ASX RELEASE

02 October 2025

CLDN18.2 CAR-T CELLS ELIMINATE PANCREATIC CANCER CELLS

- **Arovella's unique and patent protected CLDN18.2 CAR has been demonstrated to induce effective killing of pancreatic cancer cells when incorporated into T cells in a proof-of-concept *in vitro* study.**
- **Arovella's CLDN18.2 CAR performed equivalently to the leading CLDN18.2 CAR, and the anti-tumour activity of the CAR is anticipated to be superior *in vivo* when incorporated into Arovella's iNKT cell platform.**
- **Arovella is proceeding to incorporate its CLDN18.2 CAR into iNKT cells, which will be followed up with *in vivo* pancreatic and gastric cancer studies in mice.**
- **Arovella is one of very few companies developing a CLDN18.2-targeting CAR-iNKT cell therapy.**

MELBOURNE, AUSTRALIA 02 October 2025: Arovella Therapeutics Ltd (ASX: ALA) ACN 090 987 250 (Arovella or the Company) is pleased to announce that it has further confirmed the functionality of its novel claudin 18.2 (CLDN18.2)-targeting chimeric antigen receptor (CAR) by demonstrating that CLDN18.2 CAR-T cells robustly eliminate pancreatic cancer cells that express CLDN18.2. The study confirmed the potent activity of Arovella's CLDN18.2 CAR against a pancreatic cancer cell line, with pancreatic cancer being one of the more aggressive, and low survival cancer types with limited treatment options. The study was performed at the University of North Carolina, under the guidance of Professor Gianpietro Dotti.

Significance: Arovella is developing its CAR-iNKT cell platform to target a range of cancer types, including blood cancers and solid tumours. By acquiring CAR sequences and demonstrating their activity, Arovella can use its platform to target specific tumour types.

Arovella's CLDN18.2-targeting CAR is being developed to target gastric cancer and pancreatic cancer. The data generated in this study demonstrates that, as expected, the CAR targets and induces killing of a CLDN18.2-positive pancreatic cancer cell line.

Importantly, recent studies have demonstrated that CAR-iNKT cells outperform CAR-T cells in solid tumours due to their ability to reshape the tumour microenvironment and activate other cancer-killing immune cells.

This is an important milestone for Arovella's CLDN18.2 CAR-iNKT program. Arovella will now progress to incorporate this CAR into its CAR-iNKT cells, assess activity against a range of gastric and pancreatic tumour models, and generate IND-enabling safety and efficacy data required to begin testing in humans.

Arovella is one of very few companies developing a CLDN18.2-targeting CAR-iNKT cell product.

The human pancreatic adenocarcinoma cell line, PaTu8892S, naturally expresses CLDN18.2 and was selected as a model cell line for this study. Arovella's novel CAR design is based on the patent protected CLDN18.2 antigen-binding sequences of the SPX-101 monoclonal antibody, for which Arovella has an exclusive license

for use in cell therapies. CLDN18.2 CAR-T cells generated from three independent donors were cultured *in vitro* with twice the number of PaTu8892S cells for 3 days, and then the degree of cytotoxicity was measured. The results demonstrated that CAR-T cells expressing Arovella's CLDN18.2 CAR displayed robust killing of pancreatic cancer cells (Figure 1), and the activity was similar to that observed for a control CAR generated based upon the CARsgen Therapeutics CT041 CAR. CARsgen Therapeutics recently filed a New Drug Application (NDA) for its autologous CLDN18.2 CAR-T cell product which has been accepted for review by the Chinese regulator, the National Medical Products Administration (NMPA)[1]. The NDA was based on results from an open-label, multicentre, randomised controlled confirmatory Phase II clinical trial (CT041-ST-01, NCT04581473) conducted in China.

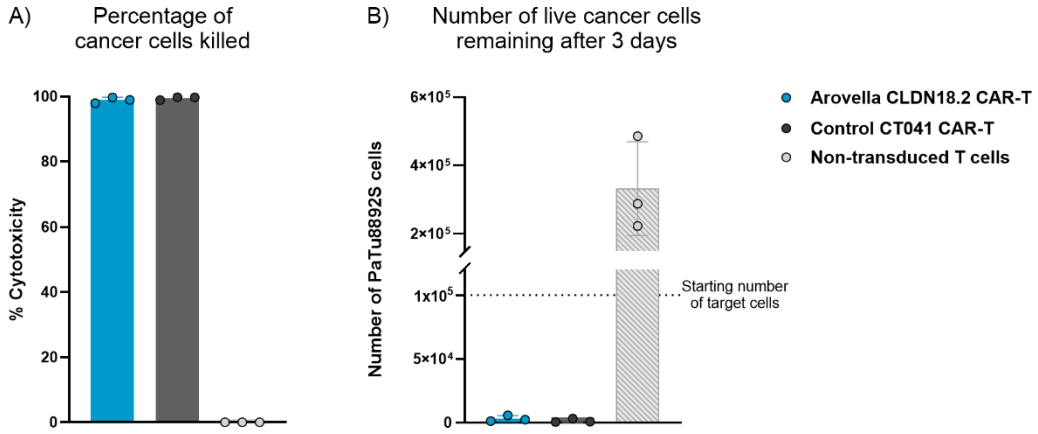

Figure 1. Cytotoxicity of CAR-T cells expressing Arovella's CLDN18.2-targeting CAR against the human pancreatic adenocarcinoma cell line, PaTu8892S. CAR-T cells were cultured with PaTu8892S cells at an effector-to-target ratio of 1:2 for 3 days and then analysed by flow cytometry. (A) Percentage cytotoxicity calculated relative to PaTu8892S target cells cultured with non-transduced T cells, (B) Number of live PaTu8892S target cells remaining following the co-culture with CAR-T cells or non-transduced T cells. Data is presented for three donors ± SEM.

Importantly, recent publications have demonstrated that CAR-iNKT cells outperform CAR-T cells in fighting solid tumours by shaping the tumour microenvironment (TME) and promoting the cross-priming of other cytotoxic immune cells to eliminate the cancer cells[2,3]. It is anticipated that Arovella's CLDN18.2-CAR-iNKT cells will perform better than CAR-T cells due to their additional functionality within the TME. The next steps for the program are to engineer iNKT cells to express the CLDN18.2 CAR, test the activity of these cells against CLDN18.2 positive cell lines, and commence *in vivo* pancreatic and gastric cancer studies in mice.

Arovella's CEO and Managing Director, Dr Michael Baker, commented, "Seeing the robust activity of our novel and proprietary CLDN18.2-targeting CAR against pancreatic cancer cells has the team excited as we expand our pipeline to target difficult to treat solid tumours. It is terrific to show very potent killing using our CAR, and it is encouraging that the cytotoxic potential shown in this study was equivalent to a CAR that has an NDA submitted for regulatory approval. This supports the robust performance of our CAR, and supports us incorporating it into our iNKT cell platform. With strong evidence that CAR-iNKT cells outperform CAR-T

[1] https://www.carsgen.com/en/news/20250626/
[2] https://www.science.org/doi/10.1126/sciimmunol.abn6563?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[3] https://www.nature.com/articles/s43018-024-00830-0

cells in eliminating solid tumours, we look forward to integrating the CLDN18.2-targeting CAR into Arovella's iNKT cell platform, confirming its activity in animal models."

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

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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 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

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