



SYNthesis BioVentures - Newsletter no. 2 (September 2023)

Dear collaborators and followers,

We welcome you to the second newsletter of SYNthesis BioVentures ("**SYNBV**", or "**Fund**"). As noted in our first newsletter, we will cover updates to the fund as well as highlight the science we find exciting and investable. As always, feedback is sought and welcome.

Fund Update:

1. The Fund has recently placed its second investment, A\$2.25M via a SAFE note into Aculeus Therapeutics Pty Ltd. Details on the science behind Aculeus are in the investment snapshot below.
2. The SAFE note is set to convert into equity at a 20% discount to the share price of the next qualified financing (a raise of at least another \$4.5M from outside investors as described below).
3. Other investors in Aculeus include 27 individual investors; most of whom were investors in the SYNthesis Group and have supported Aculeus from incorporation. Notably, the assets in Aculeus have had an aggregate sum of >A\$45M already invested through the Cancer CRC, SYNthesis Research and the previous entity that held the newly acquired phase 2 asset.
4. An innate immunity oncology focused company, Aculeus has a pipeline targeting 3 immunological pathways proven to trigger the body's immune response to cancer and other antigens: TLR-9, STING, and ENPP-1. Aculeus has recently acquired an asset in phase 2, Pixatimod (TLR-9 agonist), and is working towards the imminent start of clinical studies for its STING agonist lead candidate in early 2024.

Team Member in Focus: Fabio Turatti (Managing Director)

Fabio is one of the three Managing Directors SYNBV. Fabio is a successful C suite executive in the Australian high-innovation sector. Schooled in Australia, Fabio spent 10 years of his 20-year career in Europe, developing and managing novel high-innovation technology platforms. In 2007, Fabio returned to Australia to take up the role of Research Manager of Avipep Pty Ltd. Fabio led Avipep's technology platform to a first-in-man study. In 2011, Fabio took on the role of CSO of Sienna Cancer Diagnostics Limited, and was part of the team that led to the commercialisation of Sienna's technology.

In 2013, Fabio took on the role of COO of SYNthesis Research and became CEO as of 2021. He manages the drug development and expert management team that supports all SYNBV investee companies.

Fabio has extensive experience in pharma licensing and partnering transactions, start-up funding, investment and capital models, risk analyses for high-tech programs, change management and corporate restructuring. Since 2007, Fabio has taken a key or leading executive role in all investment strategies and capital raising rounds transacted by the companies and subsidiaries he has been employed in, or consulted to, amounting to over \$50 million.

Fabio has a Bachelor of Biotechnology from the University of Wollongong (NSW) and a PhD in Immunology and Immunotherapy from Open University London, for his research performed at

the Italian National Tumour Institute (L'Istituto Nazionale dei Tumori) and the FIRC Institute of Molecular Oncology (Milan, Italy).

Investment Snapshot – Aculeus Therapeutics Pty Ltd

Overview

- Address: Bio21 Institute, 30 Flemington Road, Parkville VIC 3052, Australia
- Web: <https://aculeustx.com/>

Snapshot:

Immuno-oncology

Immuno-oncology (I/O) is one of the most promising avenues of therapeutics for cancer patients to emerge over the past few years. Cancers often express “molecular switches” known as checkpoint inhibitors. Under normal circumstances, checkpoint inhibitors keep the immune system in check and prevent it from attacking the body’s own, normal, cells. Many cancers utilise these checkpoints to shut down the immune response to the cancer and divert it from the tumour’s uncontrolled growth. A class of I/O drugs known as Checkpoint Inhibitors reverse this and are able to reactivate the immune system’s ability to detect and destroy cancers.

However, despite their popularity and significant sales figures, I/O drugs – such as the checkpoint inhibitors Optivo and Keytruda—only demonstrate limited efficacy, particularly with solid tumours. Very often, this is because such tumours are “cold”, i.e. have limited penetration and activity of immune cells within them.

Multiple molecular pathways are able to turn “cold” tumours into “hot” ones in which a robust immune response is mounted by the body against such tumours, and enabling the subsequent activity of checkpoint inhibitors. It is on three of these pathways—TLR-9, STING and ENPP-1—that Aculeus is focused.

The market for I/O drugs and their combination with drugs designed to enhance their efficacy is huge and growing fast; it is expected to grow from US\$35B today to over \$57B in 2025, with much of the growth attributed to drugs that enable the improved function of checkpoint inhibitors, such as the drugs Aculeus is currently developing.

Aculeus

Aculeus was established in 2019 as a spin off from the Federal government funded Cancer CRC program, with the SYNthesis group as its main investor. In the beginning of 2023, Aculeus licensed a phase 2 asset. All told, over \$45M have been invested in its 3 programs:

1. Pixatimod, a phase 2 asset targeting the TLR-9 pathway. TLR-9 (or Toll-like receptor 9) is a protein receptor found on immune cells called antigen-presenting cells (APCs), including dendritic cells and macrophages. TLR-9 is primarily involved in recognizing and responding to microbial and viral DNA. However, it also has a critical role in activating the immune response to cancer, including inducing the death of tumour cells and the activation of dendritic cells which in turn trigger a wider immune response to cancer. The asset has been shown to have compelling efficacy in early phase 1b trials in combination with Nivolumab (Opdivo) in a subset of colorectal cancer patients.
2. ACU-0943, a preclinical asset targeting the STING pathway currently in IND enabling studies, expected to enter the clinic in Q1 2024. The STING (Stimulator of Interferon Genes) pathway is a cellular signaling pathway that plays a crucial role in innate immune responses against microbial infections, as well as in the detection and control of tumor cells. The stimulation of Interferons leads to the activation of immune cells, such as

- natural killer (NK) cells and T cells, which can directly eliminate malignant cells. Additionally, the STING pathway promotes the maturation and activation of dendritic cells, enhancing antigen presentation and the generation of adaptive immune responses. ACU-0943 is currently undergoing IND enabling studies, which are designed to demonstrate it is safe to begin clinical testing in humans. Clinical trials are slated to begin in Australia and potentially the US in the first quarter of 2024.
3. ENPP-1 Inhibitor program, a set of preclinical molecules which inhibit the ENPP-1 enzyme. ENPP1 (Ectonucleotide Pyrophosphatase/Phosphodiesterase 1) is an enzyme encoded by the ENPP1 gene. It is a type II transmembrane glycoprotein that is expressed on the cell surface and in the extracellular matrix of various tissues. While ENPP-1 plays a role in a wide variety of cellular processes, it is significant in the context of cancer since its inhibition induces the expression of STING. As such, the two proteins are closely related. Aculeus is expected to select a final candidate for IND enabling studies in the coming months, which will allow the lead molecule in this program to begin clinical testing in late 2024 or early 2025.

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