ASX:**ALA**

arovella THERAPEUTICS

Corporate Presentation

March

2024

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Arovella's strengths

Off-the-Shelf iNKT Cell Platform

Developing off-the-shelf iNKT cell therapies to target blood cancers and solid tumour cancers

Lead Product Advancing to Clinic

ALA-101, potential treatment for CD19-expressing blood cancers, progressing to Phase 1 clinical trials, expected to commence in 2024

Addressing Key Unmet Need

Our iNKT cell platform is well positioned to solve key challenges that hamper the cell therapy sector

Strong Leadership Group

Leadership team and Board have proven experience in drug development, particularly cell therapies

Strategic Acquisitions

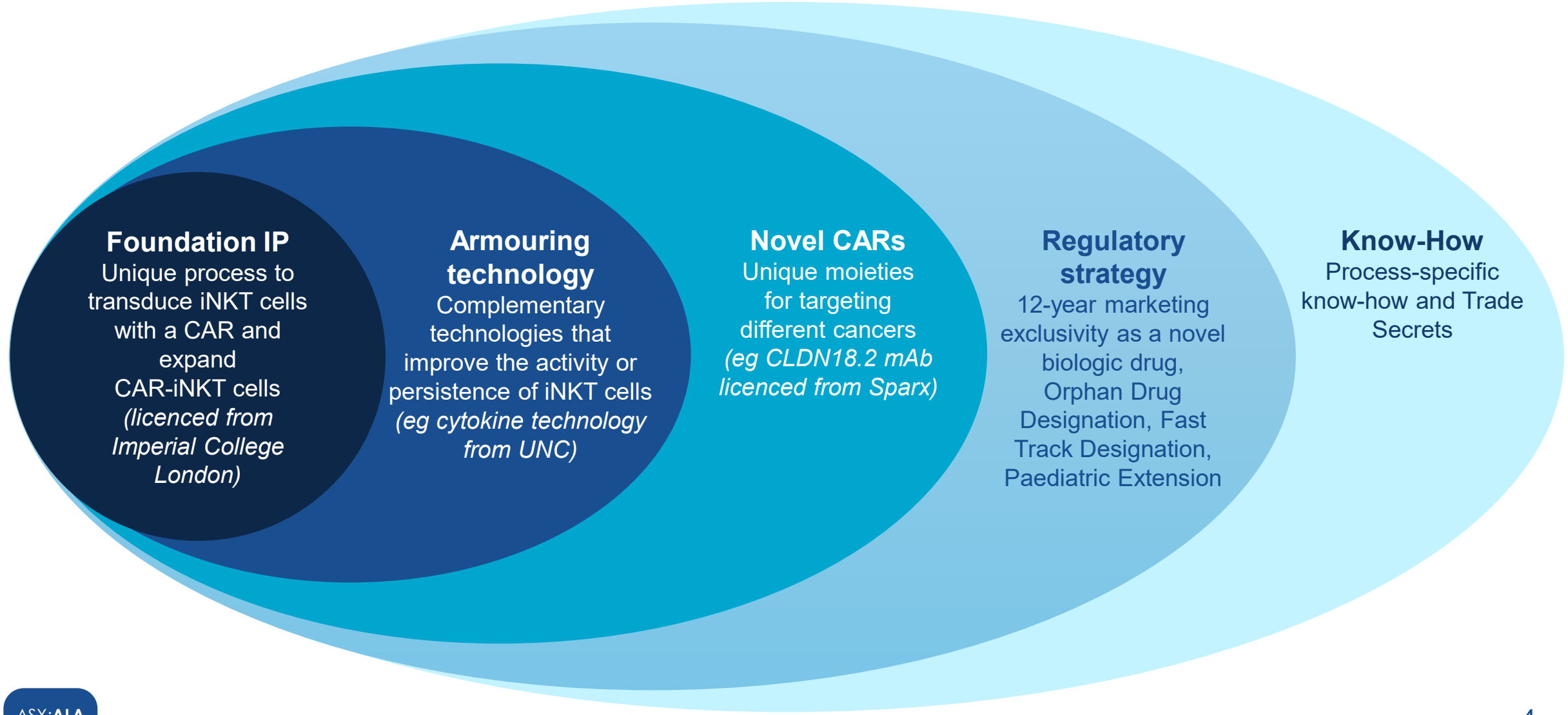
Focused on acquiring innovative technologies that strengthen its cell therapy platform and align with its focus areas

Unique Value Proposition

Arovella is among few companies globally developing an iNKT cell therapy platform

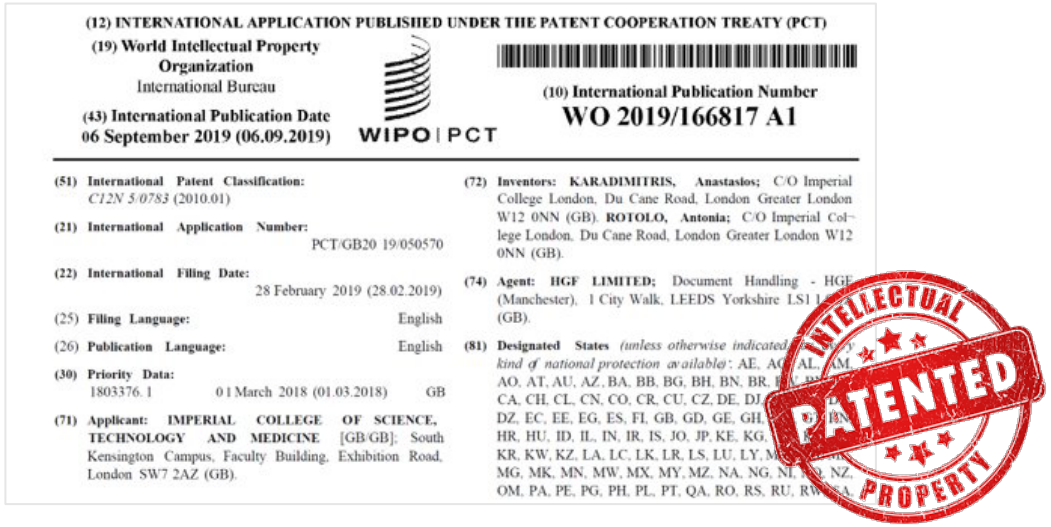
Arovella's iNKT cell strategy

Incorporating world class IP to target a range of tumour types



Exclusive worldwide rights to granted patents

Further patent claims and applications actively being pursued



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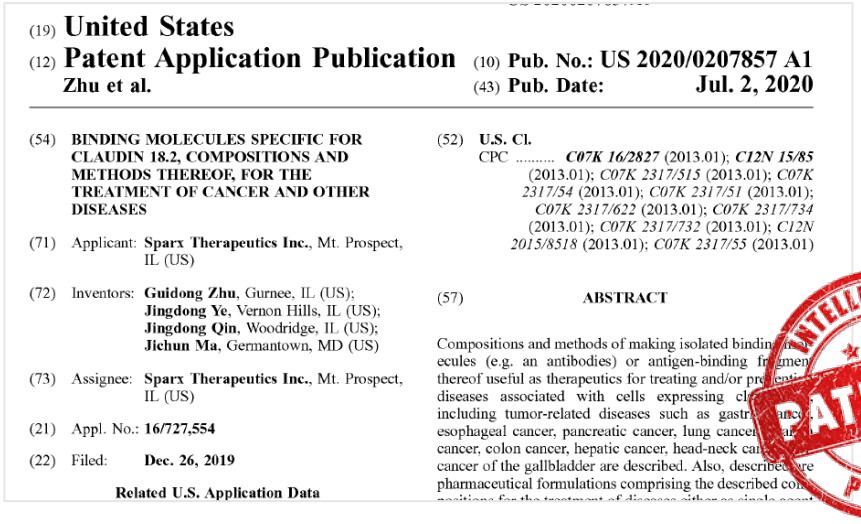
Transduction and Expansion of Cells

- Patent life until 2038
- Method of manufacture, cell population claims
- Applicant: Imperial College of Science Technology and Medicine
- Granted in Europe, Canada and Hong Kong, pending in USA, China and Australia
- Worldwide exclusive rights for human disease



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(54) BINDING MOLECULES SPECIFIC FOR CLAUDIN 18.2, COMPOSITIONS AND METHODS THEREOF, FOR THE TREATMENT OF CANCER AND OTHER DISEASES

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(72) Inventors: **Guidong Zhu**, Gurnee, IL (US); **Jingdong Ye**, Vernon Hills, IL (US); **Jingdong Qin**, Woodridge, IL (US); **Jichun Ma**, Germantown, MD (US)

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(57) ABSTRACT

Compositions and methods of making isolated binding molecules (e.g. an antibodies) or antigen-binding fragments thereof useful as therapeutics for treating and/or preventing diseases associated with cells expressing claudin 18.2, including tumor-related diseases such as gastric cancer, esophageal cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, hepatic cancer, head-neck cancer, and cancer of the gallbladder are described. Also, described are pharmaceutical formulations comprising the described compositions for the treatment of diseases either as single agent

Binding Molecules Specific for Claudin 18.2

- Patent life until 2038
- Composition of matter claims for a unique CLDN18.2 monoclonal antibody sequence
- Applicant: Sparx Therapeutics Inc.
- Granted in USA, pending in Europe, China, Japan and South Korea
- Worldwide exclusive rights for use in Cell Therapies

Strong Leadership

Leadership

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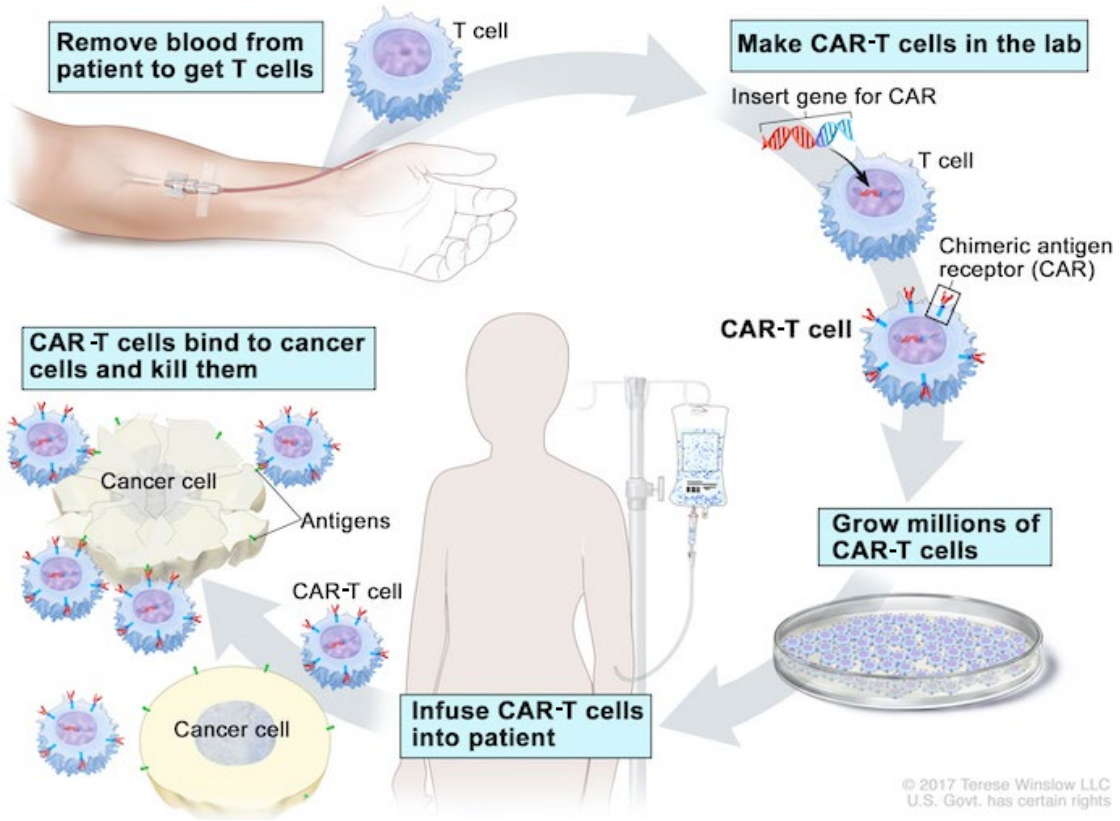
DIRECTOR

About CAR-T cells

How original CAR-T cell therapies work

CAR-T cell therapy is personalised medicine



T cells = immune cell

T cells are a common type of immune cell that fight infections and can help fight cancer.

T cells from patient 'reprogrammed'

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 can recognise cancer cells through a target antigen.

CAR-T cells find & kill tumour cells

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 revolutionised blood cancer treatment

CAR-T cells have demonstrated their curative potential in blood cancers

The Cell Therapy market is expected to reach

$61.2 billion

by 2030[1]

Cure

CAR-T cells have demonstrated ability to **cure haematological cancers**

Strong Sales

40-60%

Patients relapse post-CAR-T therapy[2]

Product	Approval Year	2023 Revenue
YESCARTA (axicabtagene ciloleucel)	2017	US$1498m[3]
KYMRIAH (tisagenlecleucel)	2017	US$509m[4]
Abecma (idecabtagene vicleucel)	2021	US$472m[5]

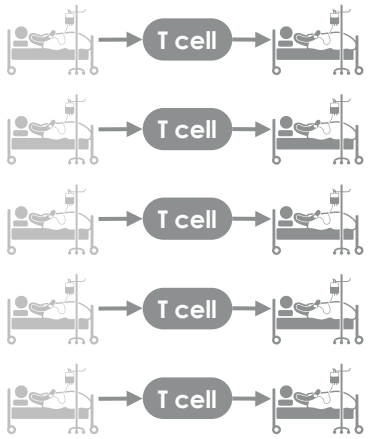
1. *https://www.businesswire.com/news/home/20230529005130/en/Global-Cell-Therapy-Market-Report-2023-Advancements-in-Biotechnology-Drives-Growth---ResearchAndMarkets.com*
2. *Zinzi et al., 2023 Pharmacological Research - 10.1016/j.phrs.2023.106742*
3. *https://www.gilead.com/news-and-press/press-room/press-releases/2024/2/gilead-sciences-announces-fourth-quarter-and-full-year-2023-financial-results#:~:text=Yescarta%C2%AE%20(axicabtagene%20ciloleucel)%20sales,%E2%80%9D)%20outside%20the%20United%20States.*
4. *https://www.novartis.com/sites/novartis_com/files/2024-01-interim-financial-report-en.pdf*
5. *https://news.bms.com/news/details/2024/Bristol-Myers-Squibb-Reports-Fourth-Quarter-and-Full-Year-Financial-Results-for-2023/default.aspx*

Emily Whitehead - **Celebrating 10 years of CAR-T cell therapy**

https://emilywhiteheadfoundation.org/10-years-of-car-t/

Autologous CAR-T pose challenges

The current manufacturing costs and time are limiting



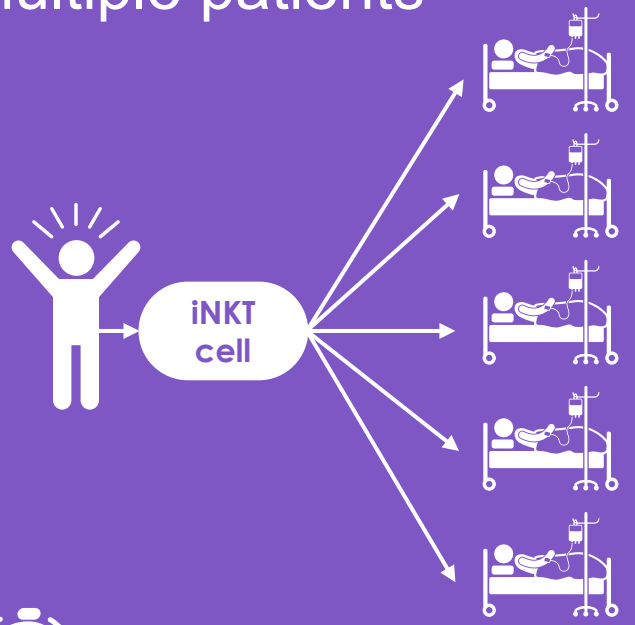
Each manufacturing batch is **patient-specific**

Patient must wait **3-4 weeks** for therapy

- Manufacturing & supply chain **costs are high**
- T cells **can be compromised** due to disease
- **Limited centres** can collect and manufacture
- **Time is an issue** for patients with aggressive disease
- Manufacturing run **failures can occur**

Allogeneic

A single healthy donor batch = treatment for multiple patients

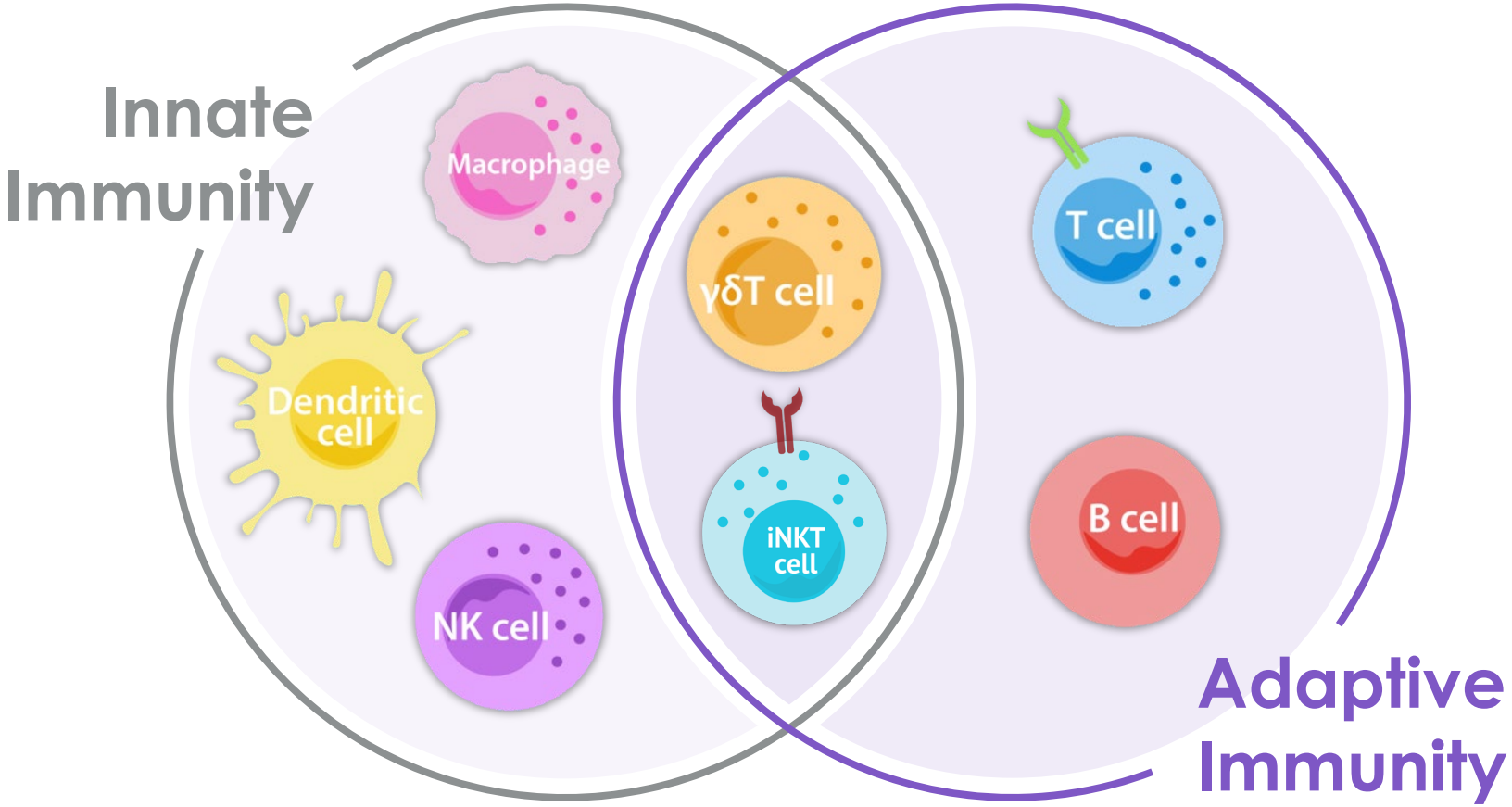


1 week

Patients ready to dose within 1 week

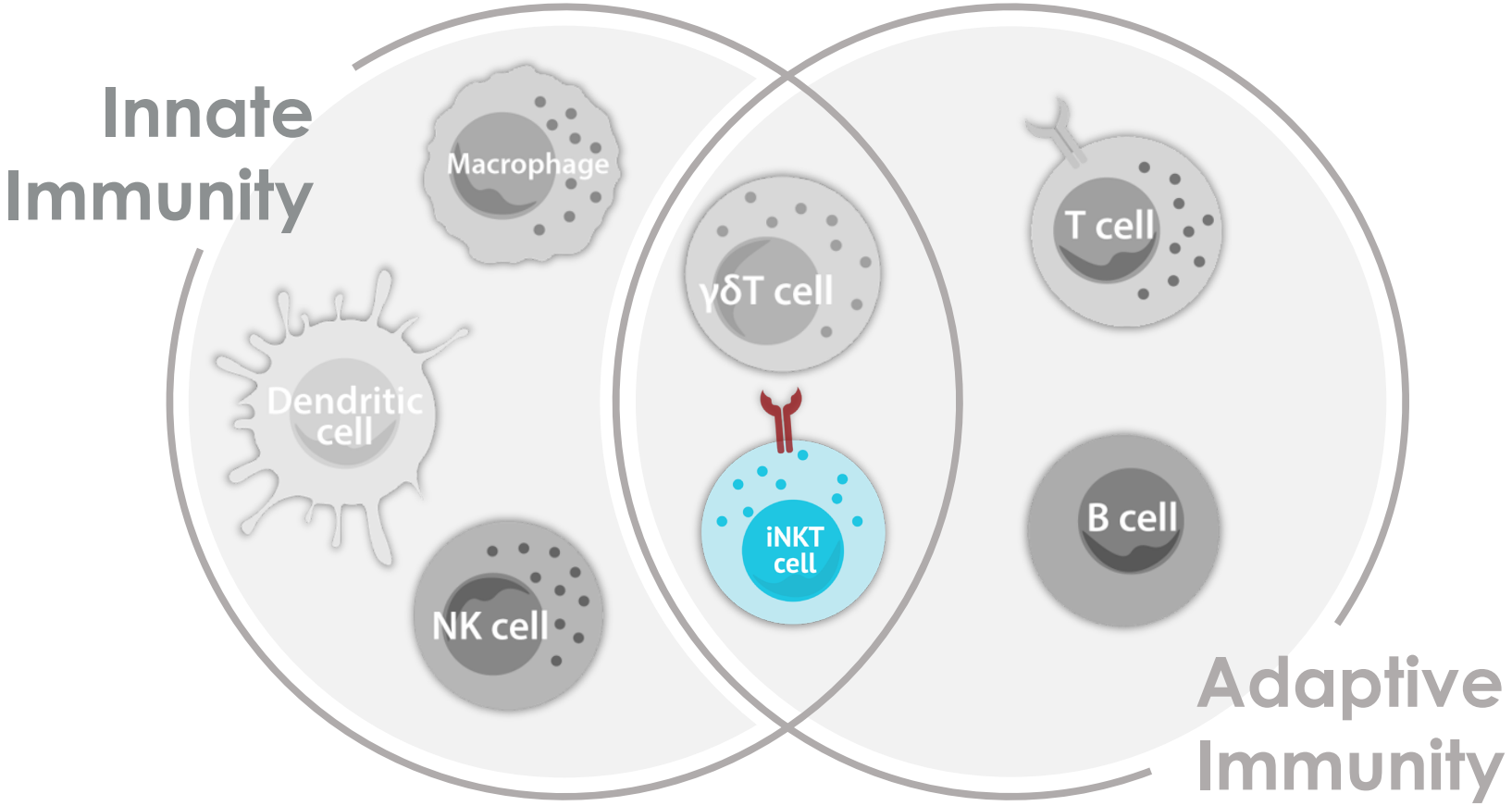
Introducing invariant Natural Killer T (iNKT) cells

Bridging the innate and adaptive immune system



iNKT cells represent a next-generation cell therapy

Properties make them ideal for use in cell therapy



Strong safety profile

- Don't cause graft versus host disease (GvHD)

Front line of the human immune system

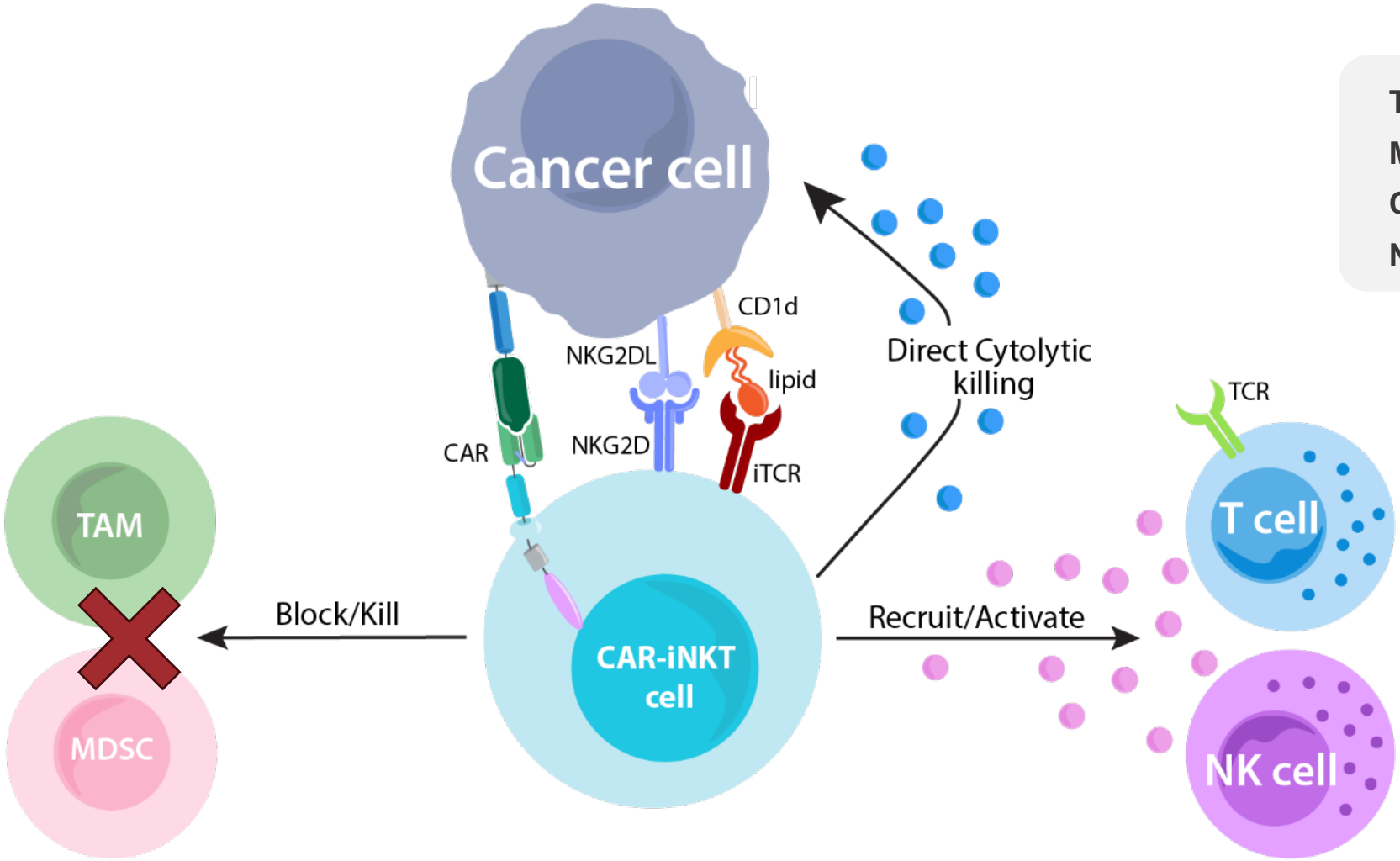
- Bridge innate & adaptive immune responses
- Contain both T cell & NK cell killing mechanisms
- Naturally target & kill cancers that express CD1d

Multiple anti-cancer properties

- Shape the tumour microenvironment by blocking/killing pro tumour cells (TAMs/MDSCs)
- Infiltrate tumours & secrete signaling molecules to activate other immune cells to kill tumour cells

CAR-iNKT cells have multiple ways to kill cancer cells

Also recruit 'good' immune cells and block 'bad' immune cells

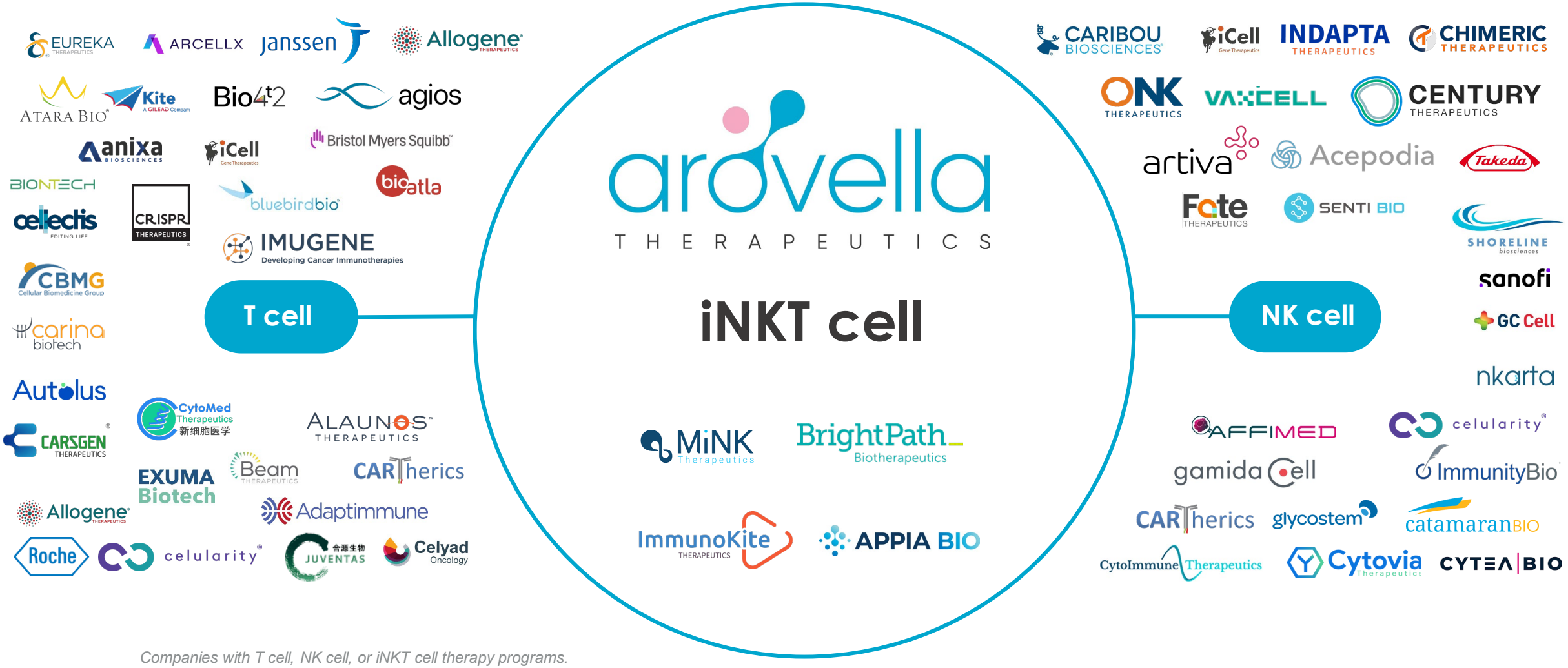


TAM	Tumour Associated Macrophage
MDSC	Myeloid Derived Suppressor Cell
CAR	Chimeric Antigen Receptor
NK	Natural Killer

1. **Via the CAR**
   - Specific target depending on tumour type
2. **Via the NKG2D pathway**
   - NKG2D ligands are upregulated in cancer cells
3. **Via lipid-bound CD1d**
   - Several cancers naturally express CD1d

A differentiated position

T cell and NK cell sectors are competitive



Companies with T cell, NK cell, or iNKT cell therapy programs.
Source: Company analysis based on public information

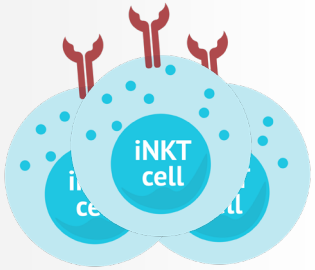
CAR-iNKT cell therapy production advantages

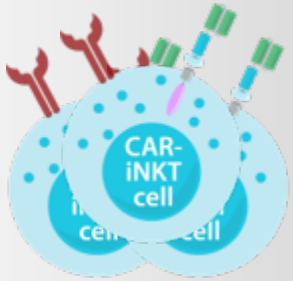
Off-the-shelf manufacturing advantages

MANUFACTURING

Collect Healthy Donor Blood

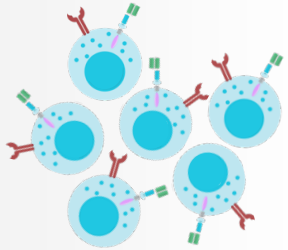
Isolate iNKT cells





Engineer iNKT cells to produce a CAR

Expand to grow billions of CAR-iNKT cells

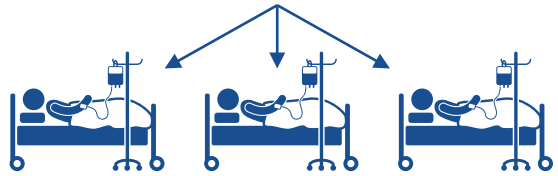


Vial and freeze CAR-iNKT cells

TREATMENT

Thaw CAR-iNKT cells

Dose eligible patients



Healthier starting material
Potentially better efficacy

Scalable manufacturing with reduced costs
Reach more patients

Faster access to treatment
Improved outcomes for aggressive cancers

Removes risk of manufacturing run failure

iNKT cell platform advantages

Efficient expansion of genetically modified cells leads to

multiple doses from a single batch

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

Uses mature iNKT cells from healthy adult donors that **do not require 'reprogramming'**

Transduction performed immediately after isolation of low number of cells, resulting in **reduction in quantity of expensive reagents required**

Maintains **highly cytotoxic** population of iNKT cells

ALA-101 (CAR19-iNKT cells)

A next generation **off-the-shelf** cell therapy for CD19 expressing cancers

CD19+ hematological malignancies

Targeting CD19+ blood cancers

CD19+ lymphomas and CD19+ leukemias

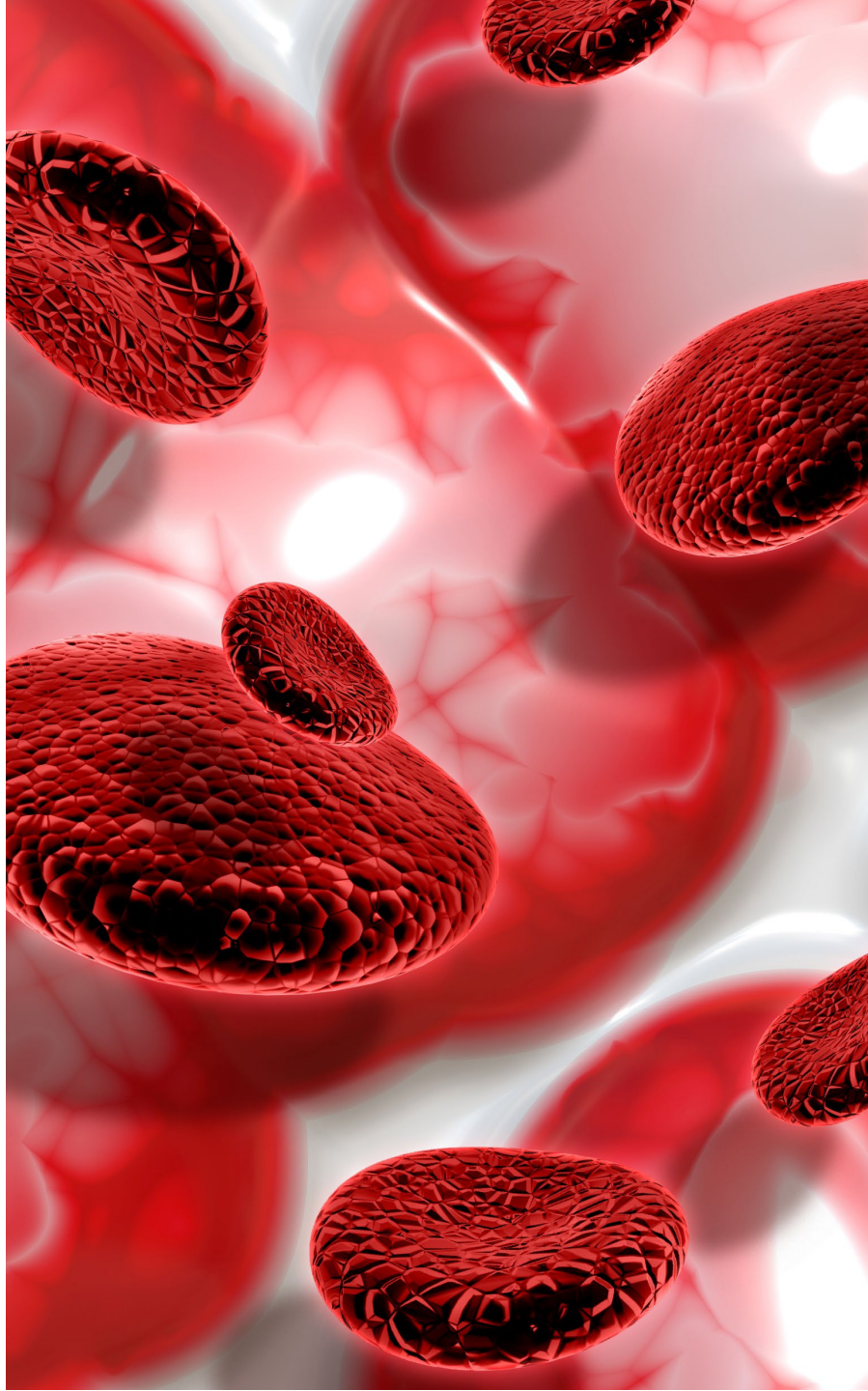
>140k cases in the US in 2023[1,2]

>40k deaths in the US in 2023 [1,2]

CAR-T products are moving to second line therapy

No allogeneic cell therapy approved to date for blood cancers

- Certain sub-types of non-Hodgkin's lymphoma and leukaemia provide opportunities to apply for orphan drug designation



1. https://seer.cancer.gov/statfacts/html/nhl.html; 2. https://seer.cancer.gov/statfacts/html/leuks.html

CAR-T cell therapies pose challenges

Targeting CD19-expressing blood cancers

Current Treatments

Four
approved autologous CAR-T products target CD19

Significant unmet need remains

6-month complete response rate in relapsed refractory DLBCL = **Only 30-35%**

Substantial safety risk = with high rates of CRS, ICANS and infections

DLBCL =Diffuse Large B Cell Lymphoma; CRS = Cytokine Release Syndrome; ICANS = Immune Effector Cell Associated Neurotoxicity Syndrome

ALA-101 Solution

Off-the-shelf
iNKT cell therapy that targets CD19 expressing cancer cells

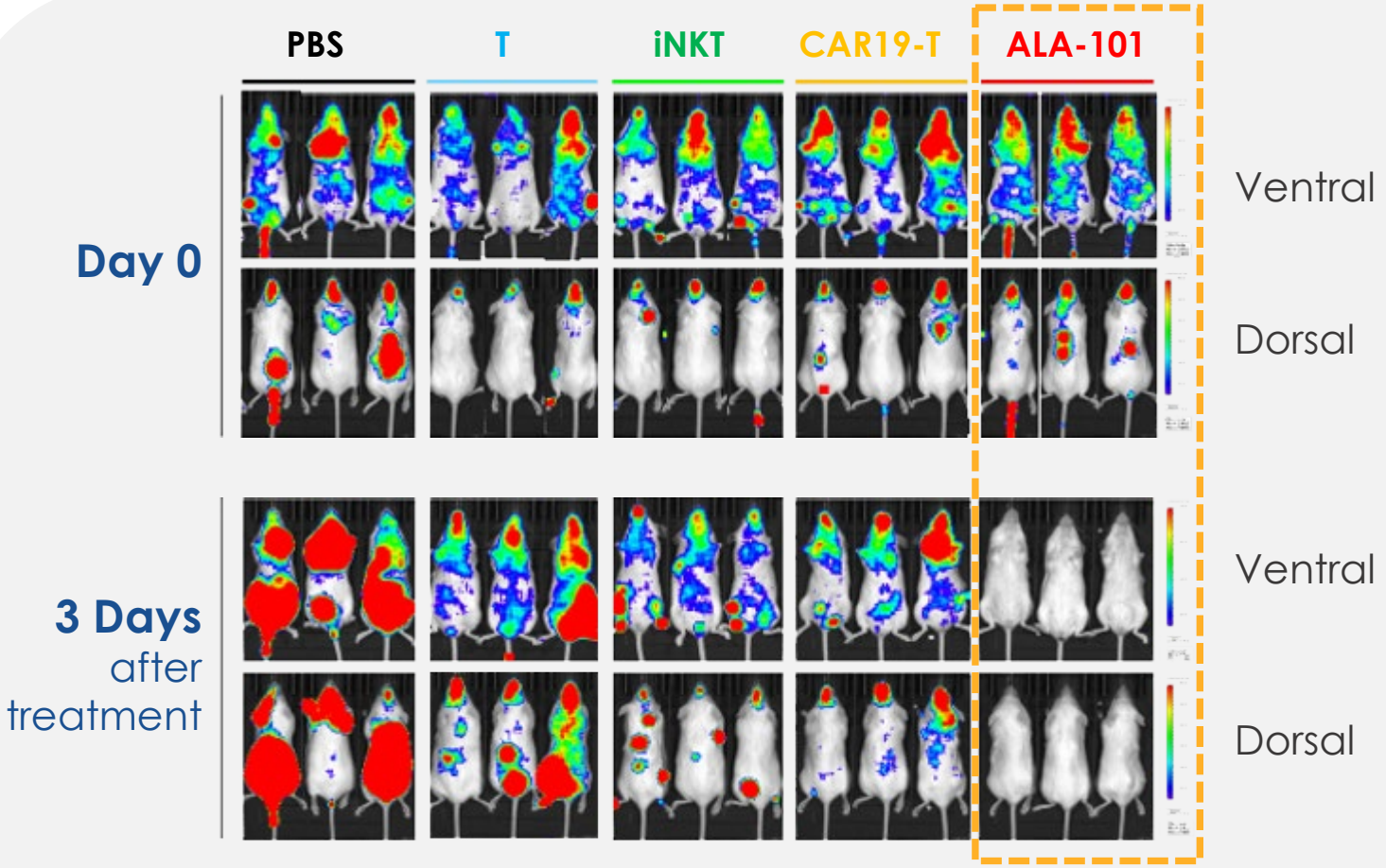
Attractive potential treatment
For B cell Lymphomas and Leukaemias

Clinical trial 2024
Phase 1 clinical trial in non-Hodgkin's lymphoma expected to commence in 2024

ALA-101: enhanced tumour killing *in vivo*

ALA-101 rapidly eradicates tumour cells in mice

- Tumour cells expressing **CD19** and **CD1d** were intravenously delivered into mice
- Mice were treated with:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - ALA-101 (CAR19-iNKT cells)
- After three days, ALA-101 resulted in significant regression of tumour cells
- In all other treatments, there was strong tumour cell persistence
- ALA-101 displays swift action

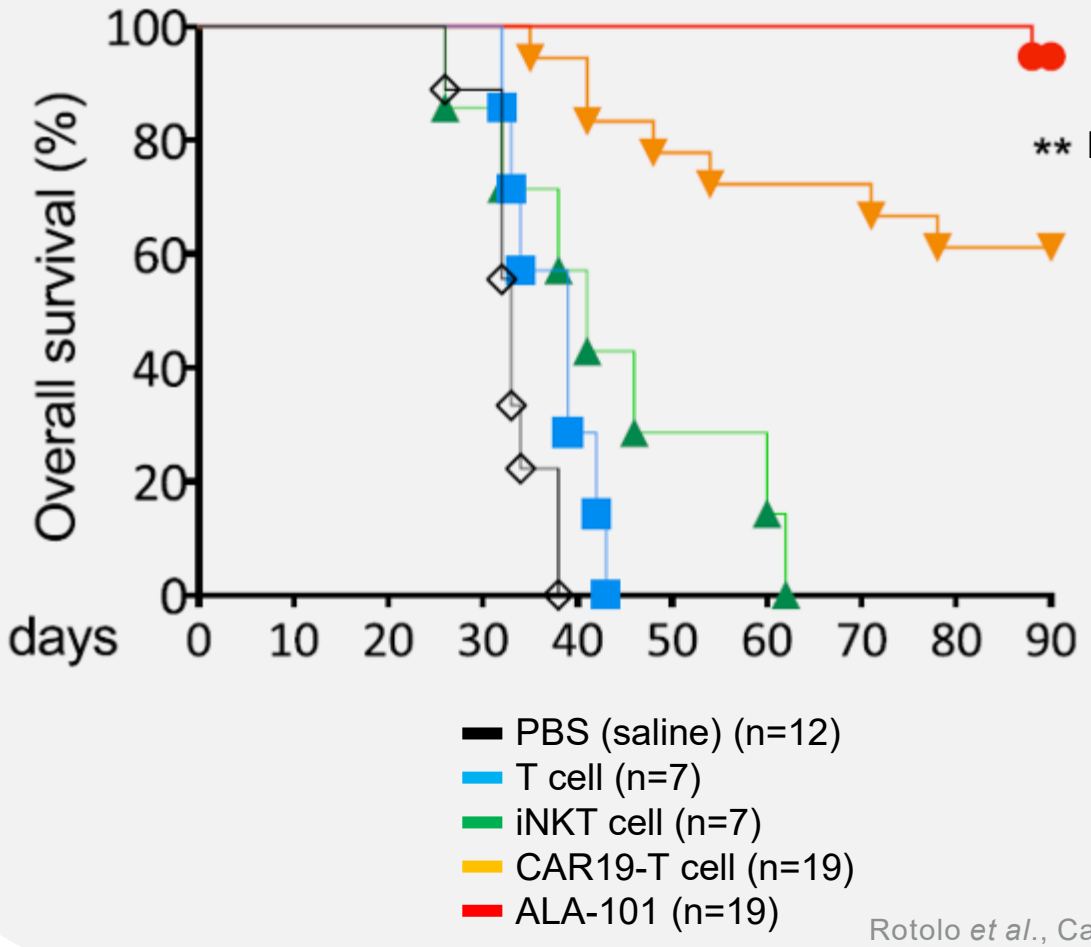


Rotolo *et al.*, Cancer Cell (2018)

ALA-101: next generation cell therapy

ALA-101 significantly increased survival in mice versus treatment with CAR19-T cells

- Tumour cells expressing **CD19** and **CD1d** were intravenously delivered into mice
- Mice were treated with:
  - PBS (saline)
  - Unmodified T cells (T)
  - Unmodified iNKT cells (iNKT)
  - CAR19-T cells
  - ALA-101 (CAR19-iNKT cells)
- After 90 days, only mice treated with CAR19-T cells or ALA-101 remained alive
- 1.5x more mice treated with ALA-101 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

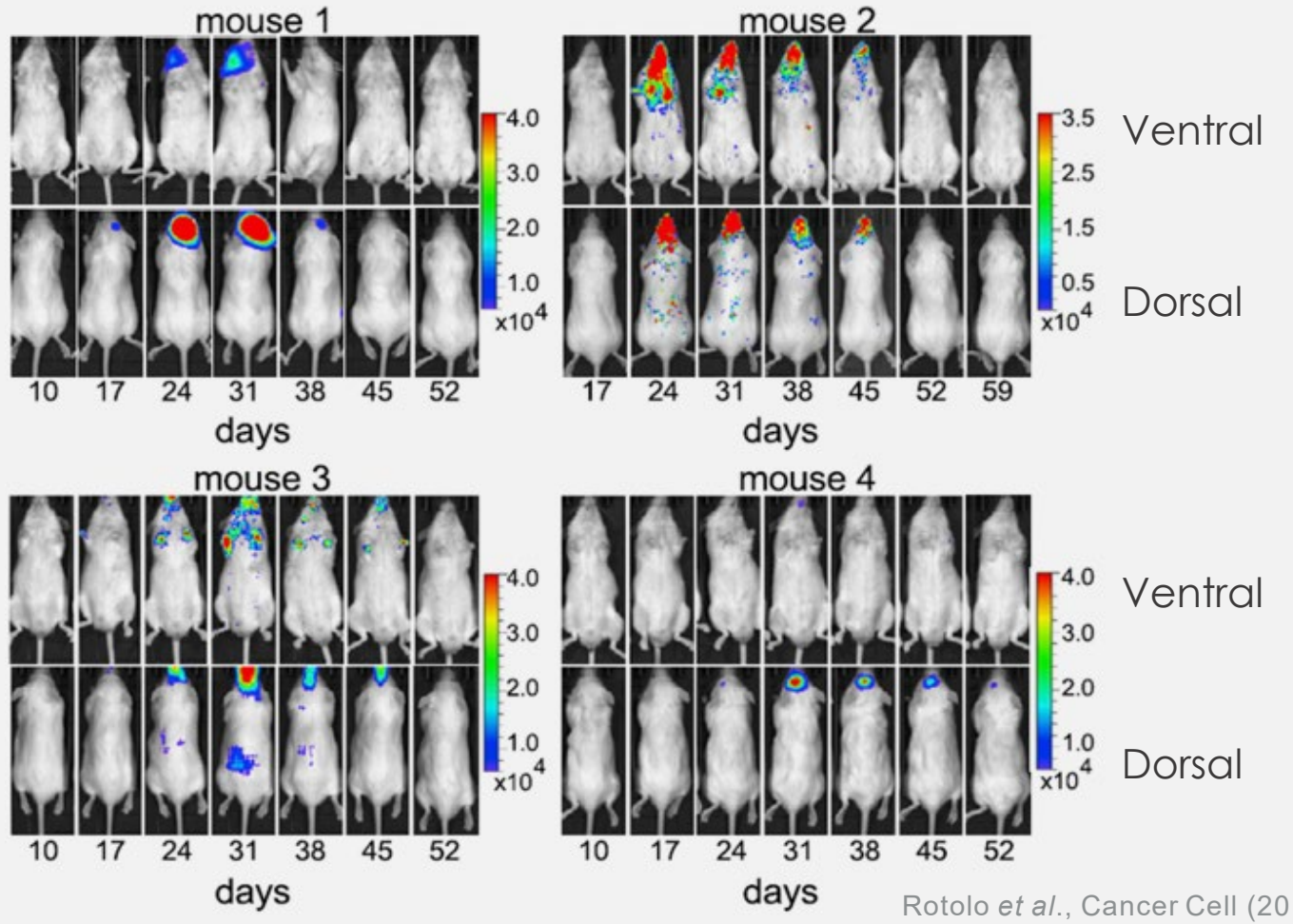


Rotolo *et al.*, Cancer Cell (2018)

ALA-101: spontaneous secondary remission

ALA-101 activity may persist to eradicate tumour cells following relapse

- Four mice treated with ALA-101 had the cancer return to the brain
- In all four mice, the cancer was eliminated a second time with no additional dosing
- This provides evidence that CAR19-iNKT cells can survive 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)

Progress towards first-in-human clinical trials

ALA-101 data confirms activity and off-the-shelf capability

Potent antitumour activity

Demonstrated efficacy of ALA-101 against CD19+ lymphomas and leukemias. Proof-of-concept data with clinical-designed lentiviral vector in animal models using thawed, “off-the-shelf” ALA-101.

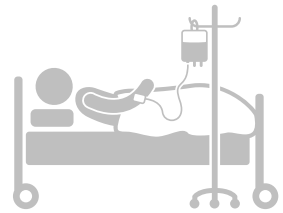
Expected to be safe

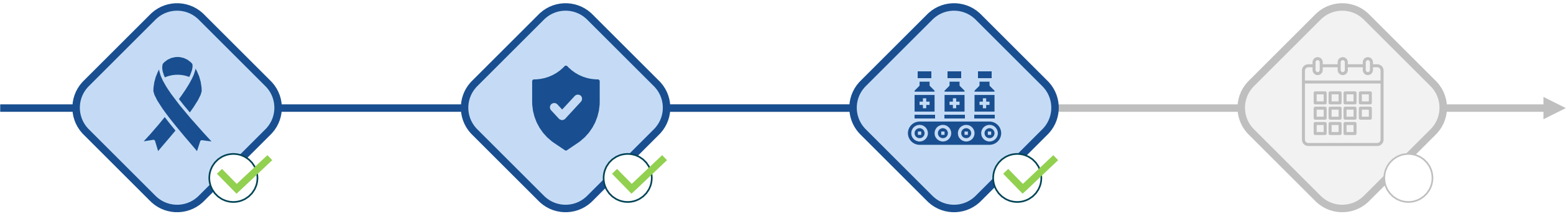
iNKT cells have been shown in clinical trials not to cause graft versus host disease (GvHD) and the CD19 targeting CAR (FMC63) is a validated targeting agent in approved cell therapies.

Multiple dose manufacturing

ALA has demonstrated that its manufacturing process can produce a high number of CAR+ cells with potent cell killing properties and has completed production of GMP-grade lentivirus for CD19 CAR expression.

Phase 1 clinical trial anticipated CY 2024





iNKT cells to target solid tumours

Arovella is implementing its strategy to target and kill solid tumours – 90% of newly diagnosed cancer cases[1]

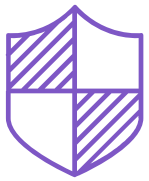
1. *https://www.cancer.gov/types/common-cancers*

Arovella's strategies to combat solid tumours

Arovella is using three approaches to expand the iNKT cell platform into solid tumours

License novel cancer targets

Identify and license new targets that are expressed in multiple cancers to incorporate into Arovella's iNKT cell therapy platform



Armour iNKT cells

Enhance the performance of iNKT cells by equipping iNKT cells with novel armouring technologies

Create unique partnerships

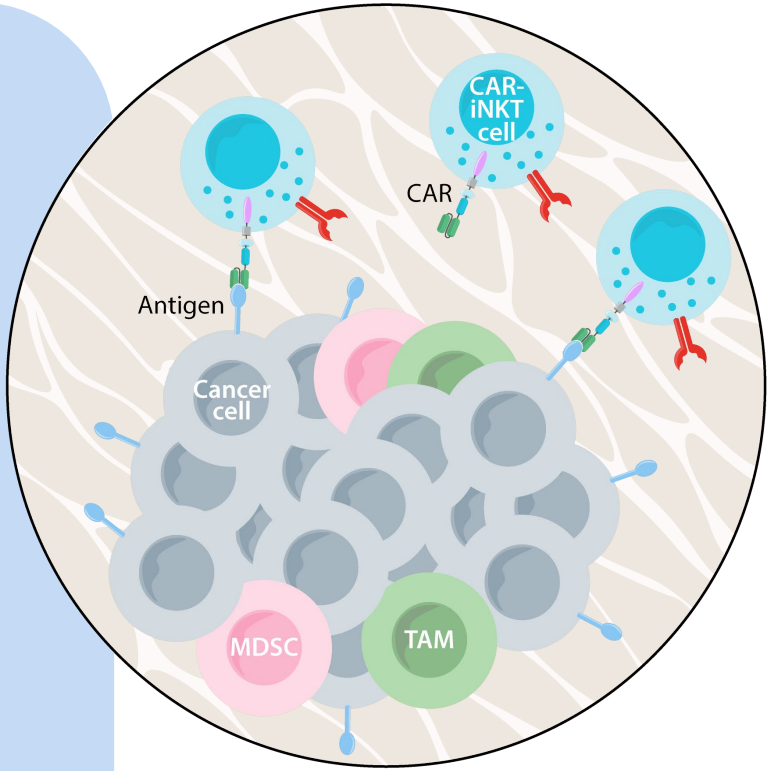
Create partnerships to use novel combination therapies with synergistic effects

Solid tumours pose challenges to cell therapies

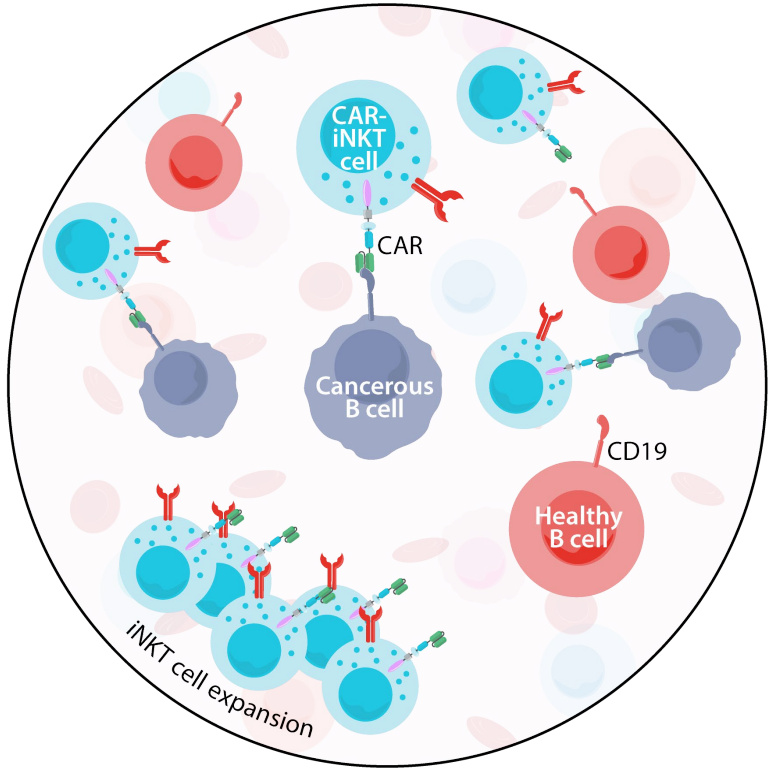
Solid tumours are more

difficult to treat with cell therapies

- Access to tumour
- Antigen specificity and uniformity
- Tumour microenvironment contains cells that support cancer cell growth



Solid tumour



Blood cancer

iNKT cells:

- Home to tissues and infiltrate tumours
- Modify the TME to block or kill cells that promote tumour growth and recruit helpful immune cells

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

Add additional CARs for novel targets

STRATEGY 1

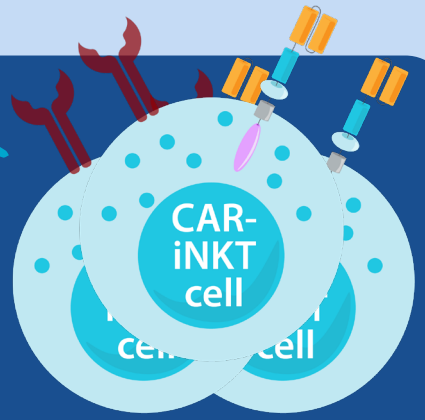
Arovella's manufacturing process can be leveraged for multiple cancer types

MANUFACTURING

CARs targeting novel antigens specific for solid tumours

can be incorporated into iNKT cells

using the same manufacturing process



New lentiviral vector generated for each new CAR

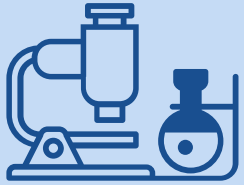
Introducing Claudin 18.2 (CLDN18.2)

A promising solid tumour target

CLDN18.2 overexpression has been

identified in several types of cancers

- gastric cancer **(GC)**
- gastroesophageal junction cancer **(GEJC)**
- pancreatic cancer **(PC)**
- esophageal cancer **(EC)**
- ovarian adenocarcinoma **(OAC)**
- lung cancers **(LC)**



Validated target

with first monoclonal antibody expected to be **approved in 2024**

Gastric cancer

market alone expected to reach **$10.7 billion** by 2031[1]

1. https://www.alliedmarketresearch.com/gastric-cancer-market-A74458#:~:text=The%20global%20gastric%20cancer%20market,cells%20lining%20of%20the%20stomach

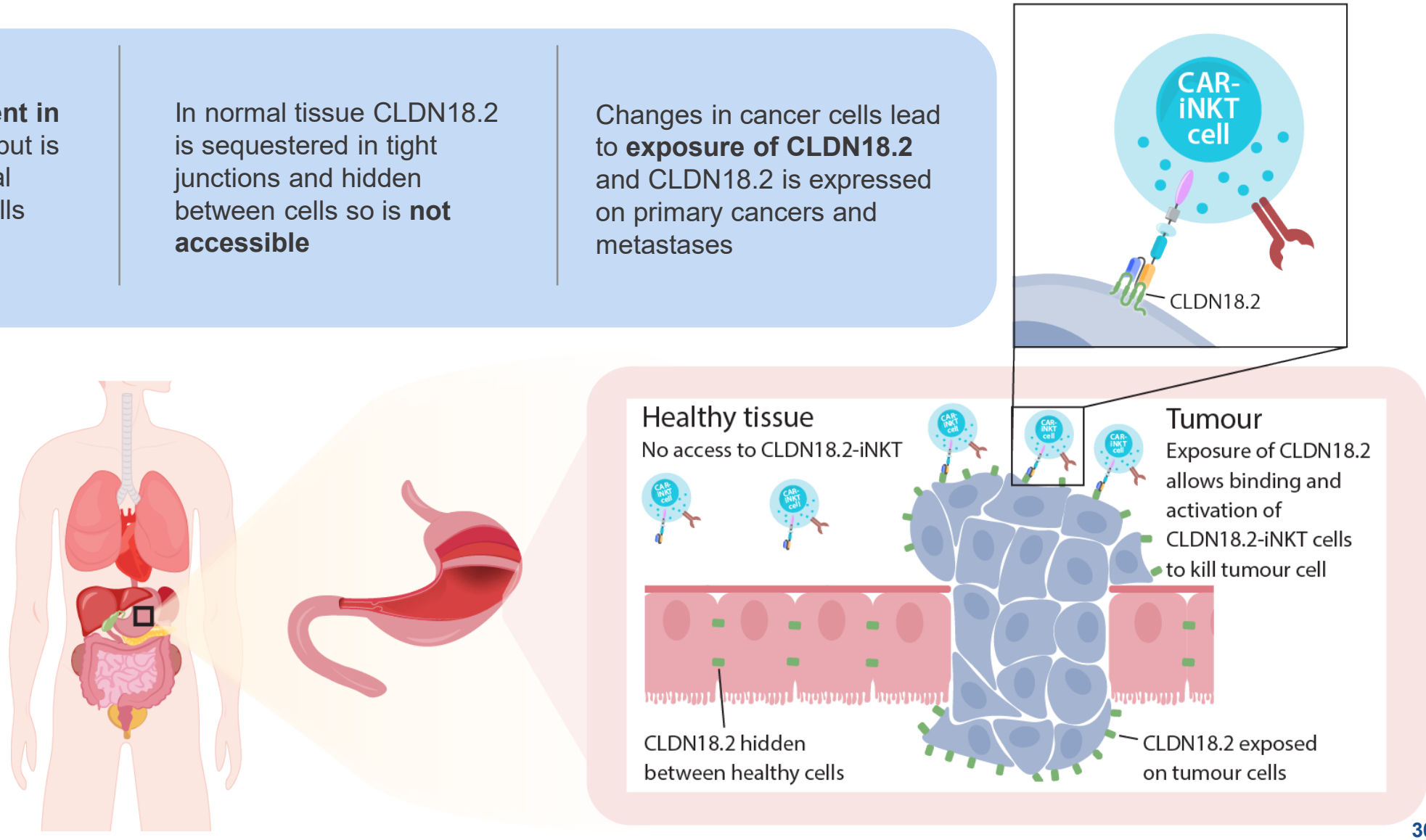
CLDN18.2 is a validated target

CLDN18.2 is hidden in healthy tissues and exposed on tumour cells

CLDN18.2 is **not present in most healthy tissues** but is found in gastric mucosal membrane epithelial cells (lining of GI tract)

In normal tissue CLDN18.2 is sequestered in tight junctions and hidden between cells so is **not accessible**

Changes in cancer cells lead to **exposure of CLDN18.2** and CLDN18.2 is expressed on primary cancers and metastases

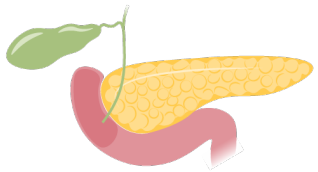


Targeting tumours of high unmet need

CLDN18.2 is found in a high proportion of gastric and pancreatic cancers

Gastric Cancer

>1,000k cases per annum globally[1]	**770k deaths** per annum globally[1]	**~6-33%** Regional and distant 5-year survival[2]	**4th highest** cause of cancer death annually[1]



Pancreatic Cancer

496k cases per annum globally[3]	**466k deaths** per annum globally[3]	**~3-15%** Regional and distant 5-year survival[4]	**No effective standard of care** For late-stage diagnosis

1. Morgan et al 2022 eClinicalMedicine - 10.1016/j.eclinm.2022.101404; 2. https://www.cancer.org/cancer/types/stomach-cancer/detection-diagnosis-staging/survival-rates.html; 3. Sung et al 2021 - 10.3322/caac.21660; 4. https://www.cancer.org/cancer/types/pancreatic-cancer/detection-diagnosis-staging/survival-rates.html

A Claudin 18.2 mAb is effective in gastric cancer

The mAb, zolbetuximab, is expected to be approved in Q1 2024

Zolbetuximab
completed phase 3

and is expecting **approval in 2024**

FDA granted
Priority Review Biologics License Application (BLA)

Priority Review **only granted for major advances in therapy** or where no adequate therapy exists

FDA

2.4 months increase
in overall survival

relative to standard of care in phase 3 study for gastric and gastroesophageal junction cancers*

Astellas acquired zolbetuximab

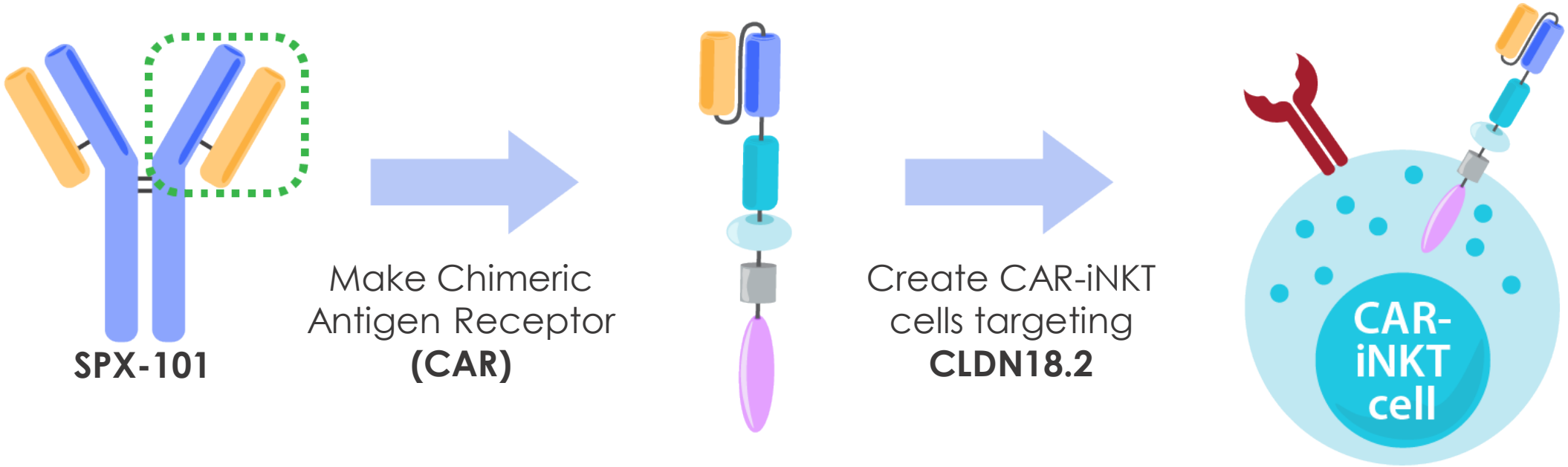
through the **acquisition of Ganymed in 2016** for an upfront payment of **€422 million** and milestones of **€860 million** and

expects peak sales of US $0.65-$1.3 billion

*Increase in progression free survival from 8.67 months to 10.61 months and overall survival from 15.54 to 18.23 months for zolbetuximab plus chemotherapy vs chemotherapy alone

Leverage the mAb to create CLDN18.2-CAR-iNKT cells

Cell therapies generally expected to have better efficacy than mAbs

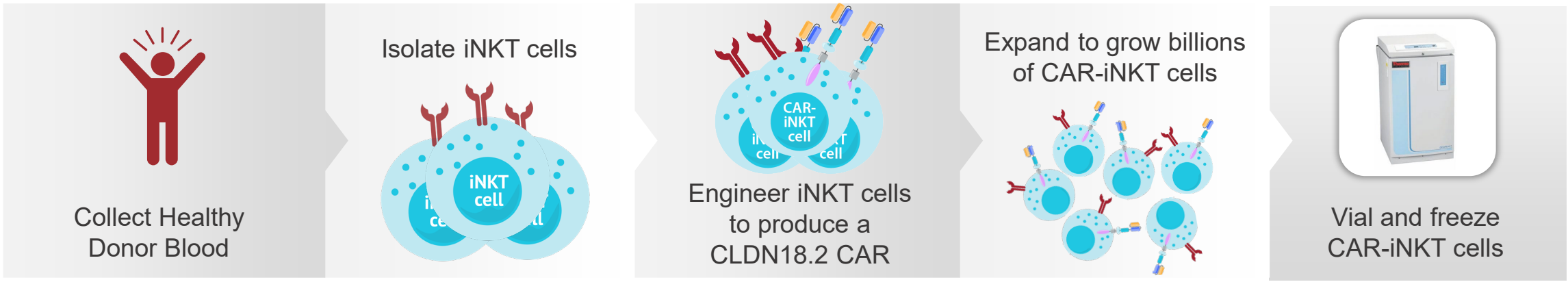


- The CLDN18.2-binding domain of SPX-101 will be used to create a CAR and incorporated into the iNKT cell platform
- This will be the **first off-the-shelf CAR-iNKT cell product targeting CLDN18.2**
  - An autologous CLDN18.2 CAR-T product is in Phase 1 and has demonstrated promising data

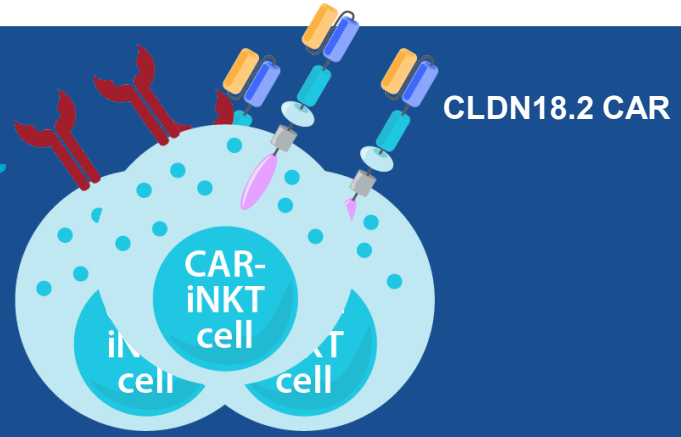
Manufacturing CLDN18.2-iNKT cells

Generation of CLDN18.2-iNKT cells will leverage existing manufacturing process

MANUFACTURING



Arovella will use its **proprietary manufacturing process** to create CLDN18.2-iNKT cells

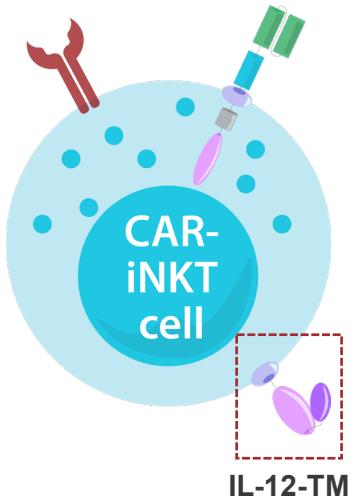


“Armouring” CAR-iNKT cells

STRATEGY 2

IL-12-TM (cytokine technology) enhances CAR-iNKT cell activity in solid tumours

IL-12-TM



IL-12-TM

IL-12-TM is a modified version of IL-12

with a membrane anchor that links it to the surface of CAR-iNKT cells. By linking it to the surface of iNKT cells, it can enhance CAR-iNKT cells without being released into the blood stream making it safer.

The IL-12-TM is incorporated into the lentiviral vector and system and

does not require changes to the manufacturing process

iNKT cells + IL-12-TM

Expand more and survive for longer
than CAR-iNKT cells lacking the cytokine

10x more circulating CAR-iNKT cells
4 weeks after treatment in a mouse model

Superior anti-tumour activity
compared to CAR-iNKT cells lacking the cytokine

The technology has been published in the prestigious, peer reviewed journal **Nature Communications**

nature › nature communications › articles › article

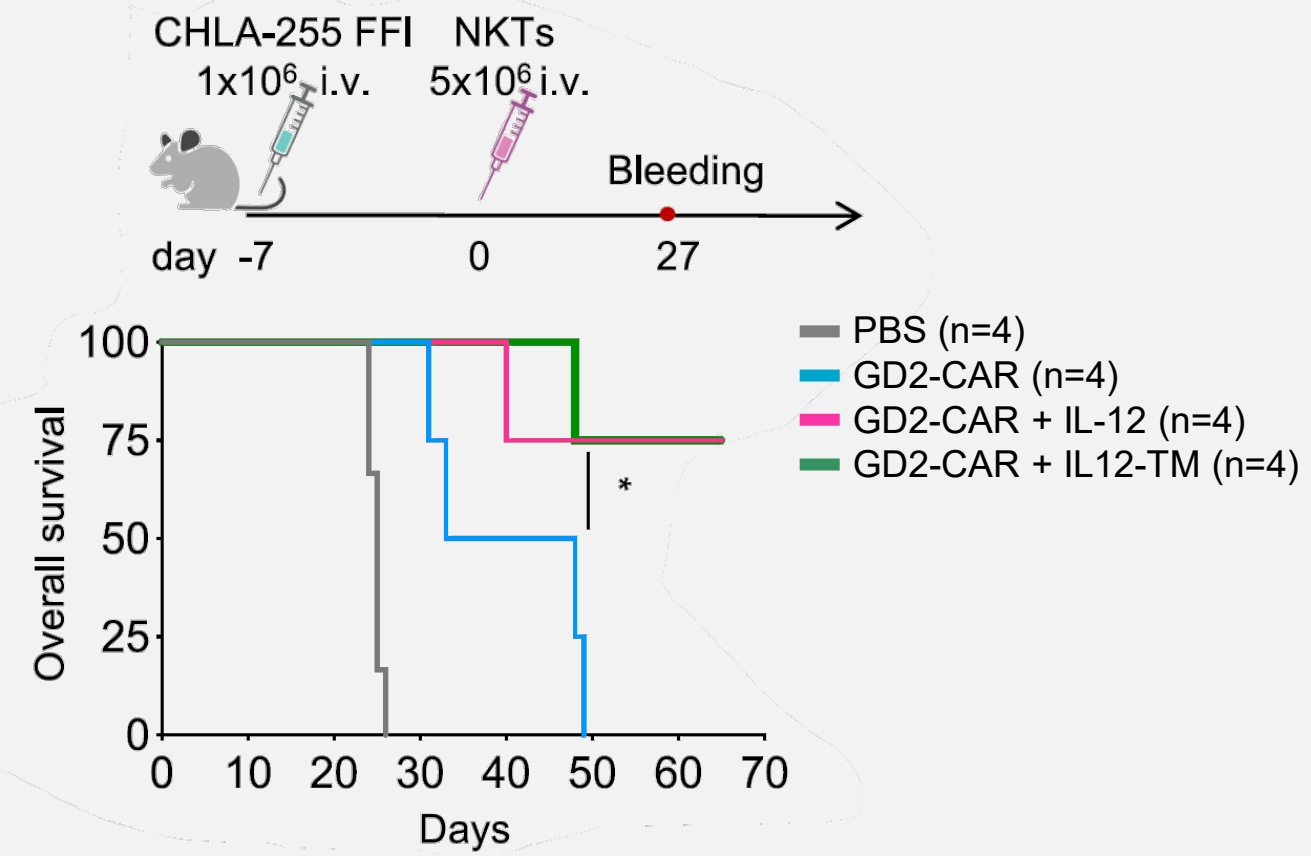
Article | Open access | Published: 02 January 2024

IL-12 reprograms CAR-expressing natural killer T cells to long-lived Th1-polarized cells with potent antitumor activity

Key benefits of IL-12-TM for CAR-iNKT cells

IL-12-TM enhances antitumor activity of CAR-iNKT cells

- Tumour cells expressing GD2 and were intravenously delivered into mice before treatment with CAR-iNKT cells
- Mice were treated with:
  - PBS (saline)
  - GD2-CAR
  - GD2-CAR + IL-12
  - GD2-CAR + IL-12-TM
- After 60 days, only mice treated with GD2-CAR + IL12 or IL-12-TM remained alive
- IL-12-TM enhances CAR-iNKT cell numbers and antitumour activity

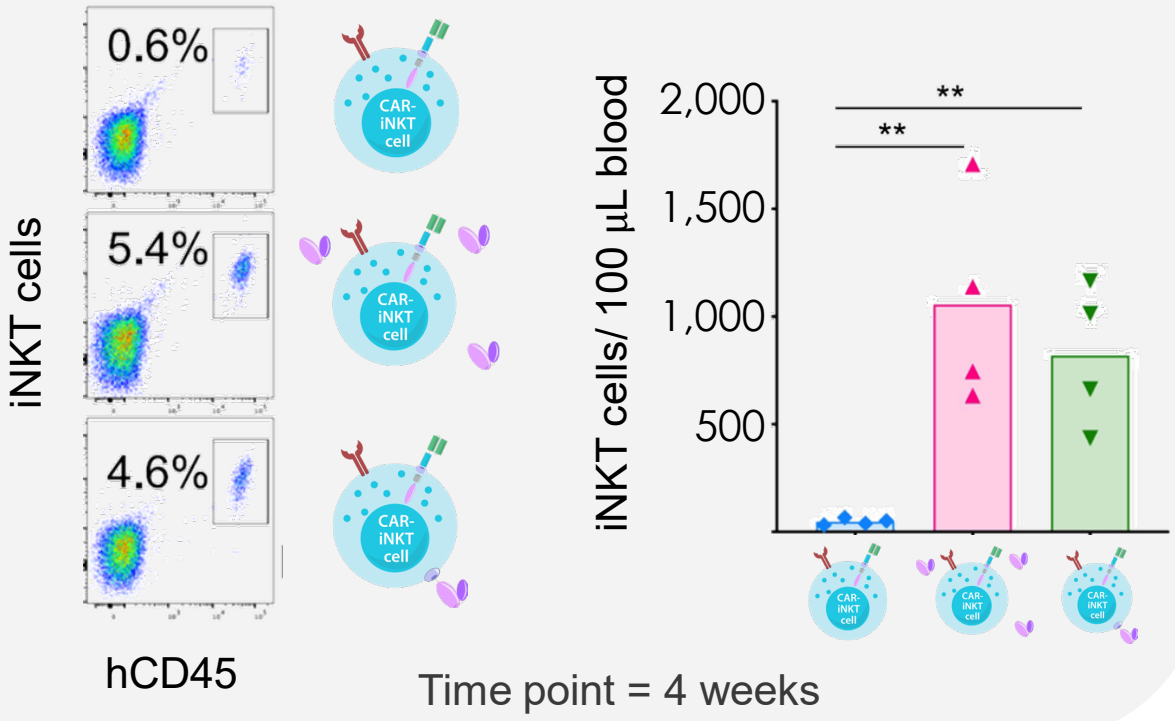


Landoni *et al.*, Nature Communications (2024)

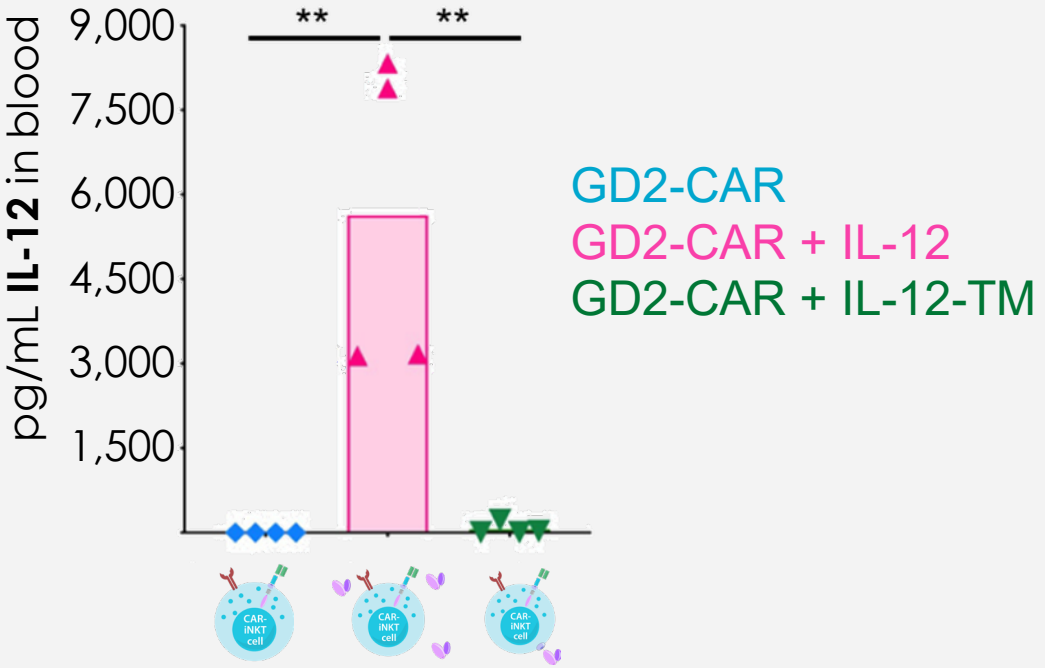
Key benefits of IL-12-TM for CAR-iNKT cells

IL-12-TM increases CAR-iNKT cell numbers and does not get released into the bloodstream

Increased CAR-iNKT cell numbers



IL-12-TM is not released from CAR-iNKT cells



Landoni *et al.*, Nature Communications (2024)

Key benefits of IL-12-TM for CAR-iNKT cells

We expect IL-12-TM to enhance Arovella's CAR-iNKT cell platform

Increases CAR-iNKT cell numbers

IL-12-TM prolongs persistence of CAR-iNKT cells. Cells continue to proliferate and increase in number.

IL-12-TM is not released from CAR-iNKT cells

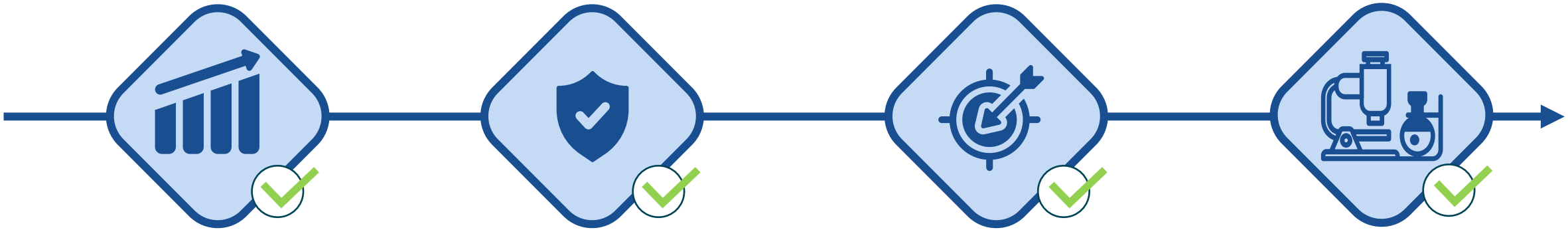
IL-12-TM is not released from CAR-iNKT cells and is expected to be safer than secreted IL-12.

Enhances CAR-iNKT cell antitumour activity

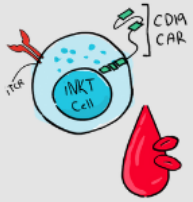
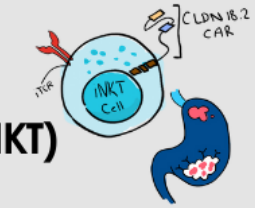
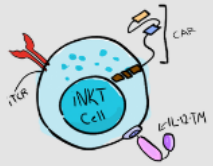
IL-12-TM enhances CAR-iNKT antitumor activity against solid tumour cancers like neuroblastoma

Integrates with existing manufacturing process

IL-12-TM incorporated into lentiviral vector and does not require changes to manufacturing process



Arovella's expanding pipeline

PRODUCT	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1
ALA-101 (CAR19-iNKT) 	CD19 Expressing cancers	CD19 Expressing Lymphoma		
ALA-105 (CLDN18.2-iNKT) 	CLDN18.2 positive solid tumours	Gastric & Pancreatic Cancers		
IL-12-TM 	Solid Tumours	Solid Tumours		

Financial overview

Financial Snapshot

ASX CODE	ALA
Market capitalisation[1]	$160.7 million
Shares on issue	918.04 million
52-week low / high[1]	$0.029 / $0.185
Cash Balance (Dec 31 2023)	$4.76 million

Major Shareholders

Shareholder	Ownership (%) [1]
THE TRUST COMPANY (AUSTRALIA) LIMITED	55,316,926 (6.03%)
RICHARD JOHN MANN	50,905,657 (5.55%)
UBS NOMINEES PTY LTD	20,620,196 (2.25%)
BLACKBURNE CAPITAL PTY LTD	17,637,456 (1.92%)
DYLIDE PTY LTD	15,666,666 (1.71%)

1. *As of 23 February 2024*

Upcoming milestones for 2024

	January 2024	July 2024	December 2024
ALA-101 (CD19)	▪ Complete cGMP manufacture for Phase 1 clinical trials ▪ Complete preparatory activities for Phase 1 study, including preparation of regulatory dossier, engagement with clinical sites and KOLs	▪ Commence Phase 1 for ALA-101 targeting CD19+ lymphoma and leukemia	
ALA-105 (CLDN18.2)	▪ Initiate proof-of-concept testing for CLDN18.2-iNKT cells to expand iNKT platform for treatment of solid tumours ▪ Optimise the CAR construct for robust efficacy	▪ Generate animal data for CLDN18.2 targeting CAR-iNKT cells against gastric cancer and/or pancreatic cancer ▪ Commence activities to manufacture ALA-105 for clinic (e.g. lentiviral vector)	
iNKT Cell Therapy Platform	▪ Integrate IL-12-TM into solid tumour programs and test its efficacy in anti-tumour models ▪ Enter into a Sponsored Research Agreement (SRA) with Professor Gianpietro Dotti's research group		

Expect to advance ALA-101 to Phase 1 first-in-human clinical trial during 2024

Dose escalation Phase 1 study in patients with CD19+ blood cancers

cGMP – Current Good Manufacturing Practice; KOLs – key opinion leaders

Summary

Novel allogeneic CAR-iNKT cell platform

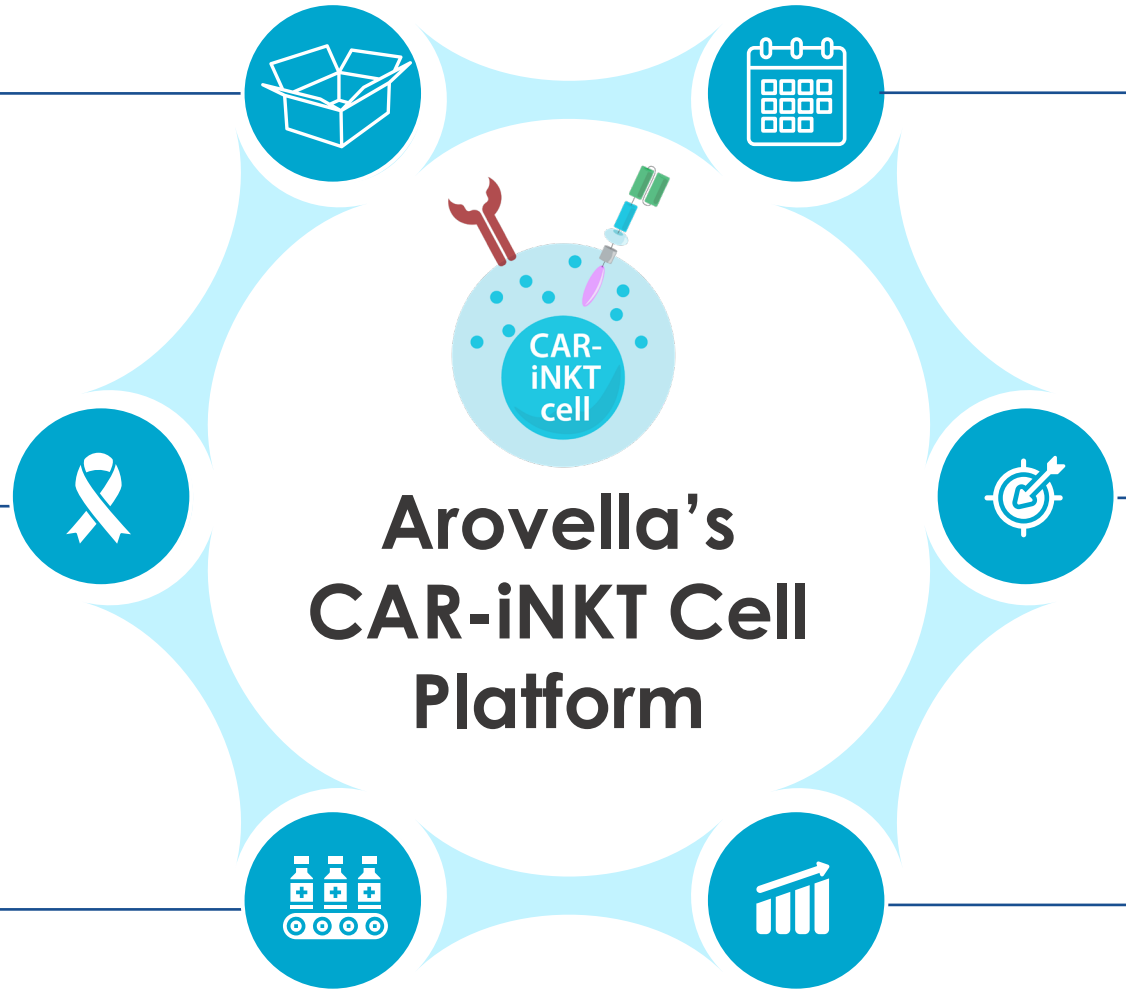
iNKT cells serve as an excellent platform to develop allogeneic, or “off-the-shelf”, cell therapies to treat cancer

Improved manufacturing logistics

Allogeneic CAR-iNKT cells will significantly improve logistics and increase patient access

CAR-iNKT cells have multiple anticancer properties

CAR-iNKT cells have multiple anti-cancer properties that may support enhanced efficacy over other immune cell types



Lead product progressing to clinical trials

ALA-101, a potential treatment for CD19-expressing blood cancers, is being progressed to Phase 1 clinical trials, expected to commence in 2024

Arovella has an expanding pipeline

Arovella continues to expand the iNKT cell platform to potentially treat solid tumours

Arovella is poised for growth

Arovella is developing a cutting-edge CAR-iNKT cell therapy platform, with an expanding pipeline and a strong leadership team

ASX:**ALA**

arovella
THERAPEUTICS

Thank You

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CEO & Managing Director

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