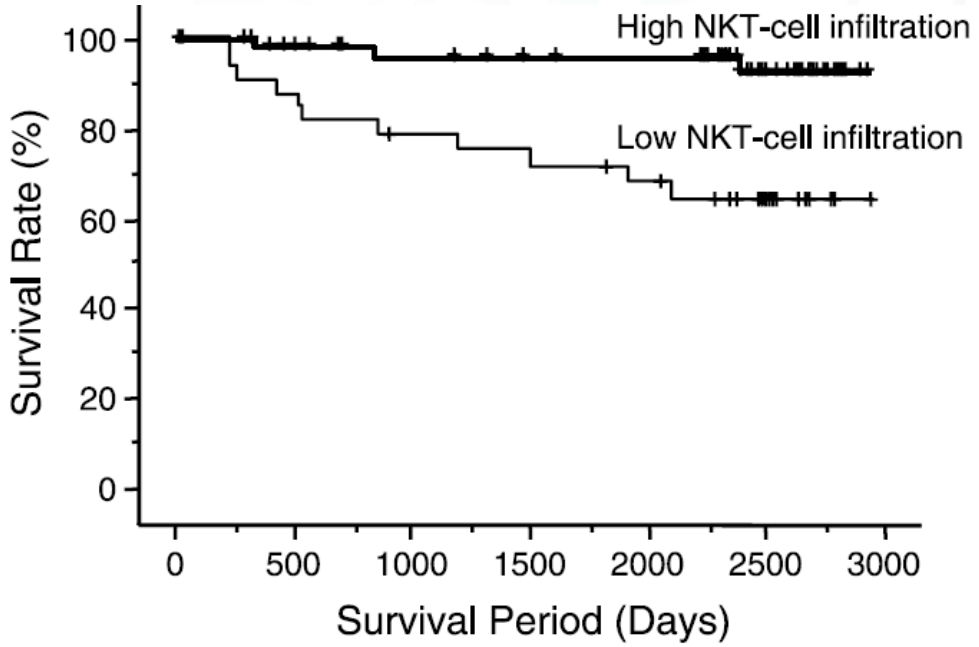
Natural Level of iNKT Cells Correlates With Patient Survival

- High levels of natural circulating iNKT cells correlate with improved survival outcomes for patients with head and neck squamous cell carcinomas



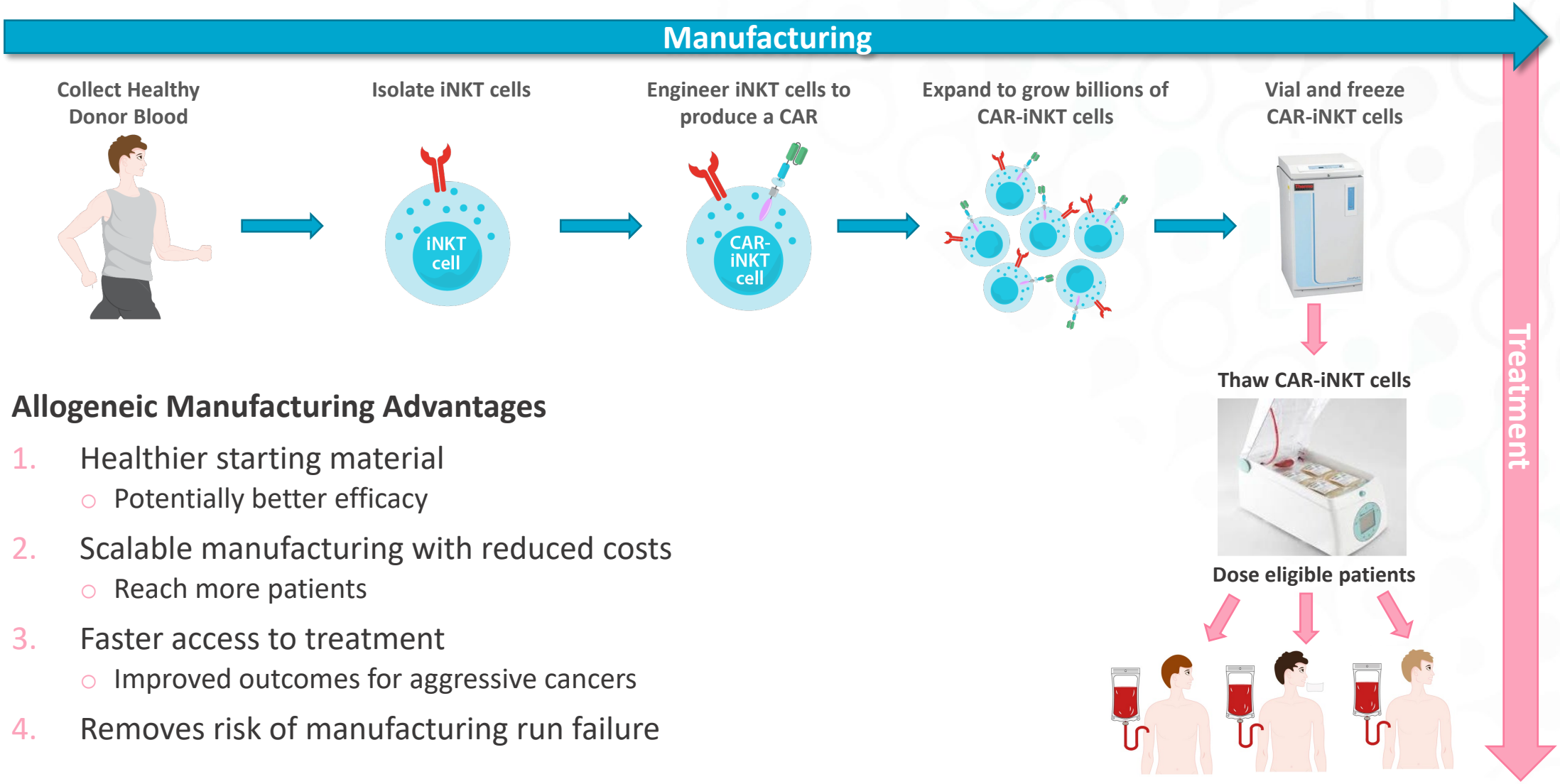
Molling et al., 2007, Journal of Clinical Oncology, 25(7)

- High natural levels of iNKT cells within colorectal tumours correlated with improved survival outcomes



Tachibana et el, 2005, Clinical Cancer Research, 11(20)

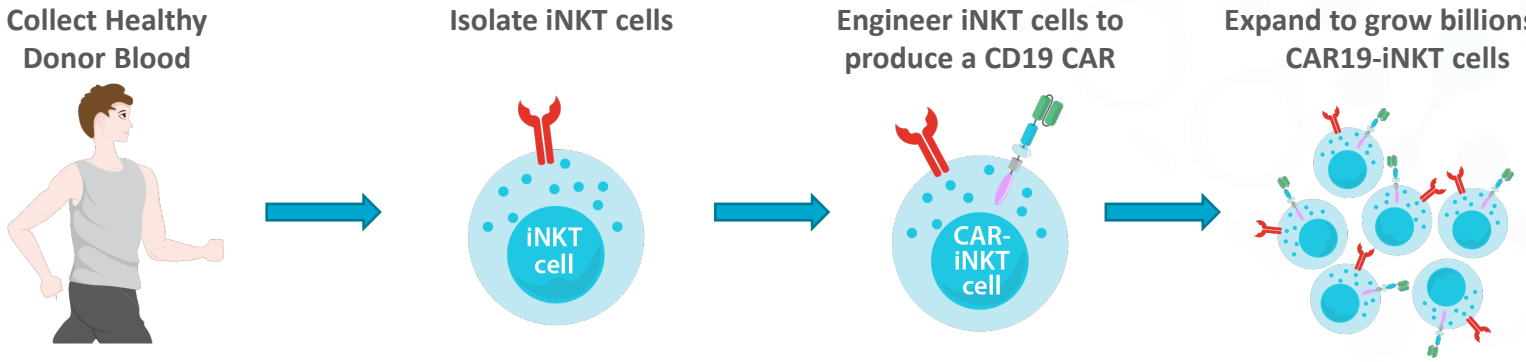
CAR-iNKT Cell Therapy Production Advantages



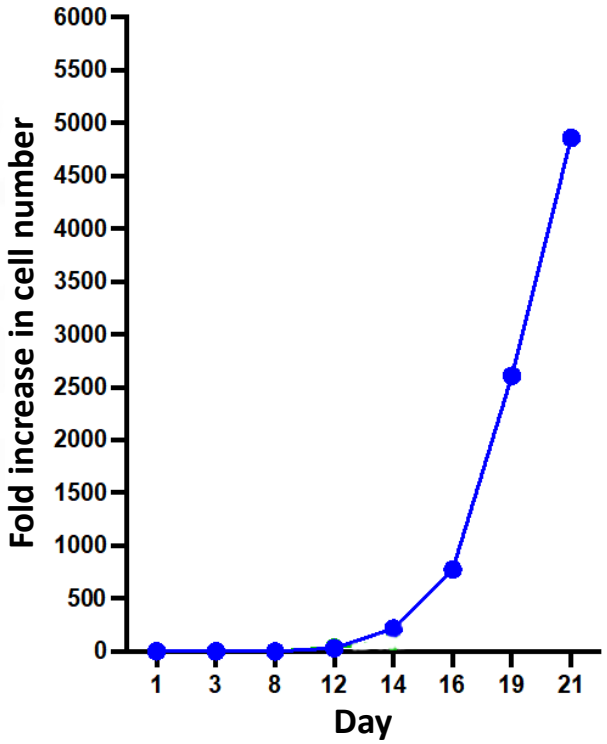
Allogeneic Manufacturing Advantages

1. Healthier starting material
   - Potentially better efficacy
2. Scalable manufacturing with reduced costs
   - Reach more patients
3. Faster access to treatment
   - Improved outcomes for aggressive cancers
4. Removes risk of manufacturing run failure

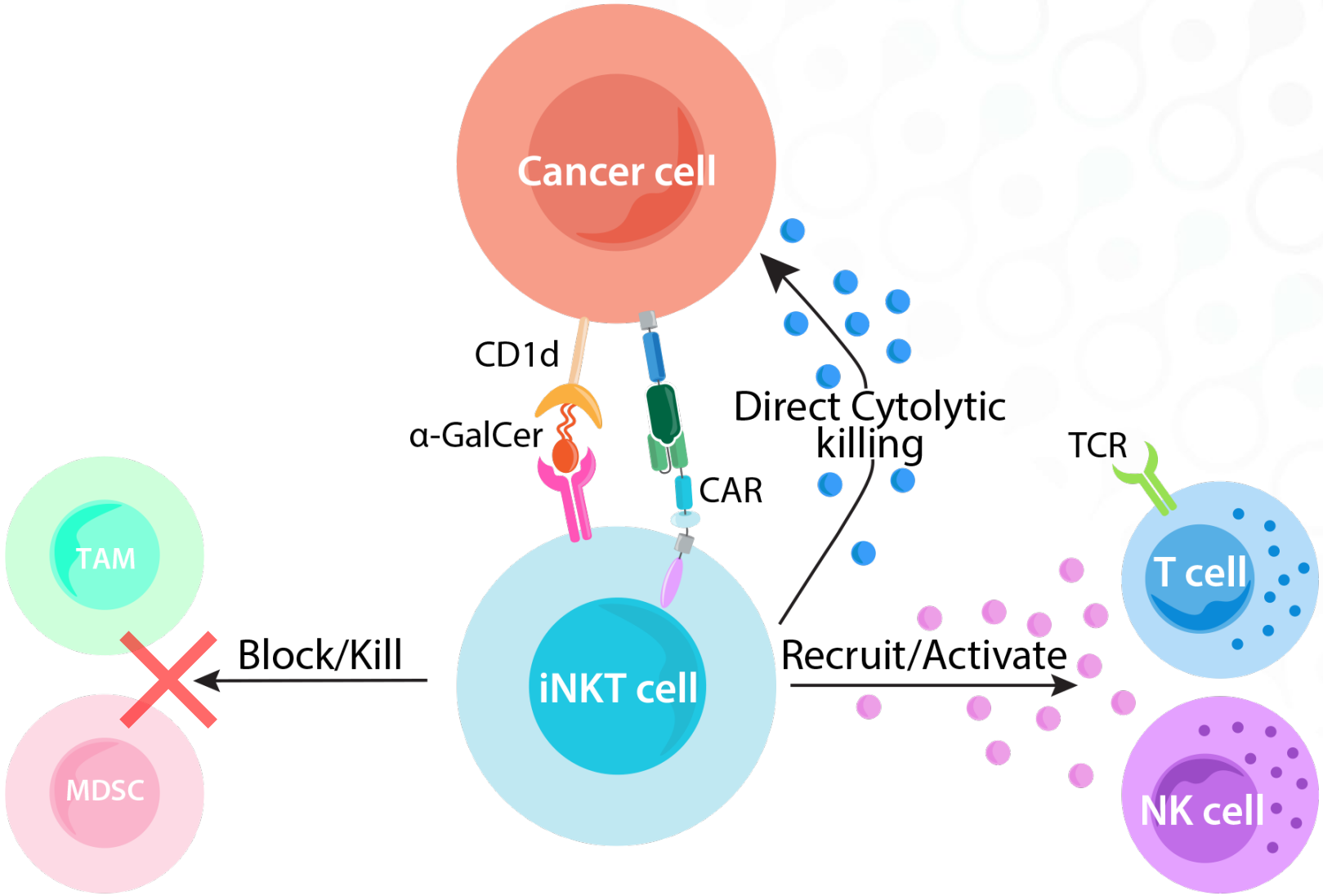
CAR19-iNKT (ALA-101) Cells Can Be Expanded



- Arovella selects healthy donor-derived iNKT cells with a phenotype to maximise their potential efficacy
- Arovella's manufacturing method modifies small numbers of cells, therefore reducing the use of expensive reagents
- Cells are then 'expanded' up to 5,000-fold to produce large numbers of cells



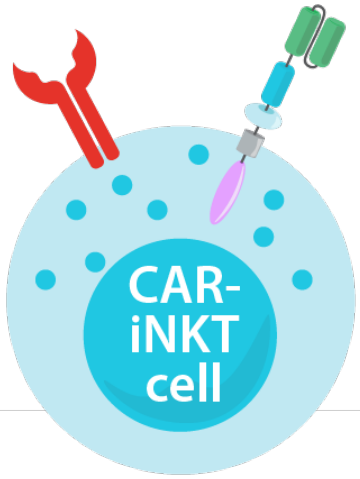
CAR-iNKT Cells Mechanism of Action

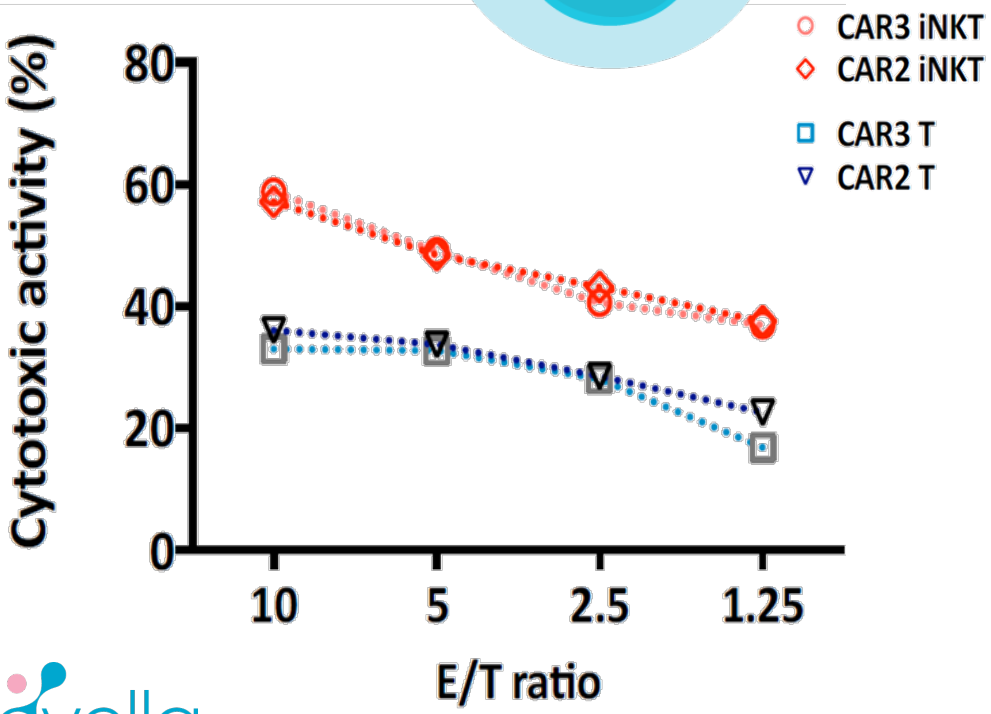


TAM = Tumour Associated Macrophage; MDSC = Myeloid Derived Suppressor Cell; CAR = Chimeric Antigen Receptor; NK = Natural Killer

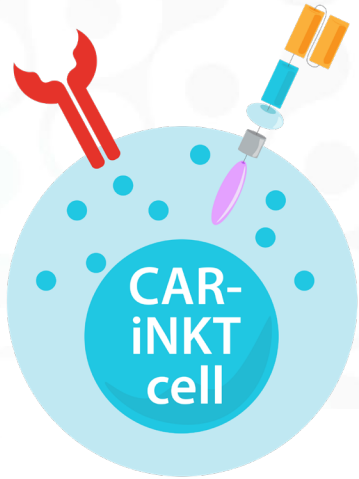
CAR-iNKT Platform Can Be Used for a Variety of CARs

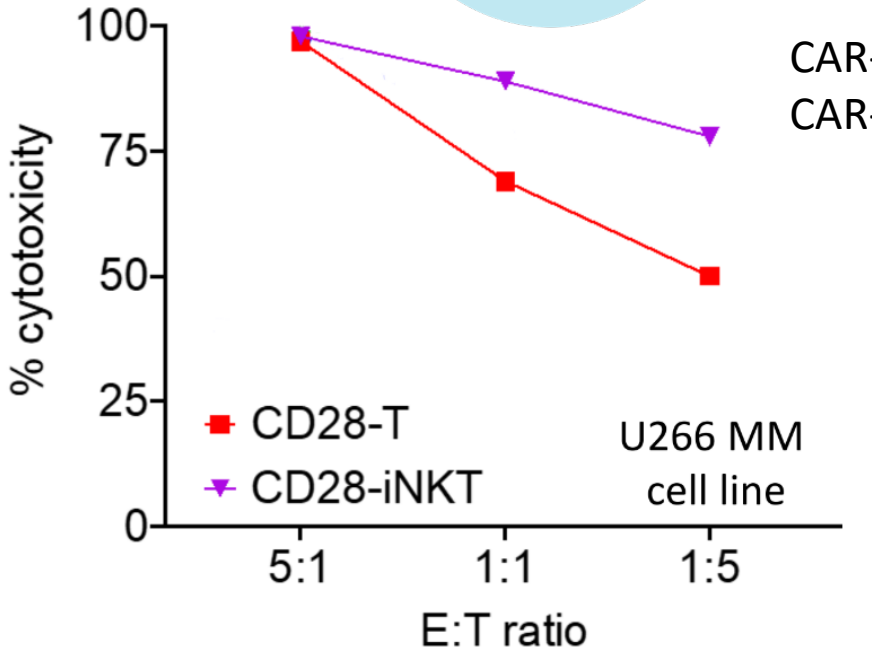
CD19-CAR





CAR targeting different protein on cancer cells

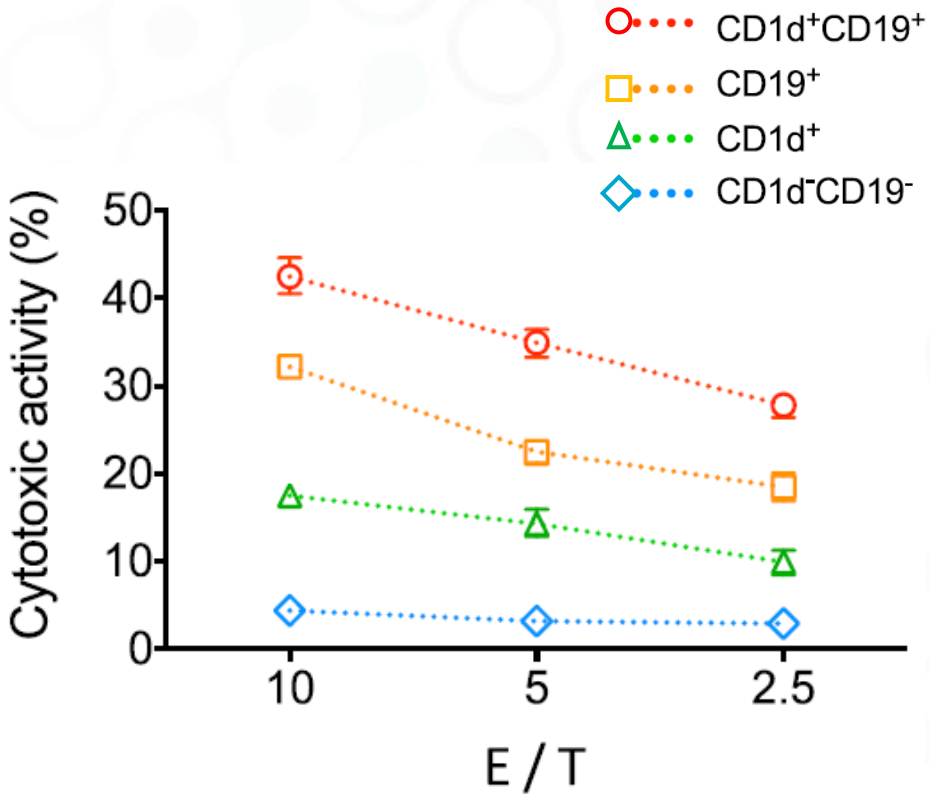




CAR19-iNKT Cells (ALA-101) are Dual Targeting

- CD19 is an antigen expressed on normal B cells and malignant B cells of leukemias and lymphomas
  - CD19-targeting CAR T-cells is a proven therapeutic approach for treating lymphoma or B-cell leukemias
- CD1d is naturally expressed on several tumour cell types, including lymphoma and myeloma
  - CD1d is not targeted by existing CAR-T therapies
- iNKT cells modified to express a CAR that targets CD19 (ALA-101) bind and kill cancer cells expressing
  1. CD19; and
  2. Glycolipid-loaded CD1d
- CAR19-iNKT cells show enhanced activity against cells that express both CD19 and CD1d

Cytotoxic activity of CAR19-iNKT cells against K562 cells expressing ±CD1d/±CD19



Rotolo et al., 2018, Cancer Cell, 34, pp596-610

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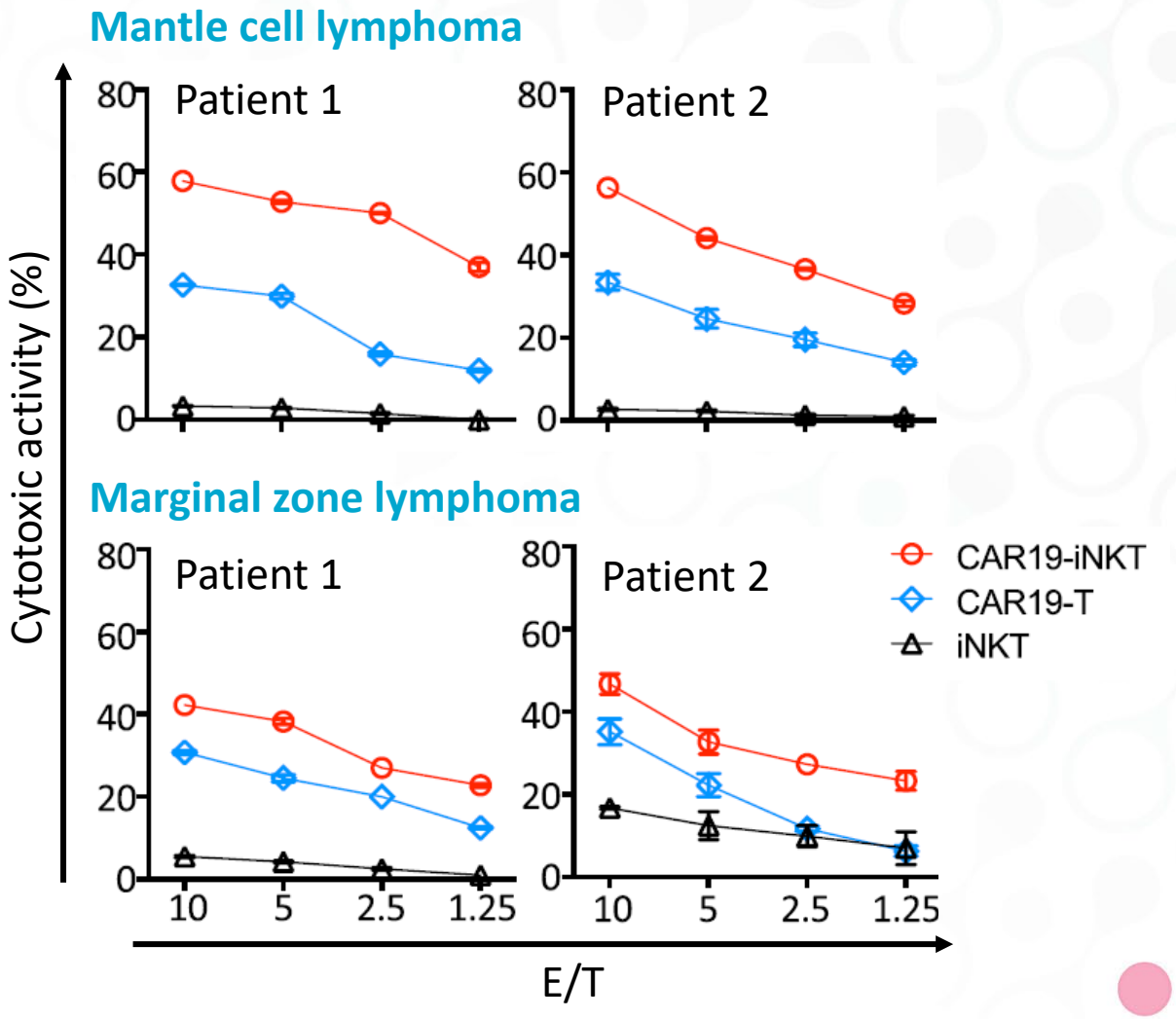
CAR-iNKT Cells (ALA-101) Kill Patient-Derived Primary Tumour Cells

- CAR19-iNKT cells kill CD19-expressing lymphoma cells more effectively than CAR T cells
  - Tested against tumour cells from multiple patients using CAR19-iNKT cells derived from multiple donors
  - Observed with Mantle Cell Lymphoma, Marginal Zone Lymphoma and Chronic Lymphocytic Leukemia

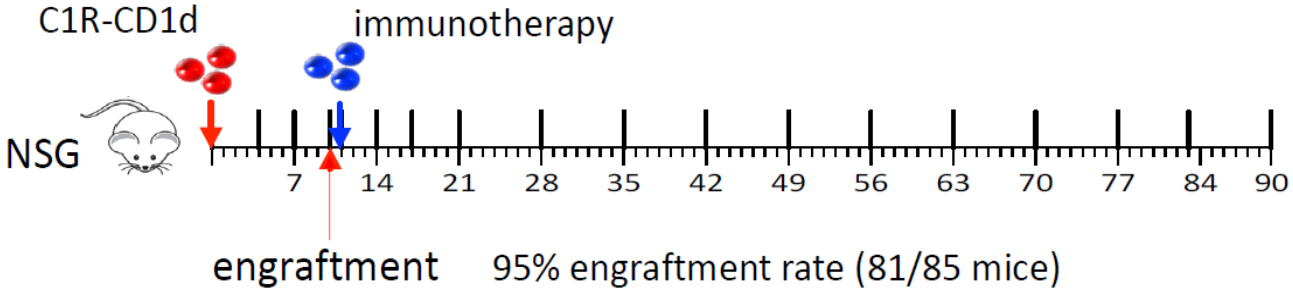


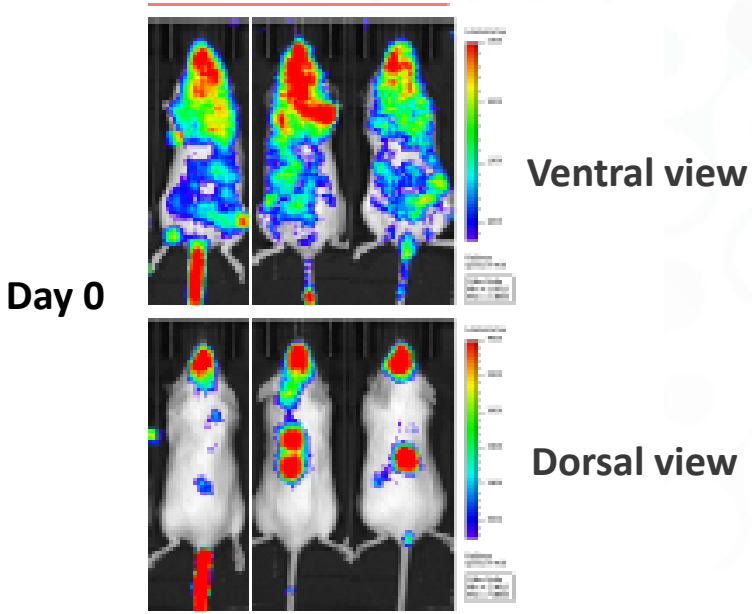
Rotolo et al., 2018, Cancer Cell, 34, pp596-610

CAR-iNKT Cells (ALA-101) Display Enhanced Tumour Killing *In Vivo*

CAR19-iNKT cells were assessed in a mouse tumour model

- Tumour cells expressing CD19 and CD1d were intravenously delivered into mice
- Tumour cells are tagged with luciferase so that they can be measured within living mice
- Once the tumours were established, mice were treated with one of:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - CAR19-iNKT cells (ALA-101)

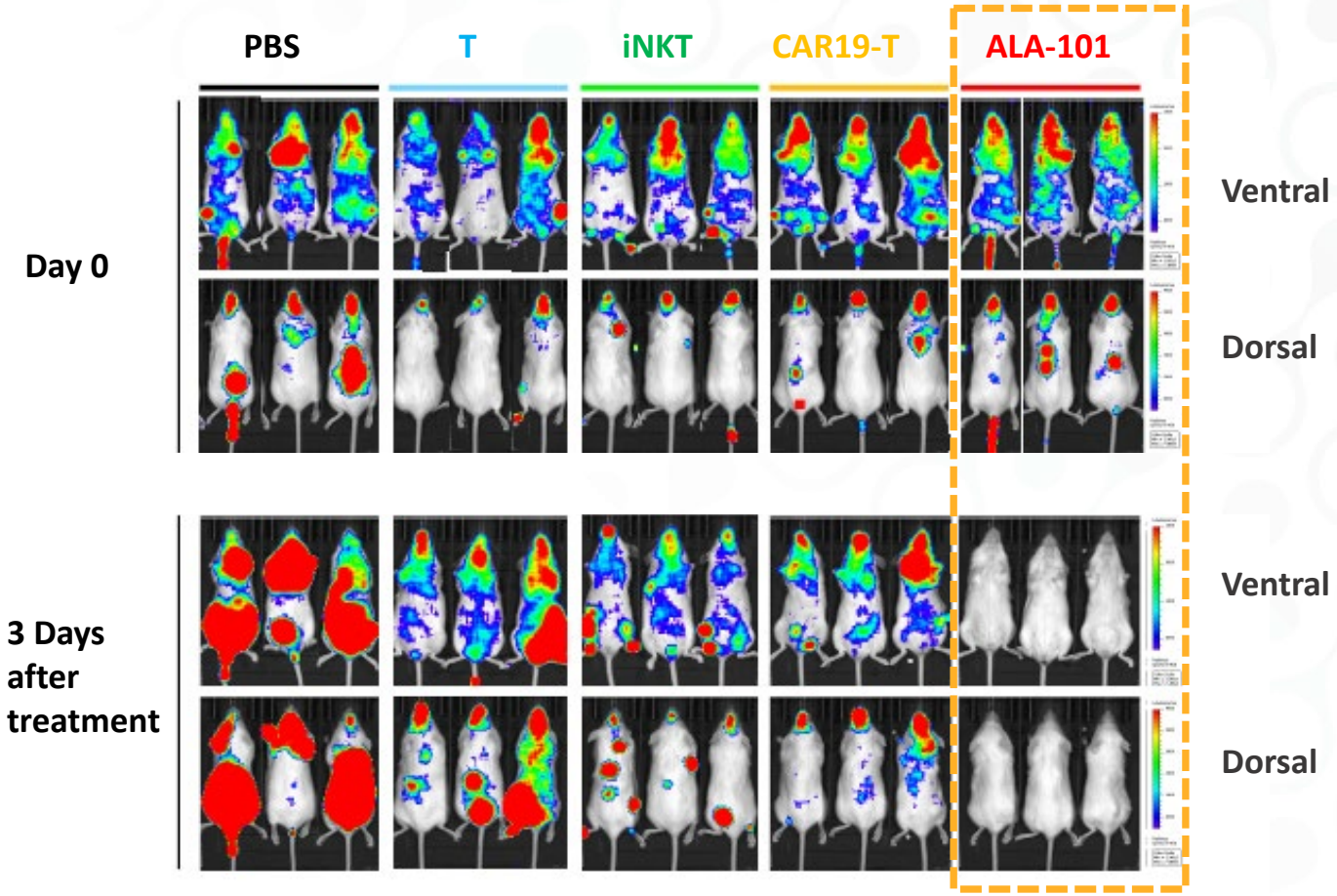




CAR-iNKT Cells (ALA-01)Display Enhanced Tumour Killing *In Vivo*

CAR19-iNKT cells rapidly clear tumour cells in mice

- Mice were treated with:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - CAR19-iNKT cells (ALA-101)
- After three days, CAR-iNKT cells led to significant regression of tumour cells
- In all other treatments, we observed strong tumour cell persistence
- CAR-iNKT response is very rapid



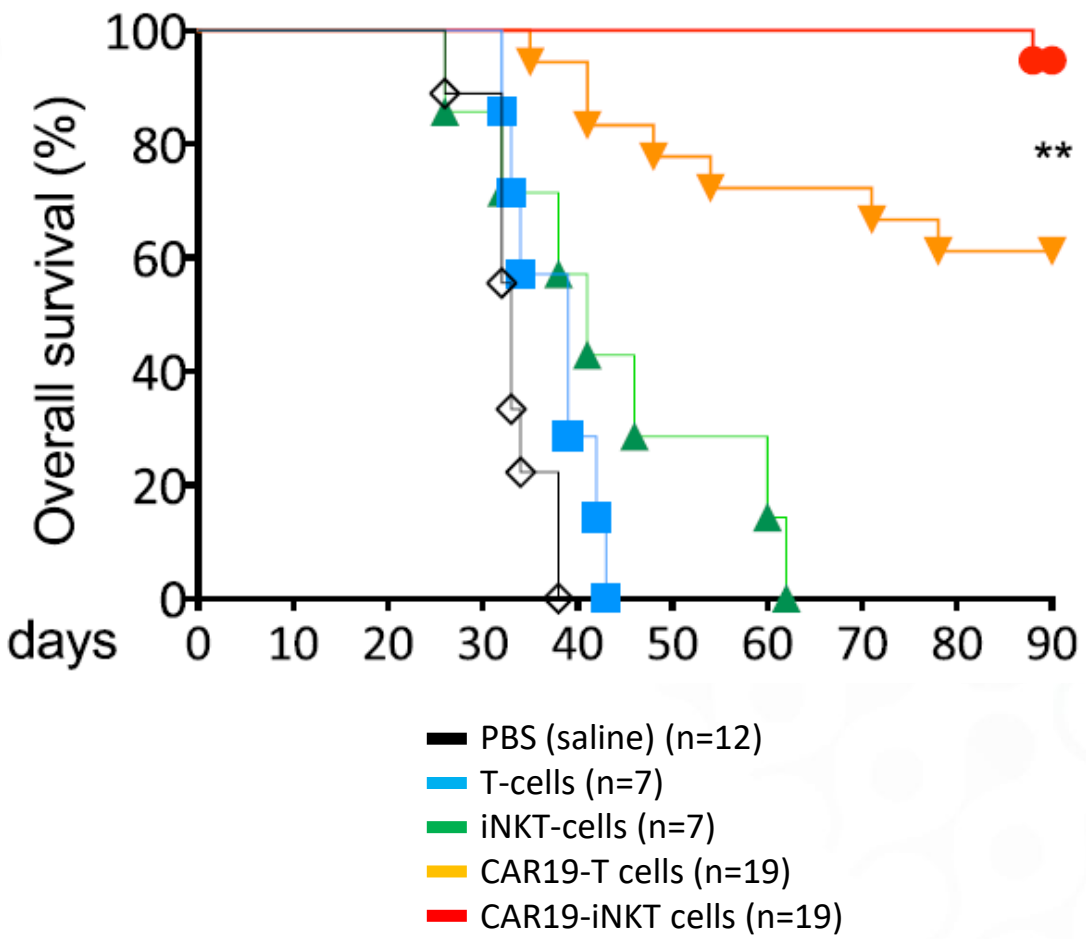
Rotolo et al., 2018, Cancer Cell, 34, pp596-610

CAR-iNKT Cells (ALA-101): Superior Animal Survival Over CAR T-Cells

CAR19-iNKT cells significantly increased survival in mice versus CAR19-T cells

- After 90 days, only mice treated with CAR19-T cells or CAR19-iNKT cells remained alive
- 1.5x more mice treated with CAR19-iNKT cells remained alive after 90 days relative to CAR19-T cells

ALA-101 has the potential to be an effective, off-the-shelf cell therapy for the treatment of CD19-expressing cancers

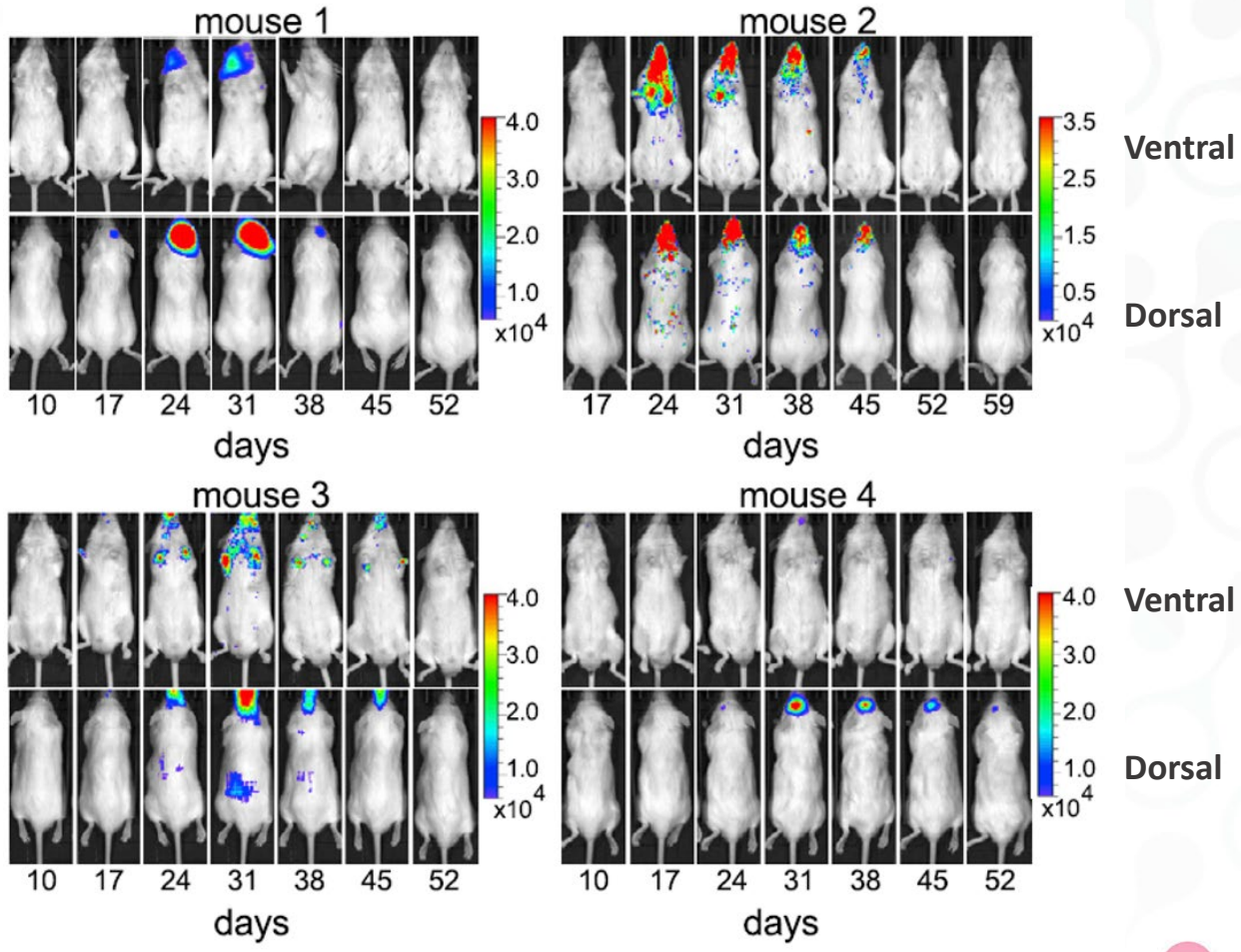


Rotolo et al., 2018, Cancer Cell, 34, pp596-610
** statistically significant, P=0.01

CAR-iNKT Cells: Spontaneous Secondary Remission

CAR-iNKT activity may persist to eradicate tumour cells following relapse

- Four mice treated with CAR-iNKT cells had the cancer return to the brain
- In all four mice, tumour cells were eliminated a second time with no additional dosing
- Provides evidence that CAR19-iNKT cells could persist and continue to protect against cancer cells *in vivo*
- Potential to use ALA-101 to treat central nervous system lymphoma or brain metastases



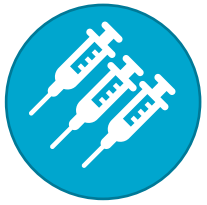
Rotolo *et al*., Cancer Cell (2018)

Arovella's iNKT Cell Platform Has Several Advantages

Uses mature iNKT cells from healthy adult donors and does not require 'reprogramming' of stem cells

High 'transduction efficiency', a high percentage of isolated iNKT cells (>60%) become modified to express the CAR

Transduction performed immediately after isolation on low cell numbers, reducing the quantity of expensive reagents required



Efficient expansion of genetically modified cells lead to multiple doses from a single batch

Maintains highly cytotoxic population of iNKT cells

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Arovella Has a Unique, Proprietary Manufacturing Process

- Developed at Imperial College London by Professor Tassos Karadimitris

Exclusive worldwide licence granted to Arovella in 2021

- Patent granted in Europe and pending in United States, Canada, China, Hong Kong and Australia
- Patent life until 2038
- Products approved in the US will also be subject to 12 years marketing exclusivity from date of approval
  - Similar protections also provided in other jurisdictions

Imperial College London

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ALA-101 Scale-Up and Preparation for Clinical Material

Complete ✓

Optimised viral vector to engineer the CAR with regulatory-friendly elements

On track ✓

Identify high-frequency iNKT cell donors

Ongoing H1 2023

Optimise manufacturing process to produce clinical-grade material

Planned H2 2023

Scale-up and and generate data required for regulatory submissions

Produce clinical material

ALA-101 is Arovella's lead product, a CD19-targeting CAR-iNKT cell therapy

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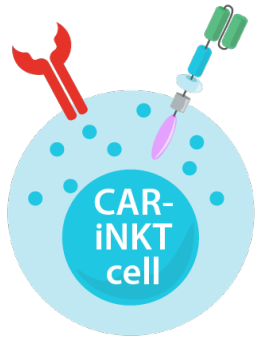
Combining ALA-101 and CF33-CD19 (onCARlytics)

- ALA-101 is very potent and is rapidly activated to kill CD19 expressing cancers[1]
- The product is being developed as an off-the-shelf product for cancer treatment



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Imperial College London

- CF33 is an oncolytic virus that targets tumour cells being developed by Imugene[2]
- CF33 has been engineered to induce CD19 expression after tumour cells have been infected – onCARlytics[3]
- Phase 1 trials for CF33 commenced October 2021 with CHECKvacc and May 2022 with VAXINIA

IMUGENE
Developing Cancer Immunotherapies

City of Hope

1. *https://pubmed.ncbi.nlm.nih.gov/30300581/*
2. *https://pubmed.ncbi.nlm.nih.gov/32032721/*
3. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9126033/*

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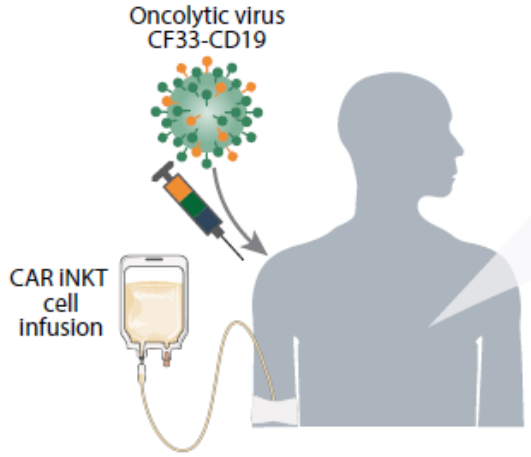
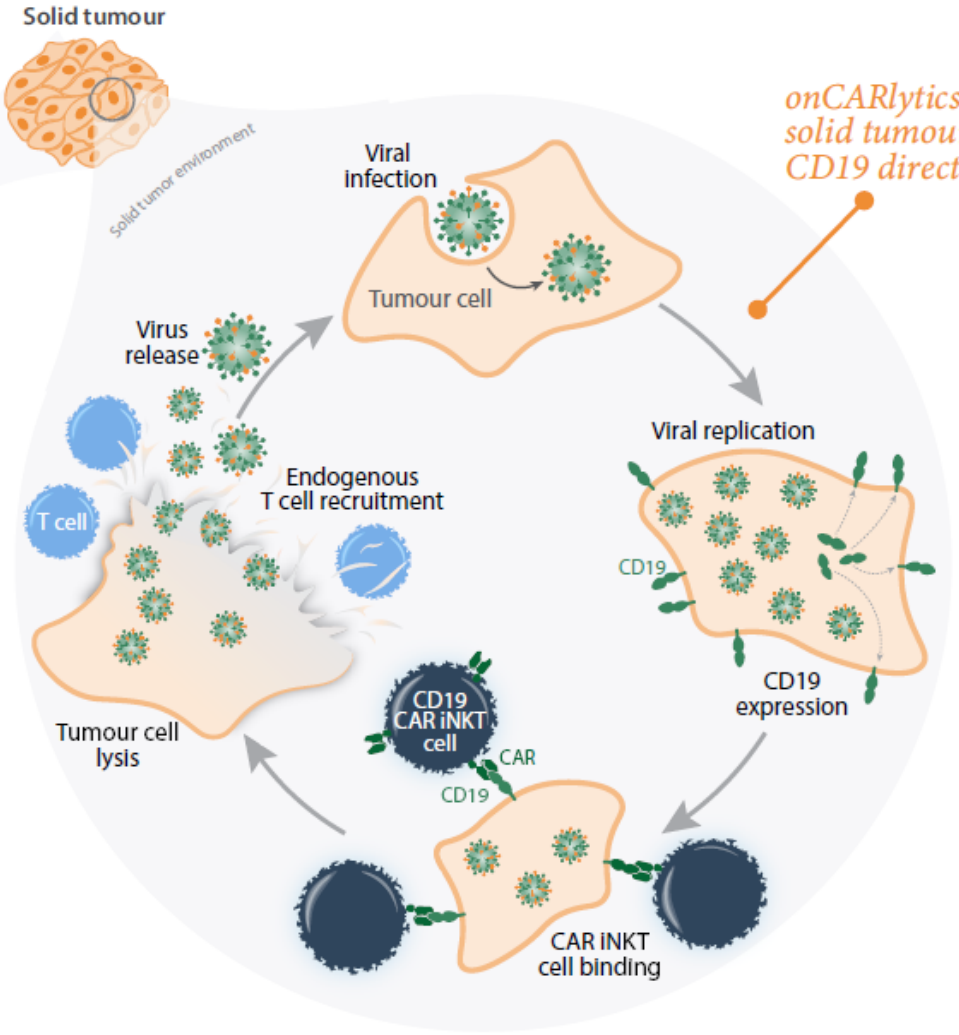
ALA-101 + onCARlytics Mechanism of Action





onCARlytics makes solid tumours "seen" by CD19 directed therapies

1. OnCARlytics infects tumour cells
2. Virus replication and production of CF33-CD19 on the cell surface enabling CD19 targeting
3. Tumour cell lysis leads to viral particle release and the combination promotes endogenous immune cell recruitment to tumours
4. Released viral particles re-initiate virus infection of surrounding tumour cells.

Research collaboration progressed to *in vivo* testing based on promising *in vitro* results

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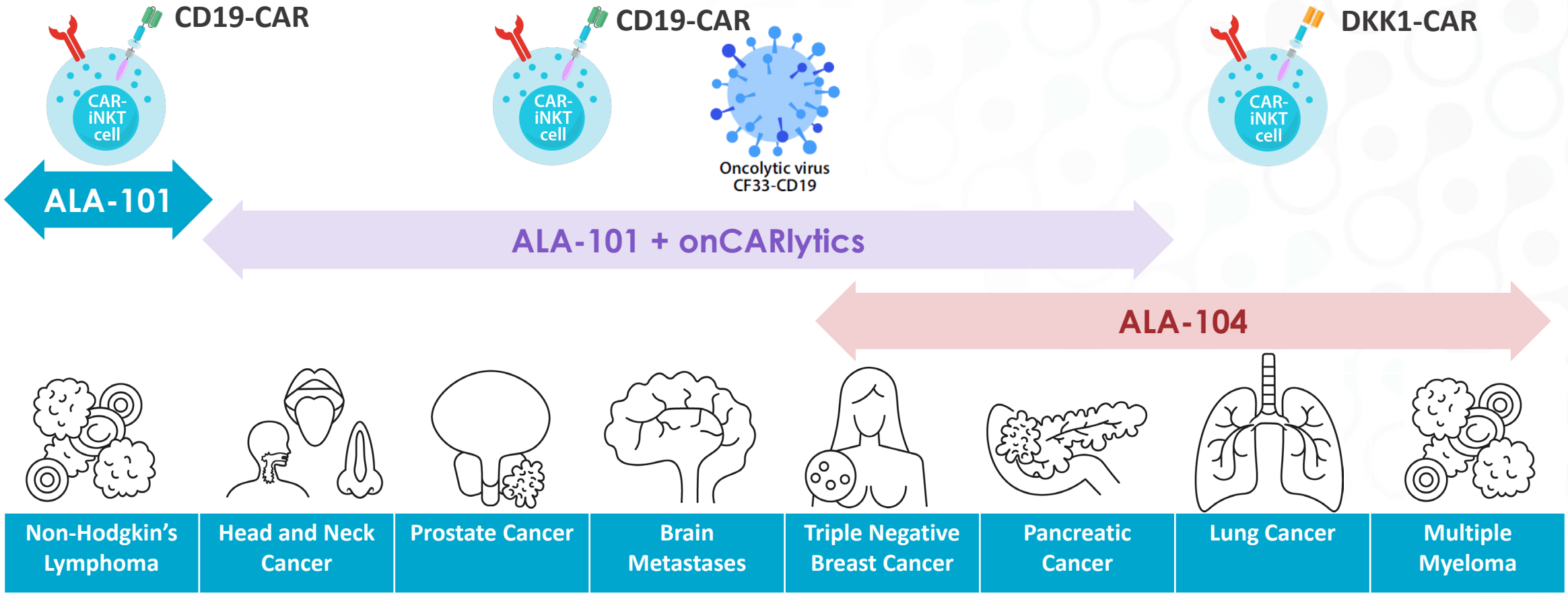
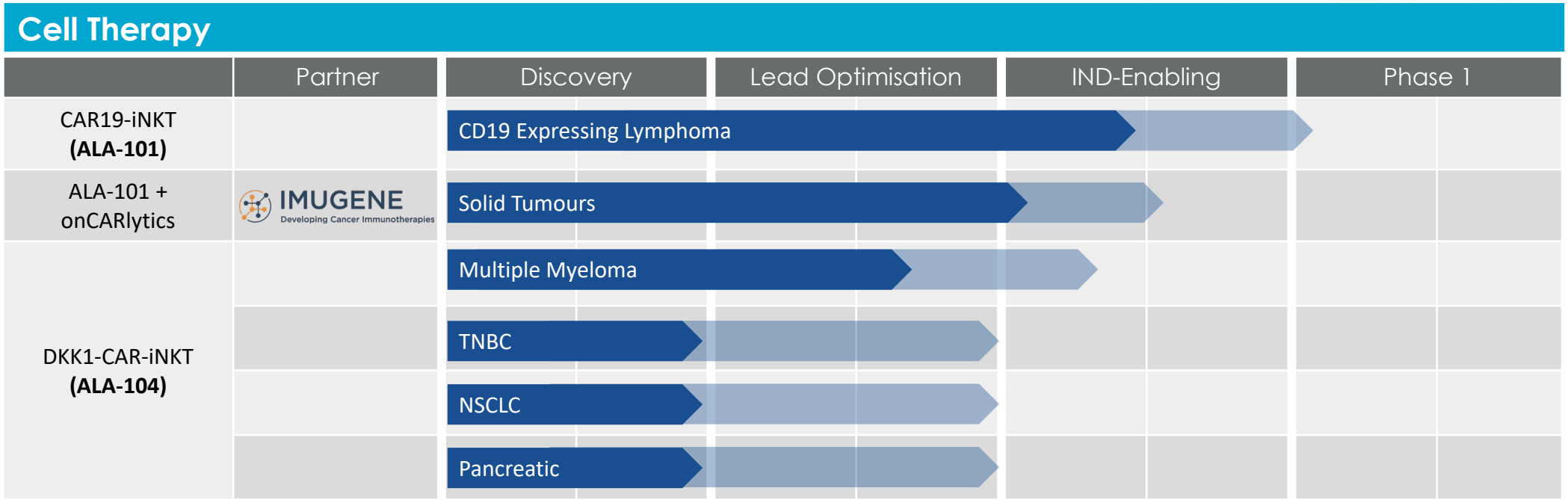
Arovella's Potential Cancer Targets



Additional CARs can be used to target different cancer types:

- **Blood Cancers** - CD20, CD22, CD79b; **Solid tumours** – mesothelin, EGFRvIII, IL13α32, GPC3, HEPG2, GD2

Arovella's Key Milestones Over 18 Months



TNBC – triple negative breast cancer; NSCLC – non-small cell lung carcinoma

- Over the next 6-18 months Arovella plans to:
  - Complete clinical manufacturing of ALA-101
  - Commence Phase 1 clinical trial with ALA-101 for Non-Hodgkin's Lymphoma
  - Complete proof of concept studies and commence IND-enabling studies for ALA-101 + onCARlytics
  - Complete CAR-optimisation for IND enabling studies for ALA-104

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Arovella Has a Strong Leadership Team

LEADERSHIP

Dr. Michael Baker
CEO & MANAGING DIRECTOR

Dr. Nicole van der Weerden
CHIEF OPERATING OFFICER

Dr. Mini Bharathan
SENIOR VP DEVELOPMENT & TRANSLATIONAL MEDICINE

Dr. Robson Dossa
SENIOR DIRECTOR MANUFACTURING & QUALITY

Ana Radeljevic
BUSINESS DEVELOPMENT

BOARD OF DIRECTORS

Dr. Tom Duthy
BOARD CHAIR

Dr. Elizabeth Stoner
DIRECTOR

Dr. Debora Barton
DIRECTOR

Mr. Gary Phillips
DIRECTOR

Mr. David Simmonds
DIRECTOR

Recent Cell Therapy Transactions

Date	Type of deal	Acquirer/Licensee	Target/Licensor	Stage	Upfront ($M)	Milestones ($M)	Total deal value
Jan-23	Acquisition	AstraZeneca	neogene THERAPEUTICS	Phase I	$200	$120	$320
Oct-22	Development collaboration	GILEAD	ARCELLX	Phase II	$225*	undisclosed	
Sep-22	Research collaboration	Genentech A Member of the Roche Group	ArsenalBio™	Preclincal	$70	undisclosed	
Aug-22	Licence and strategic collaboration	Roche	POSEIDA THERAPEUTICS	Phase I	$110	$110	$220
Sep-21	Development collaboration	Genentech A Member of the Roche Group	Adaptimmune	Preclincal	$150	$150	$300
Aug-21	Research collaboration	GILEAD	APPIA BIO	Preclinical	undisclosed	undisclosed	$875
May-21	Acquisition	Athenex	»kuur THERAPEUTICS	Phase I	$70	$115	$185
Jun-21	Acquisition	eterna	Novellus THERAPEUTICS	Preclinical	$125	$0	$125
Dec-19	Acquisition	astellas	XYPHOS	Preclinical	$120	$545	$665
				Mean	**$134**	**$208**	**$364**

**Arcellx also received a $100m equity investment from Gilead*

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Arovella Financial Overview

Financial Snapshot

ASX CODE	ALA
Market capitalisation[1]	$36.2 million
Shares on issue	755.5 million
52-week low / high	$0.020 / $0.048
Cash (30 December 2022)[2]	$5.2 million

Major Shareholders

Shareholder	Ownership (%)[1]
THE TRUST COMPANY (AUSTRALIA) LTD	52,796,657 (7.08%)
MANN BEEF PTY LTD	20,000,000 (2.68%)
UBS NOMINEES PTY LTD	15,064,640 (2.02%)
DYLIDE PTY LTD	15,000,000 (2.01%)
KAMALA HOLDINGS PTY LTD	11,500,000 (1.54%)

1. *As of 3 April 2023*
2. *Includes $1.65m proceeds from the Placement announced 19 January 2023*

Thank You

Email: investor@arovella.com

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NOTES TO EDITORS:

About Arovella Therapeutics Ltd

Arovella Therapeutics Ltd (ASX: ALA) is a biotechnology company focused on developing therapies to treat human diseases. Arovella is developing its invariant natural killer T (iNKT) cell therapy platform from Imperial College London to treat blood cancers and solid tumours. Arovella is also expanding its DKK1-peptide targeting technology licenced from MD Anderson and used in conjunction with its iNKT cell therapy platform. The Company is also commercialising ZolpiMist™, a first-in-class oral spray of zolpidem tartrate to treat short-term insomnia. ZolpiMist is approved by the FDA and the TGA and is marketed in the USA. Arovella has rights to the product outside of the US and Canada.

For more information, visit www.arovella.com

This announcement contains certain statements which may constitute forward-looking statements or information ("forward-looking statements"), including statements regarding negotiations with third parties and regulatory approvals. These forward-looking statements are based on certain key expectations and assumptions, including assumptions regarding actions of third parties and financial terms. These factors and assumptions are based upon currently available information and the forward-looking statements contained herein speak only as of the date hereof. Although the expectations and assumptions reflected in the forward-looking statements are reasonable in the view of the Company's directors and management, reliance should not be placed on such statements as there is no assurance that they will prove correct. This is because forward-looking statements are subject to known and unknown risks, uncertainties and other factors that could influence actual results or events and cause actual results or events to differ materially from those stated, anticipated or implied in the forward-looking statements. These risks include, but are not limited to: uncertainties and other factors that are beyond the control of the Company; global economic conditions; risk associated with foreign currencies; and risk associated with securities market volatility. The Company assumes no obligation to update any forward-looking statements or to update the reasons why actual results could differ from those reflected in the forward-looking statements, except as required by Australian securities laws and ASX Listing Rules.