ASX RELEASE

CLDN18.2-CAR-iNKT CELLS INCLUDING IL-12-TM ARMOURING ELIMINATE PANCREATIC AND GASTRIC CANCER CELLS

- **CLDN18.2 CAR induces effective killing of CLDN18.2-positive pancreatic cancer and gastric cancer cells when incorporated into iNKT cells in in vitro studies**
- **CLDN18.2-directed CAR-iNKT cells mediated strong tumour control following repeated addition of cancer cells**
- **Inclusion of IL-12-TM armouring enhances CLDN18.2 CAR-iNKT cell killing**

MELBOURNE, AUSTRALIA, 01 April 2026: Arovella Therapeutics Ltd (ASX: ALA) ACN 090 987 250 (Arovella or the Company) is pleased to announce that it has confirmed the functionality of its novel claudin 18.2 (CLDN18.2)-targeting chimeric antigen receptor (CAR) in iNKT cells, and its IL-12-TM armouring technology has been added to demonstrate enhanced effectiveness.

Study Details

Target Cancer Types	Pancreatic and Gastric Cancer cells that express Claudin 18.2 (CLDN18.2). CLDN18.2 is a highly prevalent, validated therapeutic target, expressed in approximately 40%–70% of gastric cancers and up to 60% of pancreatic ductal adenocarcinomas (PDAC).[1] Gastric cancer is the 5th most common form of cancer.[2] Pancreatic cancer is less common, but it is 7th in mortality.[3]
Therapeutic Immune Cells Tested	i) Unmodified iNKT cells; ii) iNKT cells modified to produce the CLDN18.2 CAR (CLDN18.2-CAR-iNKT cells); iii) iNKT cells modified to produce both CLDN18.2 CAR and IL-12-TM (armouring).
Study Focus	i) Confirm potency against pancreatic and gastric cancer cells; ii) Confirm durability of cell killing after multiple challenges of cancer cells; iii) Confirm expansion and effect of the inclusion of armouring.
Study Results	**CLDN18.2 CAR-iNKT** cells robustly eliminated pancreatic and gastric cancer cells that express CLDN18.2 in an in vitro serial tumour challenge assay (endurance and long-term effectiveness test), confirming the potent activity of Arovella's CLDN18.2 CAR (Figure 1A and 2A). **CLDN18.2 CAR-iNKT cells with IL-12-TM** (armoured) demonstrated enhanced CAR-iNKT cell expansion (Figure 1B and 2B) and resulted in better tumour control during repeated tumour challenges (Figures 1A and 2A). When tumour cells were introduced in four successive rounds, the armoured CAR-iNKT cells continued to kill more than 97% and 82% of the pancreatic and gastric tumour cells, respectively. This demonstrates the benefit of IL-12-TM in increasing the expansion potential and durability of CAR-iNKT cells. The studies were performed at UNC, under the guidance of Professor Gianpietro Dotti.

[1] https://www.nature.com/articles/s41571-024-00874-2
[2] https://www.wcrf.org/preventing-cancer/cancer-statistics/stomach-cancer-statistics/
[3] https://link.springer.com/article/10.1186/s12885-025-14110-2

Killing of Pancreatic Cancer

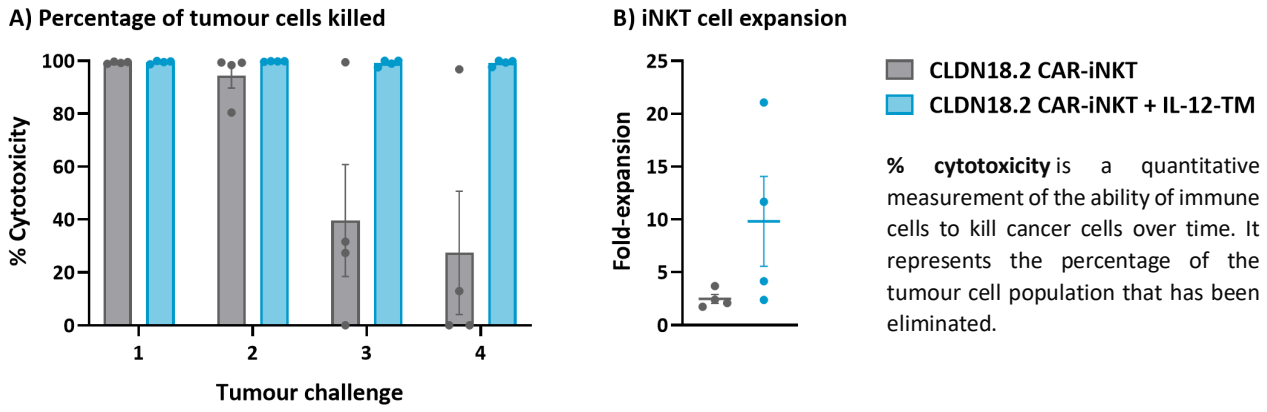

Figure 1. Cytotoxicity of iNKT cells expressing Arovella's CLDN18.2-targeting CAR with and without IL-12-TM cytokine armouring against the human pancreatic adenocarcinoma cell line, PaTu8988S. CAR-iNKT cells were cultured with PaTu8988S cells at an effector-to-target ratio of 1:1, then challenged with fresh tumour cells every three days for a total of four serial tumour challenges. Cells were analysed by flow cytometry. (A) Percentage cytotoxicity calculated relative to the number of PaTu8988S target cells remaining after co-culture with non-transduced iNKT cells, (B) Peak fold-expansion of CAR-iNKT cells relative to non-transduced iNKT cells. Data is presented for four independent donors ± standard error of the mean.

Killing of Gastric Cancer

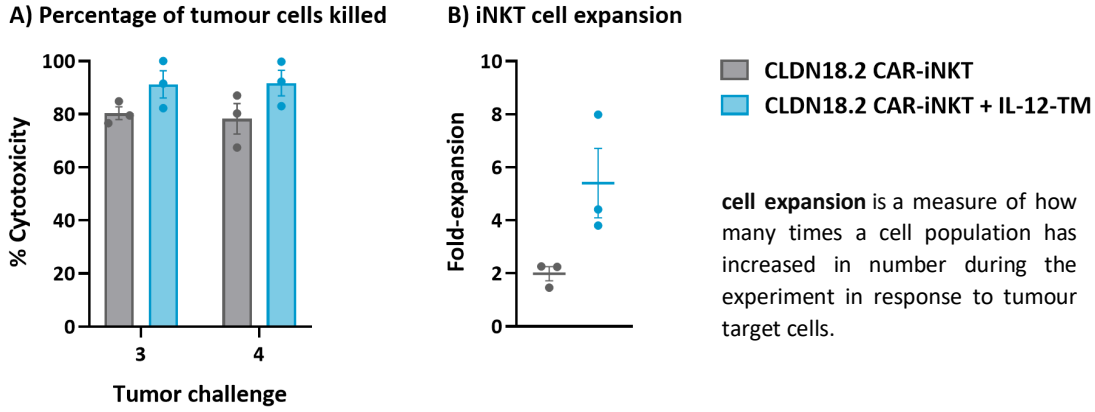

Figure 2. Cytotoxicity of iNKT cells expressing Arovella's CLDN18.2-targeting CAR with and without IL-12-TM cytokine armouring against the human gastric cancer cell line, NUGC4-CLDN18.2. CAR-iNKT cells were cultured with NUGC4-CLDN18.2 cells at an effector-to-target ratio of 1:2, then challenged with fresh tumour cells every three days for a total of four serial tumour challenges. Cells were analysed by flow cytometry. (A) Percentage cytotoxicity calculated relative to the number of NUGC4-CLDN18.2 target cells remaining after co-culture with non-transduced iNKT cells, (B) Peak fold-expansion of CAR-iNKT cells relative to non-transduced iNKT cells. Data is presented for three independent donors ± standard error of the mean.

Arovella's CEO and Managing Director, Dr Michael Baker, commented, "It is terrific to see the potent and durable activity of iNKT cells incorporating our novel and proprietary CLDN18.2-targeting CAR combined with IL-12-TM cytokine armouring technology against both gastric and pancreatic cancer cells. This is an important milestone for the company as we expand our pipeline to target difficult to treat solid tumours. We are highly encouraged by the durability of the CLDN18.2 CAR-iNKT cells expressing IL-12-TM in controlling tumour cells, particularly after multiple serial tumour challenges. These studies intentionally push the cells to the limit, and we are excited by the data."

To hear more from our CEO and MD about the data, please click here.

Questions and Answers

What is the significance of the data?
Arovella is developing its CAR-iNKT cell platform to target a range of cancer types, including blood cancers and solid tumours. Using novel CAR sequences, Arovella can use its platform to target specific tumour types. Cytokine armouring enhances the durability and potency of CAR-engineered cells and can be used across the CAR-iNKT cell platform with various CARs.

Arovella's CLDN18.2-targeting CAR is being developed to target gastric cancer and pancreatic cancer. The data generated in these studies demonstrate that when incorporated into iNKT cells, the CAR targets and induces killing of CLDN18.2-positive pancreatic and gastric cancer cell lines. Armouring of CAR-iNKT cells with a membrane-bound version of the IL-12 cytokine (IL-12-TM) further enhanced cancer cell killing.

To date, there is only one product commercially available that targets CLDN18.2, which was approved in Japan and the US in 2024, Zolbetuximab, which was the focus of a €422 million acquisition of Ganymed Pharmaceuticals AG by Astellas.[4] The CLDN18.2 market is predicted to exceed $800 million by 2030.[5]

How are the killing assays completed?
For the cell killing assays, the human pancreatic adenocarcinoma (PaTu8898S) and human gastric cancer (NUGC4-CLDN18.2) cell lines are cultured in cell culture plates. CAR-iNKT cells targeting CLDN18.2 plus and minus IL-12-TM are added to the dish with the cancer cells. After three days, additional tumour cells are added to the dish, which is referred to as a tumour challenge. For each experiment, the CAR-iNKT cells undergo four tumour challenges. Following each challenge, tumour cells and CAR-iNKT cells remaining in the dish are counted. For the experiments, cells are manufactured from three or four independent iNKT cell donors.

What did the data show and what does it mean?
CAR-iNKT cells that did not have IL-12-TM were able to control the tumour cells for two tumour cell challenges. CAR-iNKT cells incorporating the IL-12-TM technology were able to control the tumour cells through all four challenges. This demonstrates that the CLDN18.2 CAR is highly potent, and that under high

[4] https://www.prnewswire.com/news-releases/astellas-completes-acquisition-of-ganymed-pharmaceuticals-300382348.html
[5] https://uk.finance.yahoo.com/news/claudin-18-2-targeted-therapy-090500641.html

tumour stress conditions, the addition of IL-12-TM enhances the growth of the CAR-iNKT cells and further increases their potency against gastric and pancreatic cancer cells.

The repeat challenge assay provides a rigorous measure of CAR-iNKT cell performance by assessing the durability and proliferative resilience of effector function across multiple killing cycles, thereby better reflecting persistence and sustained antitumour activity against solid tumours in vivo.

Why is claudin18.2 (CLDN18.2) a good target for therapeutic targeting gastric cancer or pancreatic cancer?
In healthy stomach tissue, CLDN18.2 is a protein expressed by the cells lining the gastric tract. It is positioned in tight junctions between cells where it helps to maintain tissue structure and where it can't be accessed by CAR-iNKT cells. Once the cells become cancerous, CLDN18.2 expression is uncontrolled and becomes exposed on the surface of the cancerous cells. Once this happens, CLDN18.2 can be accessed by CAR-iNKT cells, which allows them to kill the CLDN18.2-positive cancer cells. CLDN18.2 is not normally expressed in the pancreas but is often dysregulated and can be turned on when cells become cancerous.

Gastric and pancreatic cancer are both highly prevalent with ~1 million cases and ~0.5 million cases diagnosed annually. Many of the cases are HER2-negative and CLDN18.2-positive, making them potential targets for CLDN18.2 targeting therapies.

Now that you have data to support that the CAR is function and that the armouring strategy works well, what are the next steps?
The next step is to generate additional CLDN18.2-targeting CAR-iNKT cells, with and without IL-12-TM, and use them to assess their performance in gastric and pancreatic cancer mouse models. The models for each cancer type are currently being established.

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

Dr Michael Baker
Chief Executive Officer & Managing Director
Arovella Therapeutics Ltd
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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'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 glycolipid bound CD1d, another antigen found on the surface of several cancer types. ALA-101 has had its IND accepted by the US FDA and is being developed as an allogeneic cell therapy, which means it can be given from a healthy donor

to a patient. Arovella is also expanding into solid tumour treatment through its CLDN18.2-targeting technology licensed from Sparx Group. Arovella will also incorporate its IL-12-TM technology into its solid tumour programs.

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 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; 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.

https://www.nature.com/articles/s41571-024-00874-2
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