

SYNthesis BioVentures - Newsletter no. 1 (8th of May 2023)

Dear Investors, collaborators, and followers,

We welcome you to the first quarterly newsletter of SYNthesis BioVentures ("**SYNBV**", or "**Fund**"). This newsletter is in a format we will reproduce quarterly, giving you updates on our progress, while also providing insights into the science SYNBV finds exciting. Your feedback is most welcomed.

Fund Update:

1. SYNBV was granted its provisional ESVCLP license in July 2022, and proceeded with its fund raising efforts in tandem with the restructuring of the SYNthesis Group's holdings. As of May 1st, the Fund has obtained commitments of \$18 million.
2. We are now embarking on an effort to bring our committed capital up to A\$30M with an ultimate goal of reaching our maximum size of \$75M, and have started working with multiple parties to organise road shows in Perth, Sydney, Brisbane and Melbourne.
3. We welcomed two senior SYNthesis Group employees into key roles at SYNBV:
 - Dr Martine Keenan: Fund Chief Scientific Officer
 - Dr Simon Preston: Fund Investment Analyst.
4. The Fund has recently completed its first investment of A\$3.8M into Catalyst Therapeutics Pty Ltd, a cutting-edge joint venture between the SYNthesis Group and the WEHI, Melbourne's oldest and most prestigious Medical Research Institute. Anaxis Pharma Pty Ltd, a wholly owned subsidiary of Catalyst and the main operating subsidiary, is developing first in class drugs for the treatment of acute and chronic inflammatory diseases.
5. Other investors in Catalyst's total A\$11.7M seed round included WEHI and the Pharm Bio Pty Ltd as trustee for the Pharm Bio Trust, the unit trust of the SYNthesis Group shareholders. The company is planning to raise an additional A\$10-12M in or before the 4th quarter of 2023, in order to facilitate IND-enabling studies on its lead asset.
6. The Fund is already gearing up to make its second investment into Aculeus Therapeutics Pty Ltd, a SYNthesis Group portfolio company with a pipeline focussed on developing small molecule activators of innate immunity for oncology. The company is currently in the process of acquiring a clinical asset that will help facilitate an ASX listing in late 2023 or early 2024.

Team Member in Focus: Dr Martine Keenan (Fund CSO)

Dr Martine Keenan brings to the Fund exceptional national and international experience in translational drug discovery and development, and a reputation as a respected and accomplished executive. Martine has enjoyed a 20-year career in the pharmaceutical industry in the UK and in Australia.

She is an expert in all phases of preclinical drug development, IP creation, program due diligence, consultancy and research commercialisation. She has executed major projects managing technical, logistical, and strategic activities and leads early-stage biopharmaceutical companies. Martine has a Bachelor of Science (Chemistry) and a PhD in Organic Chemistry both from King's College London and is a Fellow of the Royal Society of Chemistry.

Investment Snapshot – Catalyst Therapeutics Pty Ltd

Snapshot:

Inflammation, which is the body's response to injury or infection, is a complex process that involves the activation of immune cells, the release of cytokines and other signalling molecules, and the recruitment of additional immune cells to the affected area. These processes can lead to widespread tissue damage and the activation of cell death pathways exacerbating the inflammatory cycle. The research team at Anaxis are world leaders in an important programmed cell death pathway called necroptosis. Necroptosis is at the core of multiple inflammatory diseases and drugs targeting this pathway provide a new approach to tackling the complex underlying mechanisms of inflammatory disease.

The burden of inflammatory disease touches over 60 million people in the US alone, with an estimated economic burden which is estimated to reach US\$5.7 Trillion per year as early as 2026. The lack of satisfactory treatments for many patients suffering from inflammatory disease conditions is recognised by regulators, payers, and pharma companies alike.

Necroptosis: A Key Driver of Inflammation

Our immune systems have evolved to simultaneously protect us from pathogenic microorganisms and prevent autoimmunity or inappropriate immune activation. The former requires a robust inflammatory responses and coordination of innate, humoral, and adaptive immunity. Conversely, the latter requires mechanisms that prevent immune recognition of self or prolonged inflammation with catastrophic effects. When the balance of these complex and essential components of our immune defence are inappropriately activated this can result in inflammatory or auto-immune diseases.

Tumour necrosis factor (TNF) is a protein produced by immune cells that plays a critical role in the regulation of inflammation and immune system responses. TNF is involved in a variety of physiological processes, including cell death, immune system regulation, and inflammation. Dysregulation of these critical signalling pathways is a known driver of inflammatory disease. Therapeutic products that target TNF are among the most successful drugs for the treatment of chronic inflammatory and autoimmune pathologies (including Remicade, Enbrel, Cimzia, and of course, Humira). The anti-TNF market was estimated at USD ~30B in 2022 for the treatment of a host of auto-immune diseases including IBD, psoriasis, rheumatoid arthritis, and others. However, up to 40% of patients on anti-TNF treatments don't respond or will lose responsiveness over time.

In recent years, it has become clear that TNF drives inflammatory responses not only directly by inducing inflammatory gene expression but also indirectly by inducing necrotic cell death, instigating inflammatory immune reactions and disease development. TNF-driven inflammatory cell death was first described in 1996 but it wasn't until 2005 that this form of cell death was termed Necroptosis. Necroptosis is a programmed cell death mechanism that occurs as a result of inflammation, whilst also promoting it. Necroptosis is initiated by the activation of specific signaling pathways which lead to the formation of a protein complex called the necrosome. The necrosome promotes the activation of specific enzymes that translocate to the cell membrane and cause the disruption of the membrane, leading to cell death. The dying cells 'burst', releasing the cellular contents that includes pro-inflammatory danger signals that cause immune hyperactivation. Designing drugs that inhibit key proteins in the necroptosis pathway is a novel and exciting approach to treating TNF-dependent inflammatory diseases.

Necroptosis has been implicated in well over 20 different human diseases with unmet medical need. These include both acute and chronic inflammatory conditions. Acute indications include kidney injury with varying aetiologies, pancreatitis and lung injury following viral infection. Chronic indications are some of the most costly to healthcare systems and include IBD, NASH, psoriasis, atopic dermatitis, arthritis, COPD, fibrotic disease, and multiple sclerosis. Successful

development of a drug that can treat so many blockbuster diseases and have such a tremendous impact on human health and disease is an exciting commercial prospect.

Anaxis has a unique pipeline which has successfully demonstrated engagement of molecular targets in the necroptosis pathway that have hitherto been considered "undruggable". It is this combination of unique science and competitive position that supports SYNthesis BioVentures investment into Anaxis Pharma, and its ambitions to leverage its market leading science to treat multiple high value indications.

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