

ASX Release

30 January 2024

AROVELLA ENHANCES SOLID TUMOUR PIPELINE BY LICENSING NOVEL CAR-INKT CELL ARMOURING TECHNOLOGY

- Arovella has entered into a global, exclusive license with University of North Carolina Lineberger Comprehensive Cancer Center to incorporate a novel armouring cytokine technology (IL-12-TM) for its CAR-iNKT cell platform
- Arovella is the only company globally developing IL-12-TM armoured CAR-iNKT cells
- This armouring cytokine technology:
 - results in a ten-fold increase in circulating CAR-iNKT cell numbers in animal models for solid tumours
 - o significantly improved CAR-iNKT anti-tumour activity
 - o significantly improved overall survival in animal models
 - enhances CAR-iNKT cells to potentially treat a range of solid tumour types
- Patent applications filed to protect the technology until at least 2043
- Investor webinar is scheduled for 11 am AEDT on Wednesday, 31st January. <u>Please register here.</u>

MELBOURNE, AUSTRALIA 30 January 2024: Arovella Therapeutics Ltd (ASX: ALA) has signed a global, exclusive License Agreement with the University of North Carolina Lineberger Comprehensive Cancer Center (UNC Lineberger) to incorporate UNC Lineberger's novel IL-12-TM (cytokine technology) into Arovella's CARiNKT cell therapy platform. The technology was developed by Professor Gianpietro Dotti, a pioneer of CARiNKT cells, and was recently published in the prestigious peer-reviewed journal Nature Communications.¹

Arovella's CEO and MD, Dr Michael Baker, commented: "We are incredibly excited to license the IL-12-TM technology from Professor Dotti's laboratory for use with our CAR-iNKT cell platform. The data supporting solid tumours is compelling and will see Arovella enhance its solid tumour pipelines and effectiveness."

Professor Dotti, a research professor at UNC and director of the Lineberger Comprehensive Cancer Center Immunotherapy Program, commented: "We have continued to make important advancements to use CARiNKT cells to treat various tumour types. What we have discovered by engineering CAR-iNKT cells to generate IL-12-TM is unexpected. We look forward to working with Arovella to test this exciting technology in clinical trials."

The licence has no immediate material financial impact on the Company as a result of signing the agreement. There is no upfront fee payable for the license, and future licensing fees will include annual license maintenance fees, stage-gated, industry-standard development milestones for the first patient dosed in a pivotal clinical trial and marketing approval. The Licence also includes a low single-digit royalty on future sales. Further details on key license terms are included below.

The data demonstrates that IL-12-TM enhances CAR-iNKT cell persistence, cell number and antitumour activity in several animal cancer models including solid tumour cancers such as neuroblastoma. Arovella

¹ https://www.nature.com/articles/s41467-023-44310-y



intends to incorporate the IL-12-TM technology into its solid tumour programs and will be the only iNKT cell company working with the technology.

IL-12-TM is a modified version of the human cytokine, interleukin 12 (IL-12). Due to bridging the innate and adaptive immunity and potently stimulating the production of IFN-γ, a cytokine coordinating natural mechanisms of anticancer defence, IL-12 was considered the ideal candidate for human tumour immunotherapy. However, side effects associated with systemic administration limited its use as a standalone therapeutic.

IL-12-TM has been modified to include a 'membrane anchor', which keeps the IL-12 attached to the CARiNKT cell and prevents it from circulating freely in the patient's bloodstream. This enables the IL-12-TM to have the desired effect on the CAR-iNKT cell and reduces the risk of off-target effects and toxicity.

When IL-12-TM is added to CAR-iNKT cells, it promotes the proliferation and survival of the CAR-iNKT cells. This means that when the CAR-iNKT cell comes in contact with a target tumour cell, it proliferates more, leading to higher numbers of CAR-iNKT cells. In addition, the cells do not get 'exhausted' as quickly and therefore survive longer, again contributing to higher CAR-iNKT cell numbers.

The IL-12-TM technology was tested in a mouse model of neuroblastoma, a cancer that can affect various regions of the central nervous system. When the number of CAR-iNKT cells was assessed in the mice four weeks after dosing, CAR-iNKT cells containing IL-12-TM were found at much higher numbers in the bloodstream (>10 times) than CAR-iNKT cells that did not contain IL-12. This correlated with substantially better antitumour activity and survival outcomes in the mice with approximately 75% of mice still alive 60 days after treatment for the IL-12-TM group while all mice in the group treated with CAR-iNKT cells lacking IL-12 had died (Figure 1).



Figure 1. CHLA-255 neuroblastoma cells were engrafted into mice before treatment with PBS, iNKT cells expressing a CAR to target GD2 lacking the cytokine technology (GD2-CAR), GD2 targeting iNKT cells with secreted IL-12 (GD2-CAR + IL-12) or GD2 targeting iNKT cells with a membrane anchored IL-12 (GD2-CAR + IL-12-TM). Landoni et al 2024, Nature Communications.



The full publication for the IL-12-TM data is available from the Nature Communications website and can be found here - <u>https://www.nature.com/articles/s41467-023-44310-y</u>.

Armouring CAR-iNKT cells to treat solid tumours

Arovella's CAR-iNKT cells are being developed as an off-the-shelf solution for cancer treatment. They have inherent properties that may make them amenable to targeting solid tumours, such as

- (i) the ability to infiltrate tissues and tumours^{i,ii},
- (ii) the ability to block or kill cells that promote tumour survival such as myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages (TAMs),ⁱⁱⁱ and
- (iii) the ability to release cytokines to stimulate an immune response and recruit other immune cells to target the tumour cells.^{iv,v}

Armouring CAR-iNKT cells is one of Arovella's strategies to further enhance and differentiate its platform to tackle solid tumours. The intellectual property licensed from UNC Lineberger was filed in 2023 and covers use of the IL-12-TM in iNKT cells and the filed patent will provide protection until at least 2043. The data generated using the IL-12-TM armouring strategy demonstrates the promise of CAR-iNKT cells, and their potential utility across a range of tumour types.

IL-12-TM is expected to complement Arovella's CLDN18.2 program, recently licensed from Sparx Group. Arovella is developing the world's first CAR-iNKT cell therapy targeting CLDN18.2 to target gastric cancers (GC), gastroesophageal junction cancers (GEJC) pancreatic cancers (PC), and other solid tumours that express CLDN18.2. GC and GEJC continue to present as high unmet medical needs with over one million new cases diagnosed per annum globally and 789,000 deaths, making it the fourth most fatal cancer globally.^{vi} Over 496,000 individuals were diagnosed with PC worldwide in 2020 with an estimated 466,000 deaths the same year.^{vii} Stage 4 pancreatic cancer has a five-year survival rate of 1% with the average patient living for approximately 1 year after their diagnosis.^{viii} The global gastric cancer market size was valued at \$2.1 billion in 2021, and is projected to reach \$10.7 billion by 2031, growing at a CAGR of 17.9% from 2022 to 2031.^{ix}

In addition, Arovella continues to work with Imugene combing its oncolytic virus platform, CF33, with ALA-101. Incorporating IL-12-TM may provide improved activity against a range of solid tumours for this collaboration.

Differentiation of Arovella's CAR-iNKT cell platform

Arovella will be the only CAR-iNKT cell company developing products incorporating this cytokine. The IL-12-TM cytokine technology was also compared to IL-15, another cytokine that has been used to enhance persistence of iNKT cells. IL-15 has been used by other groups to enhance the antitumor activity of CAR-iNKT cells against neuroblastoma. When compared directly with IL-15 in a mouse model of neuroblastoma, CARiNKT cells incorporating IL-12-TM displayed significantly improved antitumour activity. For mice treated with CAR-iNKT cells incorporating IL-15, 100% of the animals had succumbed to the cancer cells by day 42. In contrast, 80% of the mice treated with IL-12-TM containing CAR-iNKT cells were alive after 60 days, when the experiment was completed.



Key terms of the licence agreement

The licence has no immediate material financial impact on the Company as a result of signing the agreement, which has no conditions precedent and is effective immediately. The preclinical data published in Nature Communications provides the proof-of-concept studies to demonstrate the potential of the technology. The next step is to integrate IL-12-TM into Arovella's existing programs and is not expected to materially increase the costs of these programs².

In lieu of an upfront license fee, Arovella will enter into a sponsored research agreement (SRA) and a clinical trial agreement (CTA) with Professor Dotti's lab, to be negotiated at a later date. The license includes industry-standard stage-gated milestone payments for (i) the first patient dosed in a pivotal clinical trial and (ii) marketing approval of a product incorporating the technology for the first two products. Total milestone fees payable under the license agreement total US\$10 million. Future license payments also include annual license maintenance fees and low single-digit royalties associated with commercial sales of the approved products.

The timing of the cash milestones is contingent on pre-clinical development success and, thereafter, clinical trial success. The majority of the contingent cash milestone payments are due upon market approvals. Accordingly, and based on other therapeutic drug development programs, this would typically be longer than seven years, hence the timing of such payments are indeterminable.

The Licence Agreement contains standard termination provisions, and there are no associated termination fees. The Agreement shall expire at the latest of (i) expiration of the last to expire patent included in the Patent Rights, (ii) the expiration of any market exclusivity relating to a Licensed Product, or (iii) ten (10) years from the first commercial sale of a Licensed Product.

Investor webinar

Dr Michael Baker will hold an investor webinar for shareholders and interested parties to discuss this announcement and development for Arovella.

Time: 11am AEDT

Date: Wednesday 31 January 2024

Registration: https://us02web.zoom.us/webinar/register/WN_ZTCz-0DMS5W22Qi8_bbkpw

Further details on how to attend will be provided by email following registration.

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

Questions can be submitted on the day or sent in advance to investor@arovella.com.

Release authorised by the Board of Directors of Arovella Therapeutics Limited.

² https://www.nature.com/articles/s41467-023-44310-y

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NOTES TO EDITORS:

About Arovella Therapeutics Ltd

Arovella Therapeutics Ltd (ASX: ALA) is a biotechnology company focused on 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 into solid tumour treatment through its CLDN18.2-targeting technology licensed from Sparx Group. Additional tumour targeting technologies are anticipated to be used in conjunction with Arovella's iNKT cell therapy platform. Arovella's lead product is ALA-101. ALA-101 consists of CAR19-iNKT cells that have been modified to produce a Chimeric Antigen Receptor (CAR) that targets CD19. CD19 is an antigen found on the surface of numerous cancer types. iNKT cells also contain an invariant T cell receptor (iTCR) that targets α -GalCer bound CD1d, another antigen found on the surface of several cancer types. ALA-101 is being developed as an allogeneic cell therapy, which means it can be given from a healthy donor to a patient.

Glossary: iNKT cell – invariant Natural Killer T cells; **CAR** – Chimeric Antigen Receptor that can be introduced into immune cells to target cancer cells; **TCR** – T cell receptors are a group of proteins found on immune cells that recognise fragments of antigens as peptides bound to MHC complexes; **B-cell lymphoma** – A type of cancer that forms in B cells (a type of immune system cell); **CD1d** – Cluster of differentiation 1, which is expressed on some immune cells and cancer cells; **aGalCer** – alpha-galactosylceramide is a specific ligand for human and mouse natural killer T cells. It is a synthetic glycolipid.

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 the actions of third parties and financial terms. These factors and assumptions are based upon currently available information, and the forward-looking statements herein speak only 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 forwardlooking 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; the 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.

ⁱ https://pubmed.ncbi.nlm.nih.gov/29967365/



ⁱⁱ https://pubmed.ncbi.nlm.nih.gov/33046868/

iii https://pubmed.ncbi.nlm.nih.gov/19411762/

^{iv} https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4517377/

^v https://doi.org/10.4049/jimmunol.163.9.4647

^{vi} https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(22)00134-1/fulltext

vii https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21660

viii https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/pancreatic-cancer-prognosis

^{ix} https://www.alliedmarketresearch.com/gastric-cancer-market-

A74458#:~:text=The%20global%20gastric%20cancer%20market,cells%20lining%20of%20the%20stomach







LINEBERGER COMPREHENSIVE CANCER CENTER

Exclusive Global License

IL-12-TM cytokine technology from University of North Carolina Lineberger Comprehensive Cancer Center

January 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+ 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 the iNKT cell therapy platform and broaden its applications

Unique value proposition

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

iNKT cells to target solid tumours

Arovella is implementing its strategy to target and kill solid tumours – 90% of newly diagnosed cancer cases¹

Solid tumours pose challenges to cell therapies



iNKT cells to combat solid tumours

iNKT cells have several properties to attack solid tumours



Modification of the tumour microenvironment

iNKT cells



Home to tissues and infiltrate tumours^{1,2}



Block or kill cells that promote tumour growth³



Recruit other immune cells that can also kill tumour cells^{4,5}

1. Crosby and Kronenberg 2018 Nat Rev Immuno - 10.1038/s41577-018-0034-2; 2. Heczey et al., 2020 Nature Medicine -10.1038/s41591-020-1074-2; 3. Song et al., 2009 J Clin invest - 10.1172/JCI37869; 4. Gottschalk et al., 2015 Front Immunol -10.3389/fimmu.2015.00379; 5. Carnaud et al., 1999 J Immunol - 10.4049/jimmunol.163.9.4647

Arovella's strategies to combat solid tumours

therapy platform

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



Arovella's strategies to combat solid tumours

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



Introducing Interleukin 12 (IL-12)

IL-12 is a cytokine that has been well studied for immunotherapy

Cytokines for Cancer Treatment

198	36
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First cytokine approved to treat cancer >40 cytokines studied in preclinical and clinical trials 2 cytokines approved as single agents to treat cancer



IL-12

- Potent, pro-inflammatory cytokine with diverse functions
- Increases activation and cell killing capacity of T and NK cells
- Inhibits or reprograms immunosuppressive cells, such as TAMs and MSDCs
- Has demonstrated strong antitumor effects in preclinical studies
- Unwanted toxicity has limited its success as a monotherapy

Cytokines can provide "armouring" to cell therapies, enhancing their anti-tumour activity

"Armouring" CAR-iNKT cells

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

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

STRATEGY 2

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

Arovella to integrate IL-12-TM into CAR-iNKT cell platform

Exclusive, global licence with UNC Lineberger Comprehensive Cancer Center



Exclusive global licence with UNC Lineberger Comprehensive Cancer Center

to use the IL-12-TM construct in CAR-iNKT cells

DUNC

LINEBERGER COMPREHENSIVE CANCER CENTER

Attractive fee structure

modest short-term capital requirements

Industry-standard milestones

payable in cash and low single digit royalties

IL-12-TM technology

Arovella will combine the IL-12-TM technology with its iNKT cell therapy platform to target solid tumours

Many solid tumours are high priority targets of unmet need TARGET

SOLID

TUMOURS

The licence strengthens Arovella's exciting programs targeting solid tumours, leveraging its manufacturing progress for ALA-101

CAR-INKT

cell therapy

platform

IL-12-TM enhances CAR-iNKT cell activity against neuroblastoma

First CAR-iNKT cell product
expressing IL-12-TM

The Inventor – Professor Gianpietro Dotti, M.D., Ph.D.

A renowned world expert on CAR-iNKT cells







- CAR-iNKT cell pioneer, created the first CAR-iNKT cell construct
- Leading authority on CAR-T and CAR-iNKT cells
- Developed CAR-based strategies to target neuroblastoma in pediatric patients
- Medical Degree from the University of Milan, Italy
- Clinical Training and Board certification in Hematology (University of Parma)
- Post doctoral fellowship in translation research (Center for Cell and Gene Therapy at the Baylor College of Medicine)





LINEBERGER COMPREHENSIVE CANCER CENTER





- Research Professor of Microbiology and Immunology at UNC
- Director of the Cellular Immunotherapy Program at Lineberger Comprehensive Cancer Center at UNC
- More than 200 peer-reviewed research articles
- Received the Highly Cited Researchers (Top 1%) award from Web of Science, Clarivate Analytics, in 2020, 2021, 2022, 2023.

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



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

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



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

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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



Landoni et al., Nature Communications (2024)



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

First CAR-iNKT cell product with membrane-anchored IL-12. IL-12-TM is not released from the cells and is expected to be safer.

Enhances CAR-iNKT cell antitumour activity

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



Manufacturing CAR-iNKT cells to express IL-12-TM



Integration of IL-12-TM will leverage Arovella's existing manufacturing process



Robust intellectual property



Filed patent to provide patent protection until at least 2043



Composition of matter claims for a unique IL-12-TM sequence

National phase to be filed in major jurisdiction, including US, Europe, China, Japan, South Korea and Australia



Arovella is the only Company combining CAR-iNKT cells with IL-12

ENDING 2) IN SEV. CATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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IL-12-TM to enhance Arovella's solid tumour strategies

Arovella is developing several solid tumour strategies that will leverage the technology



Upcom 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 submission 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) 	Τ
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 Confirm activity of ALA-101 in combination with Imugene's onCARlytics to target solid tumours in animal models 	



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



Financial overview

Financial Snapshot

ALA	
\$119.39 million	4
918.4 million	
\$0.025 / \$0.155	3
\$4.76 million	
	\$119.39 million 918.4 million \$0.025 / \$0.155

Major Shareholders

Shareholder	Ownership (%) ¹
THE TRUST COMPANY (AUSTRALIA) LIMITED	55,613,086 (6.16%)
RICHARD JOHN MANN	50,905,657 (5.64%)
UBS NOMINEES PTY LTD	20,620,196 (2.29%)
BLACKBURNE CAPITAL PTY LTD	17,637,456 (1.96%)
DYLIDE PTY LTD	15,666,666 (1.74%)

1. As of 29 January 2024

ALA Price and Volume - 12 Months¹





6

Summary





THERAPEUTICS

Thank You

Dr. Michael Baker CEO & Managing Director

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Investor Webinar



Dr. Michael Baker CEO & MANAGING DIRECTOR

DATE: Wed, 31 Jan 2024 TIME: 11:00 AM (AEDT)

Please register here

