Newsletter

December 2023

Highlights since May 2023

- **Advanced its manufacturing activities** through a new partnership with Cell Therapies Pty Ltd in readiness to manufacture ALA-101 for clinical trials in the first half of CY24.
- Received positive data demonstrating that the **cytokine technology** under option from the University of North Carolina **can increase the persistence of iNKT cells and enhances their anti-tumour effect** in a mouse solid tumour model.
- **Finalised the closure of its Perth OroMist R&D facility** to complete the strategic refocus of the Company towards its iNKT cell platform.
- **Completed an oversubscribed Placement and SPP** to raise a total of $6.3 million.
- **Progressed its solid tumour strategy** by signing an exclusive license with Sparx Group to develop a world-first CAR-iNKT cell therapy targeting a validated target, Claudin 18.2 (CLDN18.2), which is expressed in gastric cancer (GC), gastroesophageal junction cancer (GEJC) and pancreatic Cancer (PC).

Keep an eye out for our upcoming milestones

Manufacturing updates for ALA-101

In vivo data for the combination of ALA-101 and onCARlytics

Updates on the cytokine technology

Letter from the Chair

Welcome to this edition of Arovella's newsletter. Your Company is progressing well, and I am looking forward to giving you a summary of recent and exciting developments.

Since joining as Non-executive Chairman in March 2023, the Company has continued to make significant progress developing its invariant Natural Killer T (iNKT) cell platform and expanded the potential reach of the technology from blood cancers to solid tumours.

I was delighted to have joined a company with a board and management team with such a robust level of drug development experience, combining academic research, clinical planning, and commercial transactions. It is a dynamic team, spanning Australia and the US, which aligns well with our focus of being an Australian biotechnology company with a global footprint.

For our lead program, ALA-101, which is being developed for CD19+ heamatological malignancies, or blood cancers, we have made excellent progress. We presented some of the data in April this year at the American Association for Cancer Research (AACR) annual meeting in Orlando. The data was well received, and it highlighted the significant progress the Company made bringing ALA-101 towards clinical trials.

In addition, the group made significant progress on the manufacturing front, a key step for all cell therapy products. The GMP-grade lentivirus is currently on track to be manufactured before the end of the calendar year, and we recently announced our collaboration with Cell Therapies, based within the Peter MacCallum Cancer Centre, in Parkville, Melbourne, to manufacture the material for clinical trials, which you can read more about below.

The management team scoured the globe for novel technologies that complement Arovella's iNKT cell therapy platform. To that end, the company continued its discussions with University of North Carolina, for an "armouring" technology to strengthen its iNKT cell platform. In October 2023, we were delighted to enter into an agreement with Sparx Group for their CLDN18.2 targeting technology, opening up opportunities for solid tumours such as gastric cancer and pancreatic cancer. We have already commenced scientific work to construct a novel CLDN18.2 targeting iNKT cell, with 2024 shaping up as a year where solid development in this program is anticipated.

We think this is an exciting target as Astellas Pharma, a US$22 billion Japanese pharmaceutical company, is awaiting US Food and Drug Administration approval for their CLDN18.2 targeting antibody called zolbetuximab in early 2024 for gastric cancers. This drug has been forecast by Astellas to generate up to US$1.3 billion in peak sales. An approval is expected to increase pharmaceutical company interest in this validated target. Importantly, Arovella's CLDN18.2-iNKT cells will be the only off-the-shelf CAR-iNKT cell therapy being developed for this target and will significantly increase the value of Arovella's pipeline.

As a result of some of these activities, Arovella was fortunate to buck the trend of the small cap sector. We are pleased that the share price increased from the beginning of the calendar year by more than 300%. This is a remarkable effort in what has been a difficult year for the biotechnology sector, domestically and globally both in terms of absolute share price performance, but also access to capital to continue R&D development.

We are very excited for the year ahead. Thus far, 2023 has been a transformative year for Arovella in terms of team building, strategic acquisitions and it was the year that Arovella formally made the transition to a dedicated cell therapy company. We remain optimistic about our iNKT cell platform and believe that it has the potential to impact patients globally. With that, we would like to thank all our shareholders for their continued support, and who recently supported the Company's efforts in an oversubscribed Placement and Share Purchase Plan in the middle of the year to raise $6.3 million. We look forward to continuing to build shareholder value in the years to come.

Please read on to hear more about the Company's latest activities.

Dr. Tom Duthy
CHAIRMAN

 | investor@arovella.com

The Arovella Team visiting Cell Therapies Pty. Ltd. during a recent strategic planning meeting in Melbourne. Pictured below from left: Simon Poon, Nicole van der Weerden, Michael Baker, Mini Bharathan and Robson Dossa

Progress on ALA-101

Over the past several months, Arovella has continued to make important progress on manufacturing for its lead product, ALA-101. Arovella completed key activities required for GMP manufacture of its clinical lentiviral vector for ALA-101, including generating the GMP plasmid that is required as an input for manufacture of the vector. Manufacture of GMP vector is a key milestone ahead of manufacture for clinical trials and remains on track for completion in Q4 CY23.

Arovella is now working with Cell Therapies Pty Ltd for clinical manufacturing of its ALA-101 product. Cell Therapies has over 20 years of experience delivering cellular therapy products to patients around the world and is based within Melbourne's Peter MacCallum Cancer Centre. Its GMP manufacturing facility holds licenses and accreditation from Australia's TGA and Japan's MHLW, with increased capacity courtesy of its new commercial-scale expansion that was opened in July of this year. Cell Therapies has the expertise to support Arovella's products as we progress from concept to commercialisation and is an ideal partner for Arovella.

In October, the Arovella team met in Melbourne for a strategic planning meeting. This also afforded the opportunity to meet with a range of groups related to ALA-101 manufacturing and suppliers to support clinical trial readiness ahead of 2024.

CAR-iNKT cells have key advantages for the treatment of solid tumours

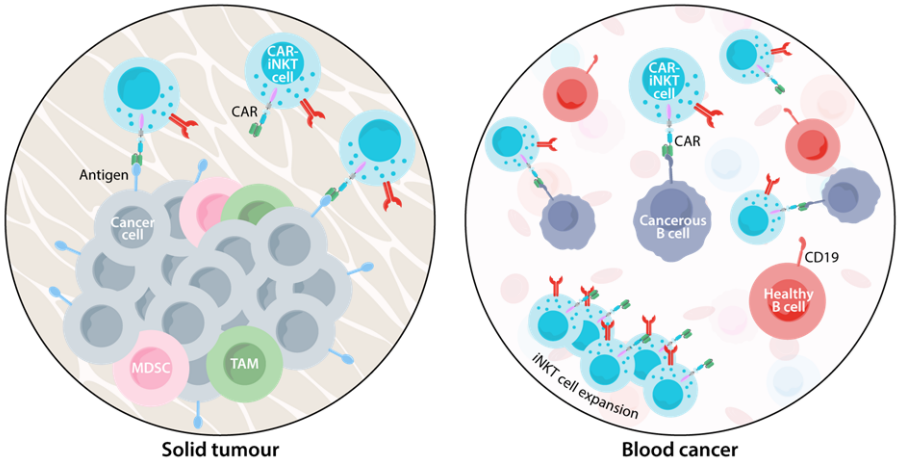
Cell therapy, in particular CAR-T, has revolutionised the treatment of haematological malignancies. There are now six FDA approved cell therapies, four targeting CD19 for the treatment of CD19+ lymphomas and leukemias, and two targeting BCMA to treat multiple myeloma. However, there is still no approved CAR-T product to treat solid tumours, and clinical success for CAR-T in solid tumours has been limited. Factors that make solid tumours more difficult to treat include (i) the immunosuppressive tumour microenvironment resulting from oxygen tension and competition for metabolites, (ii) structural barriers impairing trafficking of immune cells into the tumours, (iii) heterogenous expression of target antigens resulting in incomplete killing of tumour cells (iv) immunosuppressive cytokines, regulatory T cells and anti-inflammatory macrophages that promote tumour growth and (iii) [1].

1 https://onlinelibrary.wiley.com/doi/epdf/10.1002/eji.202250039

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 tumours comprise a mass of cancer cells which cell therapies can have difficulty accessing. In contrast, blood cancers such as leukaemia are caused by cancerous cells that are circulating in the blood stream which are more easily accessible to cell therapies. In addition, solid tumour can cotain other cells such as tumour associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) which promote tumour growth.

Expanding into solid tumours

Arovella's iNKT cell therapy platform has several potential advantages over existing CAR-T treatments, particularly for solid tumours.

iNKT cells:

- Can be taken from a healthy donor and given to patients without causing graft versus host disease (GvHD);
- Contain an invariant T cell receptor that targets lipid-bound CD1d, an antigen present on several tumour types;
- Can be modified to produce a chimeric antigen receptor (CAR) to target specific tumours and make them dual-targeting for tumours that express the target antigen and CD1d;
- Can be expanded >5,000 fold to generate a significant number of doses from a single manufacturing batch;
- Can modify the tumour microenvironment and kill cells that support tumour growth such as myeloid-derived suppressor cells (MDSCs) and tumour associated macrophages (TAMs);
- Can recruit other immune cells to aid in tumour destruction; and
- Naturally fight solid tumours, as shown through the correlation between the natural level of iNKT cells in a cancer patient and improved prognosis in several solid tumour types, including head and neck and colorectal cancer.

Introducing ALA-105

A new program to target Claudin 18.2 in gastric and pancreatic cancers

Arovella has recently secured a global, exclusive licence for the use of a novel monoclonal antibody (mAb) sequence targeting Claudin 18.2 (CLDN18.2) in cell therapies.

The mAb, known as SPX-101, has completed all preclinical proof-of-concept, safety and specificity studies and toxicology studies required to commence a phase 1 trial to treat gastric cancers.

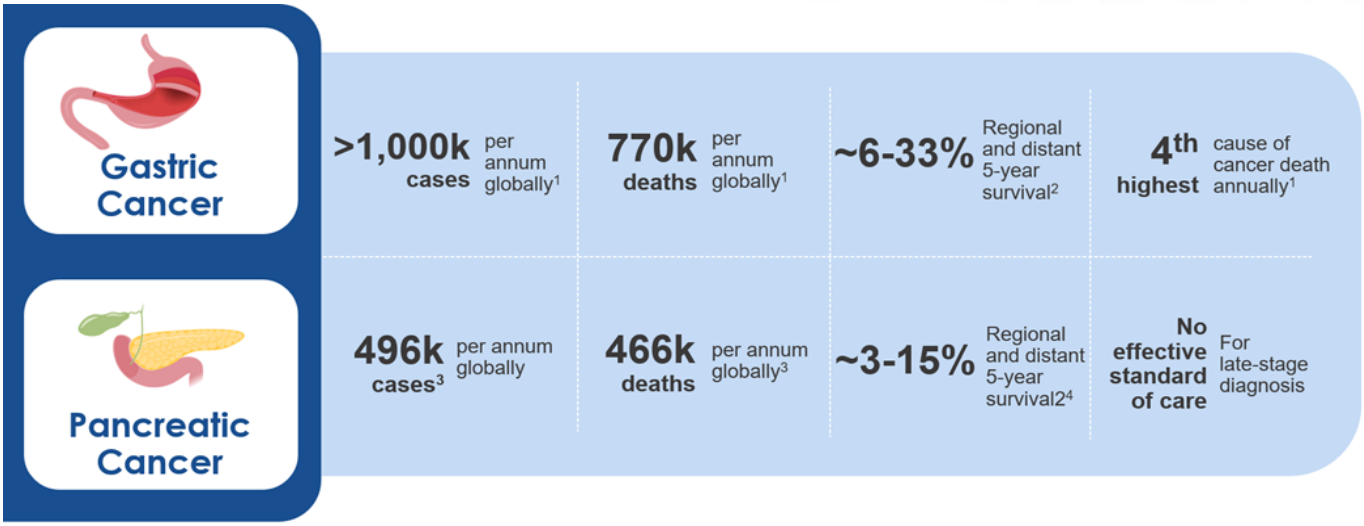
Arovella will use the sequence to develop a world-first CAR-iNKT cell therapy targeting CLDN18.2, leveraging its proprietary manufacturing process for CAR-iNKT cells.

CLDN18.2 is a validated target which is expressed in gastric cancer (GC), gastroesophageal junction cancers(GEJC) and pancreatic cancer (PC). Initial proof-of-concept data to demonstrate the potential of this approach is expected to be available in H1 CY24.

Cancer target and unmet need

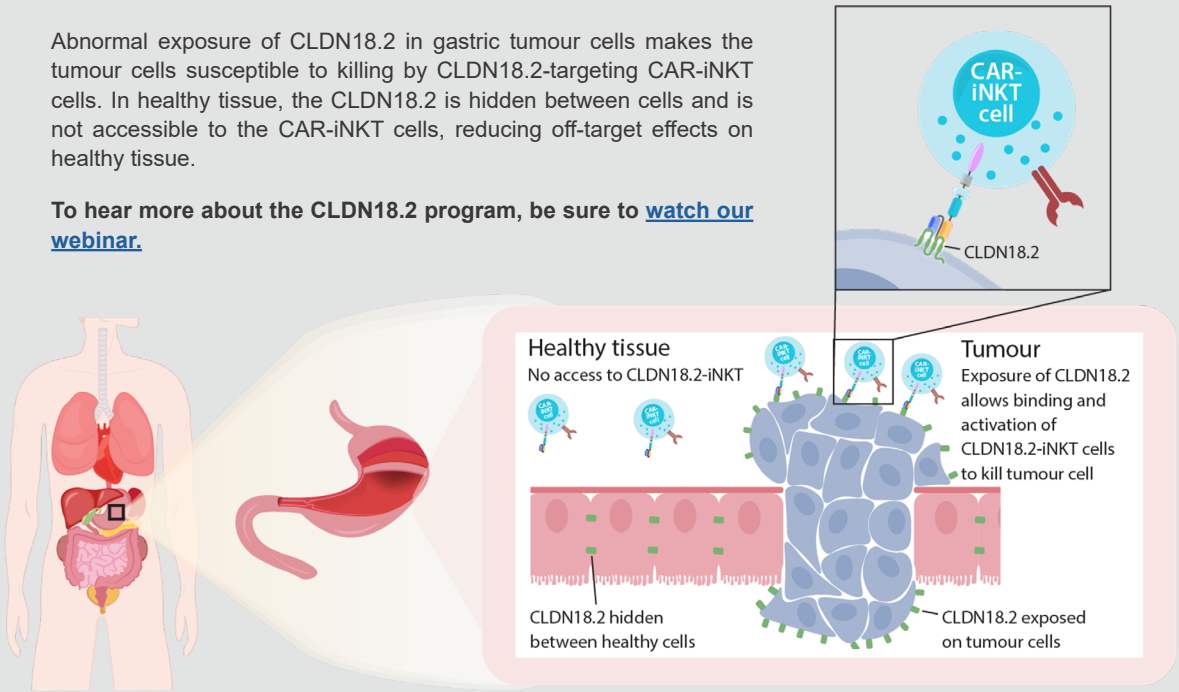
CLDN18.2 is expressed in a high proportion of GCs, GEJCs, PCs, and other solid tumours. GC and GEJC continue to present as high unmet medical needs with over one million new cases diagnosed per annum globally and 789,000 deaths, making it the fourth most fatal cancer globally.[1] Over 496,000 individuals were diagnosed with PC worldwide in 2020 with an estimated 466,000 deaths the same year.[2] Stage 4 pancreatic cancer has a five-year survival rate of 1% with the average patient living for approximately 1 year after their diagnosis.[3] 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.[4]

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*



Abnormal exposure of CLDN18.2 in gastric tumour cells makes the tumour cells susceptible to killing by CLDN18.2-targeting CAR-iNKT cells. In healthy tissue, the CLDN18.2 is hidden between cells and is not accessible to the CAR-iNKT cells, reducing off-target effects on healthy tissue.

To hear more about the CLDN18.2 program, be sure to watch our webinar.



ALA-105 will be the only CLDN18.2-targeting CAR-iNKT product in development.

Claudin 18.2 is not expressed in most healthy tissues but is found in gastric mucosal membrane epithelial cells (lining of GI tract). In normal tissues, Claudin 18.2 is sequestered in tight junctions between cells so is not accessible. Changes in cancer cells leads to exposure of CLDN18.2 and it is expressed on primary cancers and metastases.

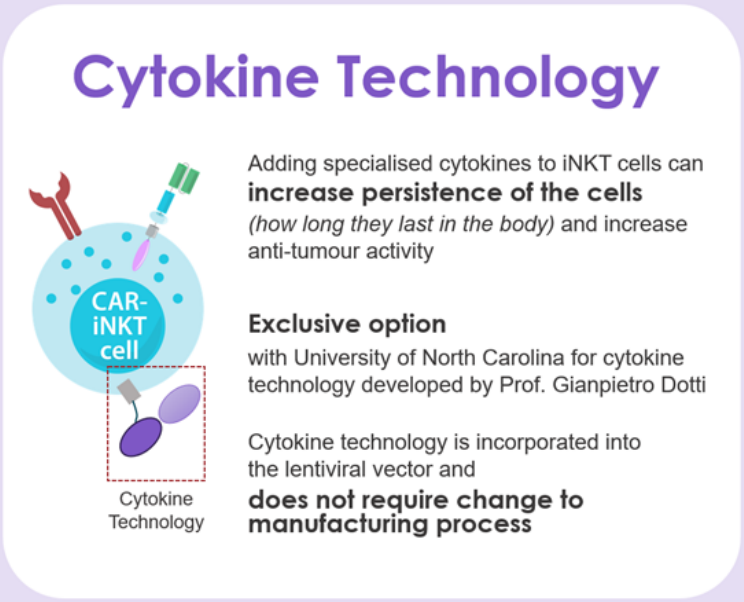
Cytokine technology enhances iNKT cell platform

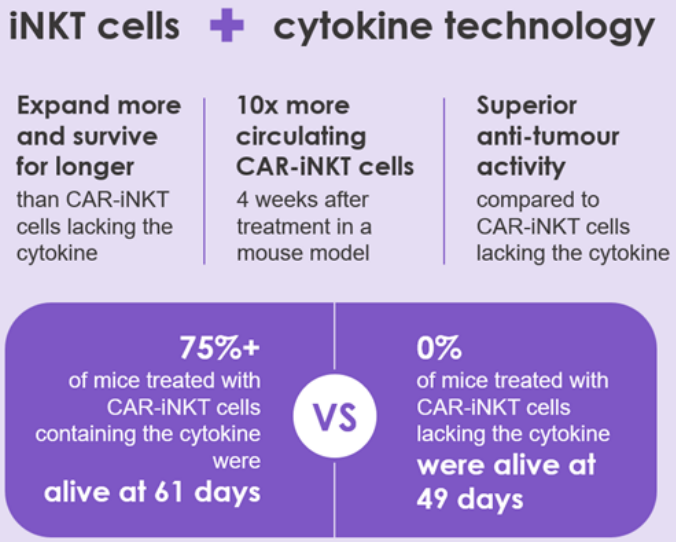
Further supporting its expansion into solid tumours, Arovella continues to assess a novel cytokine technology that is able to enhance the persistence and antitumour activity of iNKT cells.

In December 2022, Arovella announced an Option agreement for a cytokine technology out of University of North Carolina. The cytokine technology under this Option agreement incorporates the production of a specialised cytokine in iNKT cells, enabling them to persist longer and grow in higher numbers *in vivo*, leading to better anti-tumour activity. The technology also incorporates additional features to enhance its safety profile relative to a previously used cytokine technology.

In June, animal data demonstrated that the cytokine technology resulted in prolonged persistence of iNKT cells and higher iNKT cell numbers, which correlated with significantly greater activity against tumours in mice.

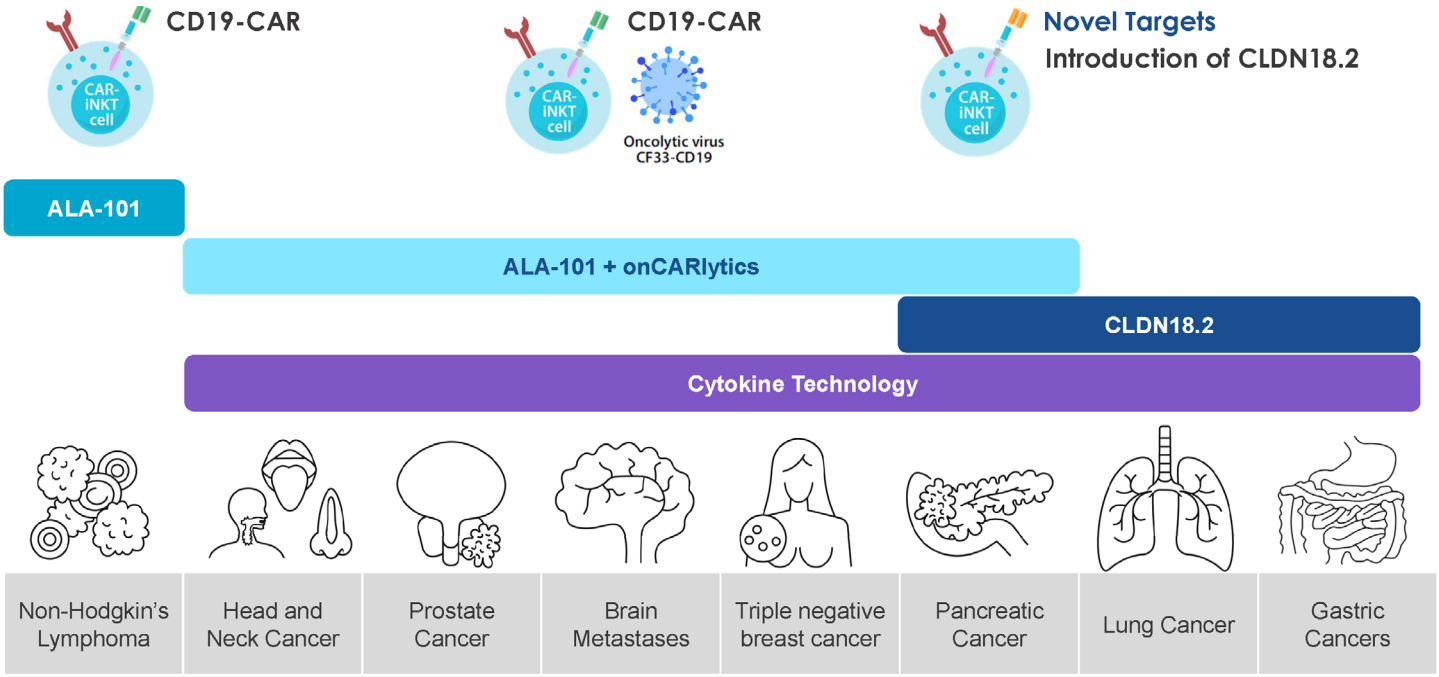
This novel technology may represent a significant advancement in iNKT cell drug development and could further differentiate Arovella's iNKT cell technology from others in the space. Arovella is one of a small group of companies globally, and the only Australian company, developing therapeutics based on iNKT cells and is focused on ensuring its position by in-licensing complementary technologies. Arovella and UNC Lineberger are currently in discussions about the terms of a formal, definitive licence agreement relating to the cytokine technology.





Arovella's expanding pipeline

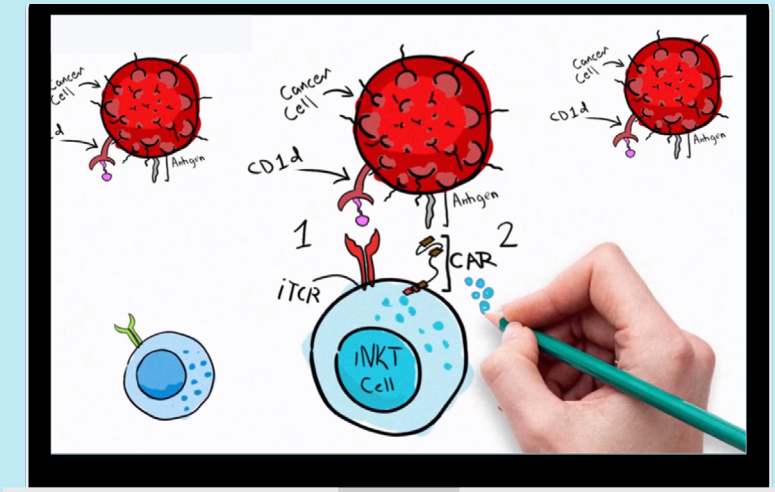
Arovella is proud to have a strong pipeline targeting both blood cancers and solid tumours. ALA-101 is being developed to treat CD19+ lymphomas and leukemias and is also being combined with Imugene's onCARlytics platform for use in solid tumours. Arovella continues to add new targeting technologies to its pipeline, including the recently acquired CLDN18.2, and it has an Option for a cytokine technology to enhance the entire platform.



Strong cash position due to Placement and SPP and R&D tax

Arovella is now in a solid financial position with a closing cash balance at the end of the September quarter of $5.32 million, compared to $5.18 million at the end of the previous quarter. Since the end of the quarter, the Company has also received its FY2023 R&D Tax Incentive refund of $1.94 million, further strengthening its cash position.

Want to know more about CAR-iNKT Cell Therapy?



Arovella has created an explanatory whiteboard video to help explain how iNKT cells, together with CARs, fight cancer cells.

The video provides investors with a simple, easy to understand overview of how Arovella is developing cell therapies for cancer treatment.

After watching the video you will be able to explain the 'cell therapy revolution' and grasp its future potential in the fight against cancer.

Watch the CAR-iNKT explanatory video

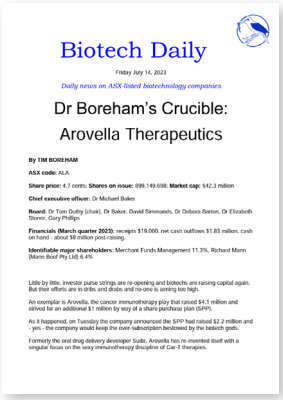
Recent communications

To catch-up on the latest news from Arovella, be sure to stream the following webinars and presentations.

Watch the Claudin 18.2 webinar

Watch the September investor non-deal roadshow

Watch the ASX Emerging Gems Conference


Biotech Daily

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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Arovella Therapeutics

By TIM BOREHAM

ASX code: ALA

Share price: 4.7 cents; **Shares on issue:** 899,149,698; **Market cap:** $42.3 million

Chief executive officer: Dr Michael Baker

Board: Dr Tom Duthy (chair), Dr Baker, David Simmonds, Dr Debora Barton, Dr Elizabeth Stoner, Gary Phillips

Financials (March quarter 2023): receipts $19,000, net cash outflows $1.83 million, cash on hand - about $8 million post-raising.

Identifiable major shareholders: Merchant Funds Management 11.3%, Richard Mann (Mann Boof Pty Ltd) 6.4%

Little by little, investor purse strings are re-opening and biotechs are raising capital again. But their efforts are in dribs and drabs and no-one is aiming too high.

An exemplar is Arovella, the cancer immunotherapy play that raised $4.1 million and strived for an additional $1 million by way of a share purchase plan (SPP).

As it happened, on Tuesday the company announced the SPP had raised $2.2 million and - yes - the company would keep the over-subscription bestowed by the biotech gods.

Formerly the oral drug delivery developer Sudo, Arovella has re-invented itself with a singular focus on the sexy immunotherapy discipline of Car-T therapies.

Read Arovella's recent coverage in Biotech Daily's Dr Boreham's Crucible

Stay up to date!

Keep an eye out on our social channels, including our new Instragram page, to stay up to date on the latest news.

 | investor@arovella.com