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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: 14 cents; **Shares on issue:** 1,050,775,660; **Market cap:** $147.1 million

Chief executive officer: Dr Michael Baker

Board: Dr Thomas Duthy (chair), Dr Baker, Dr Debora Barton, Dr Elizabeth Stoner, Gary Phillips

Financials (June quarter 2024): receipts nil, net cash outflows $1.82 million, cash balance $12.7 million, quarters of available funding: 7.0

Identifiable major shareholders: Merchant Funds Management 6.02%, Richard Mann (Mann Beef Pty Ltd) 6.16%, MB Investment Capital 2.64%, James Evans Hughes-Morris 2.1%

Fickle fashion trends don't just apply to apparel: a hot area two years ago, the cell therapies sector is struggling to retain investor interest amid hyped-up expectations, clinical setbacks and high development and manufacturing costs.

In the frank words of Arovella chief Michael Baker: "It's in the worst shape it has been since the highs of 2018 to 2020."

Dr Baker points to lay-offs and shutdowns among the expanding US cell manufacturing companies. "A lot of them came out of the woodwork but should not have and will eventually fall away," he says.

Cell therapy refers to extracting human cells from a patient or donor and tricking them up so they can fight disease more effectively.

There's a silver lining to the malaise: pharmaceutical companies are still paying big dollars for the emerging players, even at early (phase I) clinical phase.

Arovella is seeking to overcome the problems of CAR-T (chimeric antigen receptor) therapies by involving invariant natural killer (INKT) T- cells, one of the body's strongest immune cells which Dr Baker dubs the "soldiers of the blood stream".

"They are rabid killers and we can manufacture them so they are even more potent and then we will give them to patients," he says.

Arovella's lead blood cancer program is about to enter phase I trials, but the company is also eyeing developing the world's first CAR-INKT therapies to tackle gastric, oesophageal and pancreatic cancers.

"This is a very important area for the large pharma companies and we are happy to be in a very niche area of the sector," Dr Baker says.

Straight as an arrow

Arovella started out as Eastland Medical, which listed in 2001, first for syringes and then its unsuccessful Artimist sublingual malaria treatment. Eastland became Suda Pharmaceuticals in 2012 developing a spray-based oral drug delivery platform called Oromist, and took the insomnia treatment, Zolpimist, to market.

Biotech entrepreneur Paul Hopper took over as executive chair in 2019 and oversaw sweeping changes: appointing Bioscience Managers investment guru Dr Baker as CEO, ditching the oral delivery program and closing the company's Perth research and development headquarters.

In June 2021, Arovella signed a deal with Imperial College London to acquire its invariant natural killer T (INKT) cell platform.

INKT cells are a rare variant of T-cells. The acquired program, ALA-101 targets a blood cancer marker called CD19 (see below).

In October 2021, the company changed its name to Arovella, which derives from arrow (as in targeted drug delivery) and novel (as in new therapies).

Mr Hopper quit the board in June 2022, with Dr Thomas Duthy eventually becoming chair. Dr Duthy's day job is heading Neurotech, which is developing cannabinoid-based treatments for childhood neurological disorders.

In September 2022, Arovella entered a joint development program with the ASX-listed Imugene - of which Mr Hopper is chair - but in March this year Imugene said it no longer wanted to continue.

Prêt à porter cells

The US Food and Drug Administration has approved six CAR-T treatments, all of them targeting CD19 or the B-cell maturation antigen (BCMA) for blood cancers (leukaemia, lymphomas and multiple myelomas).

But because of the incidence of secondary malignancies, albeit low, they all come with an FDA ‘black box’ warning.

Most of the treatments are based on using the patient’s own cells - the autologous approach - which is more bespoke but takes longer, is more expensive and uses potentially compromised cells.

Arovella seeks to avoid the problems with the allogeneic method, by which cells are derived from healthy donors.

The doses are stored at minus 170°C and are shipped to clinical sites when needed.

Dr Baker notes that bog-standard T-cells account for 70 percent of the body’s immune cells, while 10 to 15 percent are ‘natural killer’ (NK) cells.

The elite INKTs make up 0.1 to 1.0 percent.

“Both [T-cell and NK cells) have limitations: T-cells can’t be used off-the-shelf unless they are genetically engineered, which requires an extra step,” he says.

“NK cells can be given from one person to another, but the desired level of activity has not been seen to date.”

Manufacturing - dull but important

Dr Baker says Arovella didn’t invent INKT cells - nature did - but the company’s smarts are tied up in a multi-step manufacturing process that can be done in numerous ways.

“Manufacturing doesn’t sound that interesting but it is an enormous milestone for us,” he says.

“It turns us from a potentially one-product company to a platform company with a number of shots at goal.”

Dr Baker says CAR-Ts are curing patients, but the autologous approach means doses have to be made every single time.

In the US, more than 80,000 lymphoma and more than one million gastric cancer patients are diagnosed every year.

“How do you manufacture that many doses of cells with proper quality control?” he asks. “If you have to quality control every dose there is a bottleneck.”

ALA-101 trial, here we come

Arovella's lead program, ALA-101, is showing early promise as a treatment for CD19-expressing blood cancers.

Earlier mouse work involved the rodents being infused with CD19-expressing, aggressive B-cell acute lymphoblastic leukaemia cells. At the 90-day mark, 95 percent of those treated with ALA-101 (CAR19-INKT cells) remained alive, while only 60 percent of those treated with CAR-T therapies survived.

This week, the company said it had received a response from the FDA for its pre-investigational new drug (IND) meeting, with the feedback providing "clear and achievable" requirements for a submission.

The planned phase I study will be in two parts: a dose escalation stanza with nine to 12 patients and then a phase Ib expansion to more patients. The company expects to lodge its IND application by April 2025.

Targeting solid tumors

In October 2023, the company licenced a technology revolving around the protein Claudin18.2 (CLDN18.2), from the Chinese-US Sparx Group.

Known as ALA-105, the program uses the same manufacturing platform, but with a different lentivirus carrying the genetic material to make a CAR-targeting CLDN18.2.

CLDN18.2 is expressed on gastric, pancreatic and oesophageal cancers and some ovarian and lung cancers (not healthy cells).

The company is using its INKT cell platform to target such solid tumors.

"This is because of the INKT cell's ability to infiltrate tissues and tumors, to block cells that promote tumor survival and to release cytokines to stimulate an immune response," Dr Baker says.

Dr Baker says CLDN18.2 is positioned to be like the next human epidermal receptor growth factor-2 (HER-2), the common biomarker expressed in one in five breast cancers and some bladder, ovarian, pancreatic and stomach cancers.

He notes that a CLDN18.2 targeting drug, Astellas Pharma's zolbetuximab was approved in Japan for gastric cancers, while an FDA application has been lodged.

While the drug is based on a monoclonal antibody rather than a cell, Dr Baker says the drug validates the CLDN18.2-targeting approach even though trial results were pretty ordinary.

In January, after 18 months of effort, Arovella made its first lentivirus - which delivers the requisite genetic material to the INKT cells.

Tickling up

In January, Arovella further licenced a cytokine ‘armoring’ tech called IL-12-TM, from the University of North Carolina’s Lineberger Comprehensive Cancer Center.

IL stands for interleukin and TM is trans-membrane not just the trade mark.

As the name suggests, the technology will strengthen the INKT platform’s ability to target solid tumors; and was developed by Prof Gianpietro Dotti, who is on Arovella’s scientific advisory board.

Animal data published in Nature Communications shows IL-12-TM “enhances CAR-INKT persistence, and therefore cell numbers, which provides better anti-tumor activity (including solid tumors such as neuroblastomas)”.

The Viagra of the immune-oncology sector, the program could result in more potent and longer lasting INKT cells.

Finances and performance

At the end of the June quarter, the company had cash of $12.7 million following a $12.5 million placement - enough to start dosing patients and capturing data.

The over-subscribed offer was struck at 10 cents a share, with attaching one-for-one options exercisable at 15 cents a share within the next three years. Shareholder assent was required but investors waved the proposal through at a May meeting.

Over the last 12 months Arovella shares have traded between 4.0 cents (August 2023) and 19 cents (February 2 this year). They hit a record low of two cents in early 2023, but surged 180 percent in the past year.

Dr Baker says the register has transformed since 2020. The biggest holders are the ubiquitous Merchant Group and beef baron Richard John Mann, who has invested in other biotechs including Imugene.

Almost ‘virtual’ in nature, the company prides itself on a low cash burn and you will rarely find Dr Baker at the pointy end of the plane.

Sizing the rivals

The CAR-T space has competition from dozens of drug developers, with a good smattering of NK-focused companies as well.

But the INKT space is a different matter: Arovella ranks among only five of them globally.

Setbacks have abounded.

(Quasi) rivals are the Nasdaq-listed, $US76 million market cap MINK Therapeutics (phase I stage) and the private, pre-clinical Appia Biotech (which is in partnership with cell therapy leader Kite Pharma).

The nearest exemplar to Arovella, Appia uses a different manufacturing method but is not yet in clinical trials.

Deals included Astrazenca acquiring Graycell last December for $US1 billion up-front for a phase Ib technology.

Dr Boreham's diagnosis:

Dr Baker says now that the company has a genuine platform, it will sniff around for new CAR-T programs that leverage the know-how.

"We are constantly looking for 'CARs' like this that we can integrate into our manufacturing platform and develop for a range of cancers."

The company cites one million new diagnoses of gastric and oesophageal junction cancers a year, with 789,000 deaths. That makes them the fourth most fatal cancer.

The gastric cancer market was worth $US2.1 billion in 2021 and is forecast to be worth $US10.76 billion in 2031.

The deadliest is pancreatic cancer: in 2020, 496,000 patients were diagnosed and 466,000 died. Stage four pancreatic cancer has a miserable five-year survival rate of one percent.

While earlier-stage biotechs aspire to be taken over, Dr Baker says "at a philosophical level" the company wants to progress its tech to commercialization.

Given the six FDA approved CAR-T products were approved at phase II with fewer than 100 patients, Arovella has a fighting chance.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort - even at a philosophical level