PITT STREET RESEARCH

AdAlta Limited

I-bodies finally in the clinic

Share Price: $0.11

ASX: 1AD

Sector: Healthcare

28 July 2020

AdAlta is developing antibody-like drugs called i-bodies with the same target specificity and affinity as a monoclonal antibody, but about 90% smaller. It will also more likely be cheaper to make, easier to administer and capable of addressing difficult-to-treat diseases such as fibrosis. AdAlta had originally intended for the first clinical product from its platform to be AD-114, initially for the treatment of Idiopathic Pulmonary Fibrosis (IPF). In 2018 it replaced this programme with AD-214, an Fc-Fusion protein with much longer half-life and enhanced activity that is expected to broaden the clinical indications beyond IPF. AdAlta's new drug entered the clinic in July 2020.

AdAlta may have a blockbuster drug in AD-214

We believe that AD-214 can be game-changing in IPF. While there are two existing drugs for this condition, they have limited efficacy in individual patients, either having no effect or only slowing down disease progression. AdAlta has shown with its drug that it can reduce fibroblast migration to the lungs and seems to work on both 'slow progressors' and 'fast progressors'. We believe there is a billion-dollar opportunity for AD-214, initially in IPF, and after that in other fibrotic diseases.

AdAlta's platform technology has considerable upside

Monoclonal antibodies are a workhorse of modern medicine with global sales of >$US115bn pa. But they are expensive to make, and their molecule size makes them too big for use against many important drug targets. They also require heavy dosing, and this must be delivered by intravenous infusion. AdAlta's i-bodies are a much more elegant alternative. We think this platform can yield a strong pipeline of candidates beyond AD-214 over the next few years.

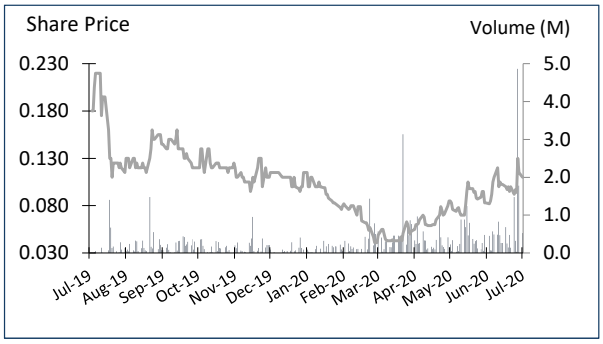
Valuation

We value AdAlta at 25 cents per share base case and 52 cents per share optimistic case, using a probability weighted DCF valuation approach. We see AdAlta being re-rated by the market as Phase 1 work on AD-214 gets underway and the company builds out its pipeline of i-body drug candidates.

Market Cap. (A$ m)	18.0
# shares outstanding (m)	163.9
# share fully diluted	163.9
Market Cap Ful. Dil. (A$ m)	18.0
Free Float	100%
12 months high/low	$0.22 - $0.041
1 / 3 / 12-month performance	16% / 120% / -44%
Website	adalta.com.au

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)



Source: FactSet, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A$)	0.25 / 0.52
WACC	15.2%
Assumed terminal growth rate	None

Source: Pitt Street Research

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Table of Contents

Introducing AdAlta (ASX: 1AD)

Who is AdAlta? AdAlta is a Melbourne-based drug development company focused on a new class of protein therapeutic called the i-body. I-bodies are small, human protein 'scaffolds' that mimic some powerful antibody components originally derived from shark antibodies. The result is a drug that has the advantages of monoclonal antibodies, namely, high target specificity and affinity, but at only 10% of the size of a standard monoclonal, so that the same drug is easy to deliver and can access difficult targets traditionally only associated with small molecules. AdAlta's platform allows highly stable i-bodies to be engineered against any extracellular drug target of interest. The company is going after targets that have up until recently been difficult to target with monoclonal antibodies, most notably G Protein Coupled Receptors (GPCRs) and ion channels. The company's original lead candidate until 2018 was AD-114, which targets a GPCR called CXCR4 with an initial indication in the Orphan lung disorder Idiopathic Pulmonary Fibrosis (IPF). In April 2018 AdAlta made the decision to replace AD-114 with AD-214, an Fc-Fusion protein with much longer half-life and enhanced activity to support application in a wider range of clinical indications for fibrosis beyond IPF. That drug entered its first clinical trial in July 2020.

Monoclonal antibodies are a significant drug class today

What are monoclonal antibodies and why are they important? Antibodies are Y-shaped proteins naturally created by the immune system to fight disease. They work by binding to a particular molecule, called the antigen, which the immune system has identified as foreign. Each particular antibody generated by an immune response is highly specific, in the two tips of the Y, for a particular antigen. Monoclonal antibodies, in mainstream clinical use globally since around 1997, are antibodies that are used as drugs, where the drug developer has engineered a particular antibody specific to a disease target and mass-produced that antibody using the techniques of biological drug manufacture. The reason monoclonal antibodies are so important to modern medicine is their targeting power, their long serum half-life[1], and the relative ease with which they can be engineered. Using widely available antibody platforms, drugs can be created that hit disease targets, and only those disease targets, with exquisite specificity, often without a complete structure of that target being available. That's why healthcare systems and the pharma industry alike have embraced monoclonal antibodies in a serious way. From a standing start in the late 1990s monoclonal antibodies have grown to be a >US$115bn drug class today[2].

Why the need for new, antibody-like drugs? The trouble with monoclonal antibodies is that they are large molecules[3]. This means that they can only be delivered by intravenous infusion, require large doses because of the relatively low level of tissue penetration, and historically have only been good for extracellular targets[4]. They are also expensive to make. Consequently, ever since monoclonal antibodies began to mainstream as drugs in the early 2000s, the push has been on for new, antibody-like drugs, engineered around standardised protein scaffolds, that have the targeting properties of monoclonals but that are smaller. AdAlta with its i-bodies sits in a long tradition of companies such as Domantis (acquired by GSK for US$454m in

[1] Meaning they can be therapeutically effective for a long period of time. Antibodies of the IgG1 isotype, the most common isotype used for FDA-approved monoclonals, have a serum half-life of around three weeks (see Br J Pharmacol. 2009 May; 157(2): 220–233). The IgG1 isotype has historically been used because its generation and binding has historically been more consistent than the other isotypes.

[2] Lu et.. al. (2020), *Development of therapeutic antibodies for the treatment of diseases*. J Biomed Sci 27, 1 (2020).

[3] IgG1 antibodies have a molecular weight of approximately 150 kDa.

[4] Although that has been changing as techniques to engineer cell-penetrating antibodies are developed. See, for example, Mol Cancer Ther. 2012 Oct;11(10):2169-73. Epub 2012 Aug 3.

late 2006) and Ablynx (acquired by Sanofi in 2018 for US$4.8bn) that have created such scaffolds and started taking the Monoclonal Antibody Revolution to the next stage.

I-bodies function like antibodies but have many of the good drug qualities of small molecules

What are i-bodies and why are they special? And what do they have to do with sharks? AdAlta can trace its origins back to work that was done in the early 2000s on shark antibodies. Sharks generate a kind of antibody called the IgNAR whose variable binding region is around a tenth the size of human antibodies but notable for its ability to target antigens because of a unique long binding loop. Around 2004 a number of Melbourne-based scientists associated with the Cooperative Research Centre for Diagnostics[5] realised that the binding region of the IgNAR resembled a common human protein structure called the I-Set. When one particular I-Set protein, a cell adhesion molecule called NCAM1, was engineered to have the binding regions of an IgNAR, the result was the i-body, which is basically a human protein with binding structures/shape inspired by sharks but not actually containing any shark material in terms of their amino acid sequence. The reason why i-bodies are potentially special in terms of being the basis of a new drug class is that they are small, stable human proteins that function like antibodies – and can be selected as drug candidates using the standard tools of antibody drug discovery – but also have many of the good drug qualities of small molecules at the same time.

Why the choice of CXCR4 as the first target for an i-body? In 2011, after the Perth-based VC fund Yuuwa Capital led a private funding round for AdAlta and Yuuwa's James Williams and Liddy McCall had joined AdAlta's board, AdAlta began to focus, at Yuuwa's encouragement, on applying i-bodies to an important class of drug target, the G Protein-Coupled Receptors (GPCRs). GPCRs have frequently been targeted by small molecules over the years, in many cases resulting in blockbusters. Indeed, GPCRs are today one of the largest classes of drug target. However too often small molecules to GPCRs, while effective, have off-target or other toxicity issues[6]. As for monoclonal antibodies, the complicated nature of GPCRs meant that until a couple of years ago, when a new migraine drug called Aimovig[7] came along, they had never been hit by an antibody that got approved[8]. Yuuwa were convinced, and the *in vivo* evidence for AD-114 and AD-214 has since backed them up, that GPCRs could be drugged with an i-body due to the i-body's specificity and long binding loop, without the off-target side effects common with small molecules. For their first GPCR target AdAlta chose CXCR4, a complicated chemokine receptor known to be therapeutically relevant to a range of disease conditions, most notably cancer and HIV infection, but also inflammation and fibrosis. The thinking behind GPCRs and CXCR4 was that if an i-body could drug this class and this particular target then it would stand out from the crowd and potentially drive early licensing interest.

What is Idiopathic Pulmonary Fibrosis and why is this AdAlta's first indication? Idiopathic Pulmonary Fibrosis is an Orphan lung disease characterised by scarring of lung tissue that arises from unknown causes. In the US it affects around 100,000 people annually. AdAlta chose this disease as the initial indication because, as an Orphan Drug developer, the company would enjoy certain benefits in terms of speed to market and potentially favourable pricing in its early indications, after which AdAlta could go after

[5] Cooperative Research Centres are key bodies for scientific research in Australia designed to bring together researchers in the public and private sectors with the end users.
[6] Front Pharmacol. 2018; 9: 128.
[7] Aimovig (generic name erenumab-aooe, www.aimovig.com), from Amgen and Novartis, gained FDA approval in May 2018. The drug works by antagonising a molecule that is synthesised in neurons called Calcitonin Gene-Related Peptide (CGRP) – see Clin Pharmacol Drug Dev. 2017 Nov;6(6):534-547. Epub 2017 Apr 14.
[8] For one thing, GPCRs are often expressed at low levels in cells and are very unstable when purified, so just raising antibodies to them was difficult. For another, the extracellular portion of GPCRs are typically too small to be hit with an antibody. These were two of the obstacles Aimovig's designers had to overcome.

larger market opportunities. Also, while there were two approved drugs in IPF there was room for another given the differentiated mechanism of action and due to the limited efficacy of the two approved drugs.

AD-214 is the right drug to take to the clinic

Why has it taken so long for AdAlta to get a product into the clinic? AdAlta's initial i-body against CXCR4, AD-114, was a good drug candidate, however it had a relatively poor half-life and a key challenge for the company was working out how to extend this. Various techniques were tried, including a relatively new one called PASylation, and the AdAlta team published their work in the journal *mAbs*[9] in August 2019[10], which showed that i-bodies were amenable to a variety of half-life extension techniques. The solution they finally settled on was an Fc-Fusion protein that not only had markedly better half-life but also improved activity and manufacturability. AdAlta called this new candidate AD-214 and unveiled it in April 2018. The switch from AD-114 to AD-214 as the lead candidate was a setback in terms of the time required to bring a drug to market, and there were also delays as AdAlta sought to manufacture the new drug. However we argue that the better quality of the new candidate more than makes up for this.

If AdAlta is this good, why is it only capitalised on ASX at A$18.0m or US$12.8m? AdAlta's market capitalisation is low compared to comparable companies around the world. AdAlta has had to raise substantial new capital to develop AD-214 – A$4.7m at 30 cents per share in July 2018 and A$7.0m at 15 cents in May 2019. And it only just reached the clinic after a two year wait for AD-214. Also, there are no major pharma partners or collaborators working on therapeutic i-bodies at the moment, although the recent collaboration with GE Healthcare on a diagnostic application is encouraging. We see sentiment towards AdAlta changing over time as AdAlta executes on its development plans for both AD-214 and for its i-body platform.

Eleven reasons to consider AdAlta

1. **AdAlta's lead candidate is now in the clinic**. After several years of development AD-214, which will initially be indicated for the treatment of Idiopathic Pulmonary Fibrosis, entered its first clinical study in July 2020. The first study is in healthy volunteers, and it will be followed by single ascending dose and multiple ascending dose studies in IPF patients. A pre-IND meeting with the FDA regarding the US development pathway has also been held, with the Agency indicating its comfort regarding AdAlta's Phase 1 trial design.
2. **Booming monoclonal antibodies**. Monoclonal antibodies have, over the past two decades, boomed into a >U$$115bn market opportunity, driving the search by Big Pharma for next generation antibody-like scaffolds that can extend the therapeutic power of antibodies into drugs of smaller size. AdAlta with its i-bodies, around one-tenth the size of conventional monoclonal antibodies, stand to benefit from this search so long as the drugs can be manufactured and show performance in the clinic.
3. **The success of other scaffold companies**. We see the clinical and commercial success of companies like Ablynx, which was acquired by Sanofi in 2018 for US$4.8bn, as pointing to the upside for successful scaffold companies. We list a number of scaffold companies, some with market capitalisations in the hundreds of millions or more, in Appendix VI of this note.

I-bodies are around one-tenth as large as monoclonal antibodies

[9] A Taylor and Francis journal –see tandfonline.com/loi/kmab20.
[10] MAbs . 2019 Oct;11(7):1331-1340. Epub 2019 Aug 23

4. **The unique qualities of i-bodies**. I-bodies are unique in the antibody world in that no comparable scaffold has a binding loop as long as the one used in these scaffolds. We argue that the small size of i-bodies combined with this binding loop and the fully-human nature of the scaffold gives AdAlta a potential leadership position in this field, ahead of even GSK's Domantis unit or Ablynx.
5. **The data on AD-114 looked good, and AD-214 has longer half-life and enhanced activity**. AdAlta has shown that AD-114, which targets the GPCR CXCR4, can reduce collagen content and inflammation in the lungs in the Bleomycin mouse model of IPF, as well as reduce fibroblast migration to the lungs. The drug also seems to work on both 'slow progressors' (patients that progress slowly with IPF) and 'fast progressors' (patients that progress with the disease very quickly). AD-114 has also shown to be more effective than the two currently approved drugs for IPF. AD-214, an Fc-Fusion protein of AD-114, has shown longer half-life and enhanced activity. The drug's performance in the Bleomycin mouse model, and a recent GLP tox study, cause us to be optimistic about this drug's forthcoming clinical experience.
6. **Choice of Orphan indication**. While there are two existing drugs to treat Idiopathic Pulmonary Fibrosis, this disease alone has proved to be a multi-billion dollar market opportunity. The two currently approved drugs for IPF have limited efficacy in individual patients, either having no effect or only slowing down disease progression, while there are some unpleasant side effects and a high discontinuation rates understood to be >25% in the first year. The benefits that come from being an Orphan Drug developer will also help AdAlta quickly build value.
7. **The upside from fibrosis is strong**. With many diseases having a fibrosis element to them there is potential to take AD-214 and other anti-fibrotic i-bodies into large market opportunities such as NASH, wet-AMD and renal fibrosis. Also, there is the broader opportunity in Interstitial Lung Diseases (ILDs) of which IPF is maybe one quarter, given that one of the approved IPF drugs, Boehringer Ingelheim's Ofev, is now also approved for a variety of ILDs.

AdAlta is in the early stages of building its pipeline of i-bodies

8. **Potential upside from first commercial collaborations from recent science**. In September 2019 AdAlta announced that GE Healthcare was evaluating i-bodies that can be used as imaging agents with its PET scanners. While this is a diagnostic and not a therapeutic collaboration, it still validates the i-body platform. Given the high demand by Big Pharma for access to antibody-like scaffolds, we see potential for collaborations over therapeutics to emerge now that AD-214 is in the clinic.
9. **Potential to quickly build a pipeline**. AdAlta has started to build a pipeline from its i-body platform beyond AD-214. We see any substantial moves in this regard as signaling a further de-risking of the i-body opportunity.
10. **Solid management team**. CEO Dr Tim Oldham brings drug development smarts honed over many years at Mayne Pharma (acquired by Hospira) and a private company called Cell Therapies. Backing Tim is an experienced board chaired by the Life Sciences veteran Dr Paul MacLeman which includes the US-based bio-entrepreneur Dr Robert Peach.
11. **AdAlta is undervalued on our numbers**. We value AdAlta at 25 cents per share base case and 52 cents optimistic case. We see AdAlta being re-rated by the market on the back of pre-clinical and now clinical development results for AD-214 in IPF, pipeline expansion, and the development of partnerships.

AdAlta owns a Next Generation antibody platform

AdAlta is player in the ongoing monoclonal antibody revolution. AdAlta is a drug development company being built on technology to create 'i-bodies', that is, small human proteins engineered with monoclonal antibody elements so as to combine the advantages of both monoclonal antibodies and small molecules. We believe that the drug discovery power of this platform is such that it could ultimately be sold for multiples of AdAlta's current market capitalisation. To understand the appeal that i-bodies could have for a pharma industry acquirer, we need to look first at monoclonal antibodies and how they have revolutionised medicine, then look at ways in which i-bodies and other comparable next generation antibody 'scaffolds' improve on monoclonals.

Antibodies are revolutionary because of their targeting capabilities

Why monoclonal antibodies have been regarded as revolutionary. Before monoclonal antibodies the pharmaceutical industry knew how to create drugs somewhat specific to diseased tissue, but the monoclonals took this targeting capability to a whole new level, with highly favourable patient outcomes across a range of diseases. For a good example, consider one of the early monoclonal antibody drugs - Herceptin (trastuzumab), which gained FDA approval in September 1998 for the treatment of breast cancer. Herceptin targets an antigen on the surface of breast cancer cells called HER-2/neu, relevant in around 15-20% of all breast tumours[11]. HER-2-positive breast cancers tend to be more aggressive and the prognosis for patients is poor[12]. By hitting only those cells that overexpress HER-2 – something that a monoclonal antibody can easily achieve but that is difficult with a small molecule – Herceptin is able to extend the life of HER-2-postive breast cancer patients[13] without some of the downsides of chemotherapy such as hair loss and nausea. The favourable clinical outcomes in HER2-positive breast cancer and later in gastric cancer drove peak sales of US$6.85 for Roche in 2014 before the first 'biosimilars'[14] came on the market.

Why monoclonal antibodies are a >US$115bn drug class today. Prior to the late 1990s the pharmaceutical industry had been waiting for about two decades to make drugs as powerful as monoclonal antibodies[15]. Once the tools became available, and the first more-or-less human monoclonal antibody gained FDA approval in 1997[16], the result was what we call the Monoclonal Antibody Revolution - an explosion in monoclonal antibody drug development and a boom in sales of monoclonal antibody drugs. In 2000 monoclonal antibodies were a US$2bn drug class but a couple of decades later this class was worth more than US$115bn, constituting around 6% of all drug sales worldwide. The reason for this growth is that the right target, hit

[11] See, for example, Clin Med Res. 2009 Jun;7(1-2):4-13, in which a 7-year retrospective study of 1,134 invasive breast cancer subject found 17.7% of subjects analysed were HER-2 positive.

[12] In one study, one-year survival for HER-2-negative patients was 75% whereas HER-2-negative patients without Herceptin only enjoyed 70% one-year survival. Herceptin improved the odds for HER-2-positive disease to 87%. See J Clin Oncol. 2010 Jan 1;28(1):92-8. Epub 2009 Nov 23.

[13] In the Phase 3 which gained Herceptin FDA approval, median survival was 25.1 months for the Herceptin group versus 20.3 months for standard chemotherapy - See N Engl J Med. 2001 Mar 15;344(11):783-92. In most cases Herceptin resistance develops within 12 months (see Breast Cancer Res. 2006;8(6):215).

[14] A biosimilar is a generic version of a biological drug.

[15] The original hybridoma technology for producing monoclonal antibodies was devised in 1975 (Nature. 1975 Aug 7;256(5517):495-7) and won the scientists concerned the Nobel Prize for Medicine in 1984. However, in the 1980s and 1990s there were multiple clinical failures of monoclonal antibodies. The main problem was the need to humanise antibodies, since murine antibodies from the hybridomas were unsuitable for use in people. The first humanisation technology was developed around 1988 (see US Patent 5,225,539, priority date 27/3/1986 and Nature. 1988 Mar 24;332(6162):323-7) so the first antibodies safe enough to be used in people didn't go to the clinic until the 1990s.

[16] Sure, the first FDA approved monoclonal antibody was Orthoclone OKT3 (muromonab-CD3) came on the market in 1986 for the prevention of kidney transplant rejection, but that was a mouse IgG2a antibody. The first chimeric monoclonal antibody to gain FDA approval, in November 1997, was Genentech's Rituxan (rituximab), which treats lymphomas and leukemias. The first humanised monoclonal antibody was MedImmune's Synagis (palivizumab) for the treatment of RSV infection, in June 1998. The first fully human monoclonal antibody was Abbott's Humira, for Rheumatoid Arthritis, FDA approved in December 2002.

with a monoclonal antibody, is inevitably better than the existing standard of care.

Antibodies will be a mainstay of the pharma industry for years to come

Why antibodies are still relevant today. Most drugs in clinical use today are small molecules, and the tools of small molecule drug development get better all the time. However, antibodies are likely to be a mainstay of the pharmaceutical industry for many years to come. Consider:

- The critical mass of products in development – just about every year for the last decade or so the number of antibodies in late stage clinical development has risen[17]. This in turn is a function of the fact that antibodies have historically enjoyed higher success rates in clinical development[18];
- The ease with which a drug candidate can be selected using the tools of antibody drug development, especially the *in vivo* tools;
- The widespread availability of the fundamental drug discovery tools; for example, a phage display library, in which viruses that infect bacteria are used to house a collection of antibody candidates[19], can be built in any university laboratory these days in a matter of months;
- The multitude of targets which are only druggable using antibodies – large, flat surfaces, for example, highly relevant in drugging protein-protein interactions.
- Continued improvement in the tools of antibody development. An example would be the development of tools to afucosylate (ie remove sugar groups from) anti-cancer monoclonal antibodies[20] so as to improve their cancer-killing abilities[21].
- The ability of antibodies to interact with other elements of the immune system[22]. This capability is increasingly relevant to cancer now that immuno-oncology is becoming a reality.
- The ability to augment the action of small molecules, through antibody-drug-conjugates.

The original platforms to create antibodies sold for very high prices. The boom that followed the mainstreaming of monoclonal antibodies from 1997 led within a decade to a scramble to control the companies with relevant know-how and some of the early monoclonal antibody drugs. Take just three examples:

- Amgen bought Abgenix, creator of the XenoMouse transgenic mouse, in December 2005 for US$2.2bn. Abgenix had created the cancer drug Vectibix;
- AstraZeneca paid US$1.3bn in May 2006 for Cambridge Antibody Technology, the company that had pioneered phage display for antibody discovery and had thereby contributed to the creation of Humira;
- Bristol-Myers Squibb bought Medarex in 2009 for US$2.4bn, thereby gaining ownership of another transgenic mouse called the 'HuMAb-

[17] Kaplon et. al. (2020), *Antibodies to watch in 2020*, mAbs, 12:1.

[18] A 2010 study by the Tufts Center for the Study of Drug Development found that the chances of ultimate FDA approval for a new large molecule drug entering the clinic were 32% whereas for small molecules the comparable figure was 13%. The difference lies in the fact that around half the large molecule drugs tracked were monoclonal antibodies. See Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3. Tufts researchers estimated in 2011 that between 1997 and 2010 around 17% of all humanised monoclonal antibodies gained approval, being 13% for cancer antibodies and 25% for antibodies targeted at immunological disorders (source: Tufts press release dated 8/11/2011 and headlined '*Number of monoclonal antibody products in development continues to increase*').

[19] Phage display, pioneered among others by Sir Greg Winter, works because phage can be engineered to express foreign proteins on the surface and at the same time carry the genetic information of the surface-expressed molecule within the phage capsid.

[20] Afucosylated monoclonal antibodies are antibodies where the oligosaccharides in the Fc region lack fucose sugar units, which increases ADCC.

[21] See Expert Opin Biol Ther. 2006 Nov;6(11):1161-73.

[22] Through, for example, Antibody Dependent Cellular Cytotoxicity (ADCC), where Fc receptors on the surface of 'effector cells' (natural killer cells, macrophages, monocytes and eosinophils) bind to the Fc region of the antibody, which itself is bound to a target cell. Upon binding a signaling pathway is triggered which results in the secretion of various substances, such as lytic enzymes, perforin, granzymes and tumour necrosis factor, which mediate in the destruction of the target cell. After zeroing in and binding to their target, antibodies help bring in other elements of the immune system to remove the bearer of the antigen.

Mouse', as well as for the cancer antibody Yervoy, then in clinical development.

The push is on for next generation antibody platforms. Relatively early in the Antibody Revolution various entrepreneurs realised that widespread clinical use of straight monoclonal antibodies would soon give rise to the demand for next generation antibody-like drugs to go after the 'high-hanging fruit'[23]. These platforms were designed either to address various downsides of antibodies (such as low tissue penetration and the inability to go after intra-cellular targets), or use monoclonal antibodies in more innovative ways:

Ablynx shows the potential future upside upside for AdAlta

- Domantis, founded in 2000 by the antibody pioneer Sir Greg Winter to develop antibody fragments called 'domain antibodies', was an example of the former. The idea behind domain antibodies was that they were considerably smaller than regular monoclonal antibodies, making them easier to manufacture and improving their tissue distribution. Domantis was bought in December 2006 by GSK for US$454m when all its programmes were still pre-clinical[24].
- Micromet, founded in 1993, was an example of the latter. Micromet was built around Bispecific T-cell Engager (BiTE) antibodies, which could bind the target cells to T cells. BiTE antibodies are ideal for the treatment of cancer. Micromet was in Phase 2 in Acute Lymphoblastic Leukemia before it was acquired by Amgen for US$1.2bn in January 2012.
- Ablynx, a Belgian company founded in 2002, pioneered the concept of antibody-like scaffolds derived initially from antibodies unique to camels and llamas. It was acquired in 2018 by Sanofi for US$4.8bn.

Companies with valuable platforms trade for high prices. Appendix VI lists a number of companies that have built very large market values out of their platforms, most notably:

- Genmab and MorphoSys, two of the original antibody platform plays that are still independent. Genmab is currently a US$22.9bn company[25] while MorphoSys is worth US$432bn;
- Seattle Genetics, the pioneer of the antibody-drug-conjugate, current market capitalisation US$29.2bn;
- Argenx, another Belgian company working on camelid antibody scaffolds, is currently worth €$10.3bn.

AdAlta can potentially go one better than Ablynx

AdAlta's platform has the potential to step up. As we'll see in the next section, AdAlta's platform is somewhat comparable to Ablynx and Argenx, in that it creates smaller antibody-like molecules where the original idea came from another species – in AdAlta's case, from sharks. Actually, AdAlta can go one better because its scaffold is now fully human. We see potential for AdAlta to be regarded as 'the next Ablynx' now that it can demonstrate that it can make its i-bodies under GMP and the first i-body has entered the clinic.

Why AdAlta's i-body can be the Next Big Scaffold

What is an i-body? AdAlta's i-bodies are basically small human proteins engineered with antibody-like structures that were originally identified in sharks and that have improved binding ability compared to their human counterparts. To understand i-bodies and their potential therapeutic power, let's first look at the structure of human antibodies, then the shark antibodies

[23] Nat Rev Drug Discov. 2018 Mar;17(3):197-223. Epub 2017 Dec 1.
[24] Domantis had had early funding from Peptech, an Australian antibody developer which later became Arana Therapeutics.
[25] 24 July 2020 close on Nasdaq.

known as 'IgNARs' which inspired i-bodies, before looking at the combination that became i-bodies.

How human antibodies work. The standard IgG antibody is made up of four polypeptides, that is, strings of more than 30 amino acids[26]. There are two 'heavy chain' polypeptides that form the basic Y shape of the antibody, and two shorter 'light chains' that run parallel to the upper arms of the Y made by the heavy chains[27]. Within this polypeptide structure there are two basic regions. The lower half of the antibody, which starts around midway down the arms of the Y, is called the 'constant region' and the upper half, in the tips of the Y, is called the 'variable region'. The variable region dictates the antibody's 'specificity' - what the antibody will target - while the constant region has the job of interacting with other portions of the body's immune system[28].

- The variable region hosts a number of 'complementarity determining regions', or CDRs for short, which bind to the antibody's target. There are three on each chain, called CDR1, CDR2 and CDR3, so an IgG antibody has 12 CDRs in all. In between the CDRs are the 'framework regions' which anchors the CDRs to the rest of the antibody and helps maintain the CDR's shape, the latter being an important function since what the antibody is designed to seek is a perfect match with the antigen before it can do its job.
- Each heavy and light chain has individual 'domains'. IgG heavy chains have one variable domain (VH) and three constant domains (CH1, CH2, CH3). Similarly, light chains have one variable domain (VL) and one constant domain (CL). Some of these domains together form 'fragments'. The basic idea behind 'domain' antibodies and antibody fragments as drugs is to harness the properties of antibodies but with molecules of smaller size.

I-bodies got their original inspiration from sharks

How shark antibodies suggested a human therapy. I-bodies have their origin in the discovery in the mid-1990s that sharks can generate single-domain antibodies where there is a variable-like domain in the heavy chain and no light chain (ie, VH, but no VL). The shark single domain is called the 'Ig new antigen receptor', or IgNAR for short. The structure of an IgNAR is a heavy chain of one variable and five constant domains, occurring as a dimer[29]. The structure of the IgNAR makes such antibodies tiny by human standards - the VH binding domain or VNAR is only one tenth the size of a full monoclonal antibody. However, it wasn't the size that was interesting in terms of the therapeutic potential so much as the lengthy CDR3 loop where the antibody concentrates its binding diversity, and which could potentially bind antigens unreachable by CDRs on naturally occurring human antibodies. In 2001 Dr Stewart Nuttall at the CSIRO in Melbourne identified an IgNAR from a shark native to Australian waters[30] and showed that this variable region or VNAR could be used as a scaffold for an antibody library accessible using phage display[31]. In 2002 Nuttall et. al. showed that this library could select antibodies that would effectively bind target antigens[32], and in 2004 Nuttall, his CSIRO colleague Dr Peter Hudson and others including the molecular biologist Dr Mick Foley, an authority on malaria at Melbourne's La Trobe University[33], demonstrated the power of this library by raising VNARs that, after affinity

[26] The term 'peptide' is generally used in biology to refer to amino acid strings of less than 30 'residues', that is, individual amino acids.
[27] They are joined by various disulphide 'bridges'.
[28] It also determines the isotype, that is, the individual class of antibody, of which there are five - IgG, IgA, IgD, IgM and IgE. Most approved antibodies to date have been IgG-isotype antibodies.
[29] Nature. 1995 Mar 9;374(6518):168-73.
[30] The spotted wobbegong, *Orectolobus maculatus.*
[31] Mol Immunol. 2001 Aug;38(4):313-26.
[32] FEBS Lett. 2002 Apr 10;516(1-3):80-6.
[33] Because of Foley's involvement La Trobe became a small AdAlta shareholder.

maturation (ie optimisation of the antibodies to improve binding power), could kill malarial parasites *in vitro.* They did this by targeting AMA1, a protein which facilitates malaria's invasion of red blood cells[34]. Around the time of this work, the Nuttall group published an important paper in the influential journal *PNAS*[35] demonstrating that the variable domain in an IgNAR was structurally similar to the 'I-Set' family of immunoglobulin domains[36]. To summarise this paper in plain English, what Nuttall et. al. reported is that the IgNAR variable domains may have come from sharks, but they looked like proteins that were commonplace in the human body, in this case a molecule that facilitated cell-to-cell adhesion. That suggested that a small part of a human cell adhesion molecule could be engineered with CDR1 and CDR3 loops like those from the VNAR, thus combining the binding capability of the IgNAR with the innate stability of the human cell adhesion molecule. Nuttall et. al. proceeded to do this, using NCAM1, which is domain 1 of the Neural Cell Adhesion Molecule, as the scaffold. The result was the first i-body, for which patent protection was sought by the CRC for Diagnostics in 2005[37].

Why a company was formed around i-bodies. By 2007 new generation antibody-like platforms were big business, as GSK's acquisition of Domantis showed. Also, Ablynx, founded in 2001, had demonstrated that a successful company could be built around a scaffold not unlike IgNARs – Ablynx's platform was antibodies from Camelidae (eg camels and llama), which, like IgNARs, have only a heavy chain, although in this case there is only two constant domains and one variable domain. So, it was a no-brainer for the CRC for Diagnostics to start up AdAlta to commercialise i-bodies in mid-2007[38].

How AdAlta's platform works. AdAlta built on the original phage display libraries which had developed from the IgNAR work, and now has a library of around 20 billion i-bodies. It also continues to practice affinity maturation for targets of interest, and it has worked to develop manufacturing techniques for i-bodies using microbial and yeast systems as well as mammalian systems[39].

Why are AdAlta's i-bodies so great? There are several reasons why i-bodies are excellent antibody-like drugs:

- They have the high target specificity and affinity one would expect from monoclonals, but can also go after challenging targets such as G Protein-Coupled Receptors thanks to the long binding loop.
- They are small enough - ie 10% of the size of conventional IgG monoclonal antibodies - to be manufactured in microbial or yeast systems, with the potential for direct peptide synthesis. While AdAlta won't be going down any of these paths with AD-214, and will use instead the usual mammalian cell production method for monoclonal antibodies, there is potential down the track to explore alternative manufacturing systems for i-bodies[40].
- Being based on a cell adhesion molecule, they are very stable to proteases, high temperatures and low pH. The only downside is that they

I-bodies can theoretically be made in bacteria

[34] See Proteins. 2004 Apr 1;55(1):187-97.
[35] Proc Natl Acad Sci U S A. 2004 Aug 24;101(34):12444-9. Epub 2004 Aug 10.
[36] A large group of proteins in the human body, called the 'Immunoglobulin superfamily', have in common a structure called the immunoglobulin domain. The common element in immunoglobulin domain proteins is the immunoglobulin fold, consisting of a pair of beta sheets, each built of antiparallel beta strands, that surround a central hydrophobic core.
[37] See *Binding moieties based on shark IgNAR domain*, WO/2005/118629, priority date 2 June 2004.
[38] Sam Cobb, then Business Development Director of the CRC for Diagnostics, became its foundation CEO and remained in that position until her August 2019 resignation.
[39] AD-214, being an Fc fusion, requires CHO cells.
[40] Monoclonal antibodies have to be made in very large cultures of mammalian cells followed by extensive purification steps. That's one reason why they are costly. By contrast, bacterial or yeast-based production is much less costly. For AD-114 AdAlta worked with the Swiss company Selexis SA on cell line development and a US company called KBI Biopharma on process development and formulation development.

lack the three-week half-life of IgG monoclonals[41]. In 2018 AdAlta increased the half-life to adequate levels by creating AD-214 through an Fc-Fusion with the i-body.

- The small size and stability potentially means alternate delivery routes rather than being limited to the infusion route required of monoclonals.
- The fully human nature of the scaffold reduces the risk of an immune response to the drug on the part of the patient.

I-bodies are good for 'biased' pharmacology

- There is potential for 'biased' pharmacology, where a drug can modulate the various signaling pathways for a receptor differently from a more conventionally binding molecule. For example, AD-214 when it interacts with CXCR4, is able to modulate fibroblast migration and PBMC migration but not stimulate stem cell mobilisation and migration.

Can i-bodies be competitive in the scaffold space? AdAlta argues that, if superiority of scaffold platforms is measured by the 'humanness' of the scaffolds, as well as the targets that can be hit by those scaffolds, it would be a leader in the field:

- i-bodies, with their long loop and small shape, have the ability to go after diverse targets in a similar fashion to products from the aforementioned Ablynx and Argenx, as well as from two other notable companies – Ossianix, a shark antibody company[42] and VH Squared, a camelid antibody company[43]. However AdAlta beats these latter two platforms because its i-bodies are human.
- the long loop makes i-bodies superior to other human scaffolds such as those owned by GSK's Domantis unit, the fully human VH domains used by Crescendo Biologics[44] and the so-called 'Ankyrin Repeat Proteins' used by Molecular Partners[45].

AD-214 - AdAlta's lead i-body candidate

AdAlta's lead i-body targets CXCR4. As we noted above, AdAlta chose a GPCR called CXCR4 as its first target in order to show that an i-body could drug a difficult target. Here was the challenge in a nutshell: CXCR4 as a chemokine receptor plays a major role in moving white blood cells to the site of inflammation, driven by its ligand, CXCL12 (SDF-1). Consequently, CXCR4 antagonists could be highly effective in the treatment of inflammatory disorders. However, CXCR4 is also a receptor known to mobilise hematopoietic stem cells (HSCs) from their microenvironment in the bone marrow into the bloodstream. That's useful if you need to harvest these cells for autologous transplantation into patients with Non-Hodgkin's Lymphoma or Multiple Myeloma (MM), which is what Genzyme's Mozobil drug, a CXCR4 antagonist FDA approved in late 2008, is able to do[46]. However, this could lead to cytopenias (low blood cell counts) with prolonged use[47]. AdAlta's scientists set out to develop a suite of i-body CXCR4 antagonists that could block inflammatory cell migration but not mobilise stem cells. It was able to report

[41] AD-214 has 22-29 hour half-life in monkeys; simulated to be 71 hours in humans.
[42] Stevenage, UK, privately held, www.ossianx.com.
[43] Babraham, UK, privately held, www.vhsquared.com.
[44] Babraham, UK, privately held, www.crescendobiologics.com. This company has created a transgenic mouse that produces human heavy-chain-only antibodies, allowing it to harvest completely human VH single domains.
[45] Zurich, Switzerland, SIX: MOLN, www.molecularpartners.com
[46] Generic name plerixafor, see www.mozobil.com.
[47] Interestingly, Mozobil was originally discovered as a potent and selective anti-HIV agent, however, problems with unexpected cardiac disturbances led its original developer, AnorMED, to discontinue its development.

success in this regard with an important publication in the *Journal of Biological Chemistry*[48] in April 2016[49].

AdAlta's i-bodies have exquisite targeting for CXCR4

- The binding location of the i-bodies was deep in the 'pocket' of CXCR4, showing the large reach of the i-bodies;
- *In vitro* the i-bodies could block HIV entry into cells (CXCR4 is a co-receptor for HIV[50]);
- In mouse models, the i-bodies could inhibit leukocyte migration;
- There was no mobilisation of HSCs, probably because the AdAlta candidates weren't blocking calcium flux in the cells, unlike Mozobil, which is a potent inhibitor of calcium flux.

AdAlta picked the best of its i-bodies, AD-114, for further development before developing AD-214, an Fc-Fusion protein of AD-114, as the CXCR4 i-body with the right half-life.

Idiopathic Pulmonary Fibrosis – AdAlta's first potential indication. Following selection of AD-114 as its optimum CXCR4 antagonist[51], the company chose Idiopathic Pulmonary Fibrosis (IPF) as the first indication to pursue clinically. IPF is a serious lung disease characterised by scarring of the organ, but without any known cause. Until recently, a lack of treatment options meant that patients' lung function declined quickly, with median survival of only around two or three years post-diagnosis[52]. There were four main reasons why AdAlta chose IPF:

- There is a considerable body of knowledge showing the potential utility of CXCR4 antagonism in IPF[53];
- IPF is an Orphan Disease, with an estimated US patient population of 100,000 IPF patients in the US[54]. Orphan Drug status brings developers of such drugs substantial benefits in terms of the path to market[55]. AD-114 was granted Orphan Drug designation by the FDA in January 2017 for IPF.
- From 2014 there were two new drugs on the market for IPF but these only tended to slow the decline in lung function rather than reverse it.
- The previous few years had seen strong pharma interest in new anti-fibrotic drugs.

AD-114 seems to work for both fast and slow IPF progressors

AD-114 looked promising in IPF. In the standard Bleomycin mouse model of IPF[56], AD-114 was able to reduce collagen content and inflammation in the lungs, as well as reduce fibroblast migration to the lungs, to the point where the lung tissue was almost normalised. *In vitro*, the drug also seems to work on both 'slow progressors' (test subjects that progress slowly with IPF and have a relatively low level of fibrocytes in their lungs) as well as 'fast progressors' (test subjects that progress quickly with IPF and have a high level of fibrocytes in their lungs)[57]. This evidence was published in *Scientific Reports* in February 2018[58].

[48] Impact Factor 4.573.
[49] J Biol Chem. 2016 Jun 10;291(24):12641-57. Epub 2016 Apr 1.
[50] See Future Microbiol. 2010 Jul;5(7):1025-39.
[51] See *CXCR4 binding molecules*, WO/2016/109872, priority date 9 January 2015 for *in vitro* data.
[52] Am J Respir Crit Care Med. 2011 Feb 15;183(4):431-40. Epub 2010 Oct 8.
[53] See, for instance, Int J Biochem Cell Biol. 2009 Aug-Sep;41(8-9):1708-18. Epub 2009 Mar 6 and Am J Respir Cell Mol Biol. 2007 Sep;37(3):291-9. Epub 2007 Apr 26.
[54] See Eur Respir Rev. 2012 Dec 1;21(126):355-61.
[55] The significant incentives for developers of Orphan Drugs, as outlined in America's The Orphan Drug Act of 1983, include: a) US Federal tax credits for up to 50% of the research costs; b) seven years of US market exclusivity for the approved indication; c) waivers of PDUFA fees; d) research grants to defray clinical development costs; and e) protocol assistance from the FDA.
[56] Bleomycin, an antitumor antibiotic, causes lung injury in patients (see Arch Toxicol. 1991;65(2):81-94), and the drug is therefore useful in modelling pulmonary fibrosis in mice (See PLoS One. 2013;8(4):e59348. Epub 2013 Apr 2).
[57] This 'fast progressor' and 'slow progressor' distinction was first identified by a group at McMaster University in Canada in 2009 – see Am J Respir Crit Care Med. 2009 Apr 1;179(7):588-94. Epub 2009 Jan 16.
[58] See Sci Rep. 2018 Feb 16;8(1):3212 and *CXCR4 binding molecules*, WO/2016/109872, op. cit.

AD-214 is AD-114 with a much better half-life. AdAlta spent 2016 and 2017 doing pre-clinical development on AD-114. The key issue was half-life. AdAlta's initial i-body against CXCR4, AD-114, was a good drug candidate, however it had a relatively poor half-life and a key challenge for the company was working out how to extend this. Various techniques were tried, including a relatively new one called PASylation, and in 2018 AdAlta's scientists came up with the ideal solution – they created an Fc-Fusion protein which markedly extended the half-life of the drug. AdAlta called this new candidate AD-214 and unveiled it in April 2018[59]. This drug performed very well in the Bleomycin mouse model, with statistically significant reductions in fibrosis scores at every dose tried[60].

AD-214 entered the clinic in July 2020

AD-214 is now in the clinic. The reason why AdAlta has been unable to enter the clinic with its superior i-body product until July 2020 has been the need to start again with a manufacturing process after the switch from AD-114 to AD-214[61]. Development of this process was, however, solved by 2019, allowing AdAlta to complete the requisite toxicology studies in October of that year. What the Non-Human Primate work showed was a high level of receptor binding which suggested that AD-214 might now be able to be dosed to patients less frequently than once a week. After one final pre-clinical study was undertaken in the first half of 2020 to confirm efficacy, AdAlta made preparations for the clinical studies which have now commenced. To guide this programme, AdAlta has had a pre-IND meeting with the FDA. In July 2020 AdAlta reported that this meeting had confirmed that the AD-214 programme which it had crafted confirmed with what the Agency expected.

AD-214 will now be studied in healthy volunteers and in patients in Phase 1 studies. The first study will be in healthy volunteers, to be followed by single ascending dose and multiple ascending dose studies in IPF patients, where AD-214 will be radiolabeled so as to gain better understanding of the tissue distribution of the drug. The first test subject in the health volunteers study was dosed in July 2020.

AD-214 – The upside is considerable

IPF is a US$3bn market. The two drugs which gained FDA approval for the treatment of IPF in 2014[62] are Roche's Esbriet[63] and Boehringer Ingelheim's Ofev[64]. In 2019 these drugs were both blockbusters, Ofev enjoying US$1.8bn in global sales and Esbriet US$1.2bn[65]. AdAlta sees room for another drug, since AD-214 works via a different mechanism of action, is highly specific to disease fibroblasts (unlike Ofev) and is effective on both slow and fast progressors (unlike Esbriet). The new drugs, while improvements on the previous standard of care, still have limited utility for many patients – for example, Esbriet only appears to cut in half the loss of lung function over a twelve-month period, rather than stabilise or reverse it[66].

The upside beyond IPF is significant. Fibrosis is a significant factor in the pathogenesis of a range of disease conditions. Consequently, clinical success

[59] While the switch from AD-114 to AD-214 as the lead candidate may seem a setback in terms of the time required to bring a drug to market, we argue that the better quality of the new candidate more than makes up for this and the half-life extension supports the potential for AD-214 in a broader range of fibrotic diseases.
[60] See the AdAlta market release dated 2 March 2020 and headlined '*AD-114 effective in gold-standard pre-clinical animal model of IPF*'.
[61] For background here see two AdAlta market releases, one dated 15 October 2018 and headlined *'AdAlta on track with AD-214 manufacturing'*; and another dated 2 May 2019 and headlined *'AdAlta completes confirmation run for AD-214'*.
[62] Indeed, both drugs were approved on the same day – 15 October 2014.
[63] Generic name pirfenidone, see www.esbriet.com, This drug is understood to work by interfering with the production TGF-β and TNF,
[64] Generic name nintedanib, see www.ofev.com. Ofev is a tyrosine kinase inhibitor that inhibits pathways involved in fibrosis.
[65] Source: GlobalData.
[66] N Engl J Med. 2014 May 29;370(22):2083-92. Epub 2014 May 18.

in IPF opens up considerably larger market opportunities, which explains why Roche was prepared to pay US$8.3bn to acquire Esbriet's developer, the Californian biotechnology company Intermune, in August 2014 just prior to Esbriet's FDA approval. To get a glimpse of the upside, take five fibrotic conditions in which CXCR4 is known to be a factor:

- **Wet AMD.** Age-related Macular Degeneration (AMD) affects around 5% of the US population or in excess of 8 million people, and wet AMD, in which choroidal blood vessels grow into the retina and leak damaging fluid, is around 10-15% of all AMD[67]. There is *in vivo* evidence in the literature that inhibition of CXCR4 can prevent choroidal neovascularization[68] and AdAlta has published posters with data on AD-114 in AMD. Significantly, inhibition of CXCR4 can reduce the fibrosis associated with the neovascularisation, which the VEGF inhibitors like Regeneron's Eylea cannot do.
- **Renal fibrosis**. CXCR4 significantly upregulates after renal injury, with sustained activation known to lead to kidney fibrosis. Interestingly, reducing CXCR4 also brings down kidney TGF-β[69]. Currently around 12% of the US population has CKD and the European experience is probably similar[70].
- **NASH.** Nonalcoholic Steatohepatitis (NASH), characterised by fat build-up in the liver, is understood to affect around 2-3% of the general population of most Western countries[71]. CXCR4 is known to be a key player in NASH[72].
- **Cardiac fibrosis**. CXCR4 antagonism is known to attenuate the development of diabetic cardiac fibrosis in animal models of this condition[73]. Around 8% of American adults have heart failure, often driven by myocardial fibrosis.
- **Systemic sclerosis**. CXCR4 is known to be an important player in systemic sclerosis, particularly in the early stages[74]. Systemic sclerosis, in which there is fibroblast-driven abnormal growth of connective tissue throughout the body, is potentially a second Orphan indication for AdAlta with perhaps 20,000 patients in the US[75].

Fibrosis is generating billion dollar deals these days

The pharma industry has become very interested in fibrosis. The rise of drugs like Esbriet has led to strong commercial interest by other companies in new drugs with an anti-fibrosis element. Take three recent examples of deals in the field:

- Roche paid US$390m upfront in November 2019 and may pay another US$1bn for Promedior[76]. This US company had strong Phase 2 data in in myelofibrosis with a recombinant version of the endogenous human protein Pentraxin-2, known to have anti-fibrotic properties[77].
- Boehringer Ingelheim paid €45m and agreed to €1bn in milestones for the rights to BBT-877, an autotaxin[78] inhibitor from a publicly traded Korean company called Bridge Biotherapeutics[79]. At the time, in July 2019, BBT-

[67] Estimated from Invest Ophthalmol Vis Sci. 2011 Aug 29;52(9):6842-8.
[68] Invest Ophthalmol Vis Sci. 2010 Jul;51(7):3666-72. Epub 2009 Dec 30.
[69] Am J Physiol Renal Physiol. 2015 Mar 1;308(5):F459-72. Epub 2014 Dec 23.
[70] J Am Soc Nephrol. 2006 Aug;17(8):2275-84. Epub 2006 Jun 21.
[71] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.
[72] Clin Sci (Lond). 2015 Feb;128(4):257-67.
[73] PLoS One. 2015 Jul 27;10(7):e0133616. eCollection 2015.
[74] Arthritis Rheum. 2006 Sep;54(9):3022-33.
[75] Arthritis Rheum. 2003 Aug;48(8):2246-55.
[76] See www.promedior.com.
[77] Bristol-Myers Squibb had previously paid US$150m upfront and agreed to US$1.25bn in milestones in August 2015 for the rights to buy out Promedior if the drug, PRM-151, was shown to work. It subsequently declined to proceed with the acquisition.
[78] This enzyme mediated a key pro-fibrotic event in multiple cell types – see Front Med (Lausanne). 2018; 5: 180.
[79] Seongnam, Korea, Kosdaq: A288330, 52.231.196.181/about?l=en.

877 was in Phase I and intended for use in various fibrosing interstitial lung diseases, including IPF.

- Gilead Sciences paid US$400m upfront and agreed to US$800m in milestones in April 2016 to acquire the NASH programme of Nimbus Therapeutics.

Cancer may be the next indication for AD-214. CXCR4 has long been known as a cancer target, mediating tumour metastasis among other things[80], and AdAlta generated favourable pre-clinical data with AD-114 as an anti-cancer molecule.[81] It's interesting, therefore, to look at what the Israeli drug developer BioLineRx[82] is doing in this space. BioLineRx's lead compound is Motixafortide (BL-8040), a peptide antagonist to CXCR4. Motixafortide is being studied in Phase 2 with Merck & Co.'s Keytruda (pembrolizumab), the PD-1 inhibitor[83]. which gained FDA approval in September 2014[84]. With *in vivo* evidence now suggesting that CXCR4 inhibition in the tumour microenvironment is synergistic with the checkpoint inhibitors[85], we suggest that the path is potentially open for AdAlta to become a player in immuno-oncology as well as fibrosis. Bristol-Myers Squibb has previously worked on a CXCR4 antagonist antibody[86].

Pipeline development

AdAlta has started to build its pipeline. Up until recently AdAlta has focused most of its effort on getting AD-114/214 into the clinic. In recent months, however, it has started to work on its own pipeline. In addition there are two interesting collaborations that could yield pipeline opportunities.

- **Excellerate Bioscience.** This UK biotech[87] provides various drug discovery services and has developed expertise in understanding the pharmacology of GPCRs. Under a March 2019 agreement AdAlta and Excellerate are working on exploring the use of i-bodies to drug GPCR targets of interest.

GE Healthcare has helped validate AdAlta's i-body platform

- **GE Healthcare**. This unit of General Electric, which is a world leader in diagnostic imaging equipment, announced in September 2019 that it was evaluating i-bodies that can be used as imaging agents with its PET scanners. The initial target will be an i-body that can target Granzyme B, a biomarker of anti-cancer activity by a person's immune system[88].

We don't expect strong financial upside from either collaboration at this stage but each one helps expand the audience of potential partners for i-bodies.

[80] See Pathol Int. 2010 Jul;60(7):497-505).
[81] See *CXCR4 binding molecules*, op. cit, for data on AD-114's ability to inhibit angiogenesis and tumour cell proliferation, induce apoptosis, and bind to tumour tissue.
[82] Tel Aviv, Israel, Nasdaq: BLRX, www.biolinerx.com.
[83] Short for Programmed Death 1, PD-1, also known as C279, is an immune checkpoint known to turn down an immune response. PD-1 turns down an immune response in part by promoting apoptosis in antigen-specific T cells while reducing apoptosis in regulatory T cells. PD-1 seems to regulate effector T cell activity within tissue and tumours. Merck's Keytruda and BMS' Opdivo are monoclonal antibodies to PD-1 which, by blocking this checkpoint, can help boost an anti-cancer immune response.
[84] See the BioLineRx press release dated 12 January, 2016 and headlined *'BioLineRx Announces Collaboration with MSD to investigate the combination of KEYTRUDA (pembrolizumab) and BL-8040 in Pancreatic Cancer'*.
[85] Hepatology. 2015 May;61(5):1591-602. Epub 2015 Mar 20.
[86] Oncotarget. 2016 Jan 19;7(3):2809-22.
[87] Nottingham, UK, privately held, excelleratebio.com.
[88] Eur J Surg Oncol . 2001 Mar;27(2):180-6.

Valuing AdAlta

We value AdAlta at 25 cents per share base case and 52 cents per share optimistic case

We valued AdAlta at $0.25 per share base case and $0.52 per share optimistic case using a probability-weighted DCF approach. Our approach was as follows:

- Our WACC was ~15% (Speculative)[89].
- We modelled a payoff only for AD-214 and allowed no value for the future AdAlta pipeline. We believe the building of this pipeline will allow us to gradually add value for future products.
- We assume another US$5-10m in expenditure for AdAlta to further clinical development of AD-214;
- We model around 14 years of commercial exclusivity for AD-214.

Risk weighting

- We modelled AD-214 with a 20% probability of clinical success, which is roughly what its chances would be at Phase 2. We think this is reasonable give the *in vitro* evidence related to targeting and the fact that IPF is an Orphan disease, meaning that it can quickly transition to mid and late stage clinical development after its entry into the clinic.

Commercial outcomes

- We assume that the product can license to a pharma partner in FY24 (base case) or FY23 (optimistic case) for US$30-50m upfront, US$150-300m in milestones and an 8-12% royalty.
- We assume a product launch in IPF and Wet AMD in FY25 (base case) or FY24 (optimistic case) in the US and FY26 (base case) or FY25 (optimistic case) in Europe.
- We assume peak sales for AD-214 of ~US$800-1,100m, initially from in IPF and Wet AMD.

Further capital

- We assume a further A$10m is raised to take AD-214 through to the end of Phase 1.

Re-rating AdAlta

We see a number of events helping to re-rate AdAlta to our valuation range over the next 12-18 months:

- *In vivo* data on AD-214 related to its use as a PET tracer;
- Publication of further *in vitro* and *in vivo* data showing the therapeutic potential of i-bodies in IPF and other fibrosis indications;
- Development of new i-body candidates;
- Potential partnerships or evaluation agreements around i-bodies.

AdAlta's capable leadership team

We believe that AdAlta has a board and management team capable of building a sizeable company out of the i-body platform:

[89] For a relevant discount rate, we use WACCs of between ~12% and ~16% depending on the risk for Life Science companies. This is derived from a RFR of ~2.5%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like AdlAlta); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

AdAlta's Chief Scientific Officer is an authority on phage display

Dr Tim Oldham (CEO), who joined AdAlta in 2019, brings drug development smarts honed over many years at Mayne Pharma (subsequently acquired by Hospira) and at Cell Therapies Pty Ltd, a contract manufacturer of cellular therapies owned by Melbourne's Peter MacCallum Cancer Centre.

Dr Mick Foley (CSO), a La Trobe University scientist whose scientific background is malarial research, brings corporate memory to the development of the i-body platform. He was a founding scientist of AdAlta in 2007 and key inventor of AD-114 and AD-214. Having an authority on phage display as the CSO boosts the chances that AdAlta will pick the right kind of i-bodies to develop as drugs.

Dr Dallas Hartman (Chief Operating Officer), who joined AdAlta in 2018, brings biological drug manufacturing knowledge. Immediately prior to AdAlta Dallas worked at a veterinary biotech company called Nexvet[90], whose metier was converting human antibodies to antibodies suitable for use in pets.

The AdAlta board, which includes Tim Oldham, has an enviable range of skills given the company's stage of development:

- Chairman **Dr Paul MacLeman** has a strong track record of building value in a range of Life Sciences companies including a Hatchtech[91], Genetic Technologies[92] and IDT Australia[93], the pharmaceutical manufacturing company.
- **Liddy McCall**, who is a director of Yuuwa Capital Management with Dr James Williams[94], brings corporate advisory and legal smarts to AdAlta.
- **Dr Robert Peach** brings considerable background as a US-based bio-entrepreneur. After obtaining his PhD in Biochemistry from the University of Otago in New Zealand, Peach went to San Diego and worked at the antibody pioneer Idec before becoming a co-founder of Receptos. That revolutionary company, which figured out how to crystallise GPCRs in order to drug them, was sold in 2015 to Celgene for US$7.2bn.
- **Dr David Fuller** brings early-phase drug development skills, gained among other roles at INC Research, now part of the American clinical research organization Syneos Health[95]. In his current role David oversees Syneos's Oncology Business Unit for the Asia Pacific region.

AdAlta's Scientific Advisory Board brings significant Big Pharma credibility to AdAlta, with representatives formerly with two major companies – the Novartis alumni **Dr Brian Richardson** and **Dr John Westwick** alongside **Dr Steve Felstead** formerly of Pfizer. John Westwick brings a background in respiratory medicine, Brian Richardson in musculoskeletal disease and Steve Felstead in the development of cardiovascular drugs.

Appendix I – An AdAlta glossary

AD-114 – An i-body that targets CXCR4.

AD-214 – An Fc-Fusion protein of AD-114 which AdAlta unveiled in 2018.

[90] Acquired by Pfizer in 2017 for US$85m.
[91] Developer of a next generation head lice treatment. Hatchtech was acquired by Dr Reddy's in September 2015 for A$279m in total deal value. The upfront was undisclosed but there was A$85m in pre-commercialisation milestone payments, and the remainder of A$279m being sales milestones.
[92] Melbourne, Australia, ASX: GTG, www.gtgcorporate.com. On MacLeman's watch this company was developing molecular diagnostics.
[93] Melbourne, Australia, ASX: IDT, www.idtaus.com.au.
[94] Yuuwa Capital is A$40 million venture capital fund. Like Paul MacLeman, James Williams has built multiple Life Science companies over the last fifteen years, most notably iCeutica, a drug reformulation company that was sold in 2011 for orders of magnitude more than the initial funding round, and which has since delivered multiple FDA approvals for its new owner, the Philadelphia-based Iroko Pharmaceuticals (iroko.com).
[95] Morrisville, NC, Nasdaq: SYNH; syneoshealth.com.

Antibodies – Also called immunoglobulins, antibodies are immune system proteins that can bind to an antigen and help to neutralise the potentially harmful effects of the cells carrying the antigen.

Bleomycin mouse model – An animal model of IPF in which the lungs of the mouse are scarred using the chemotherapy drug bleomycin.

Blockbuster – A pharmaceutical drug with more than US$1bn in annual sales.

CDRs – Short for 'Complementarity Determining Regions', areas within an antibody's variable region which bind to the antibody's target.

Chemokine – Cell signaling molecules that direct immune cells to migrate towards the site of a required immune response.

Choroidal neovascularisation – The growth of new blood vessels beneath the retina.

Collagen – The fibrous protein that makes up connective tissue.

C-X-C Motif Chemokine Receptor 4 (CXCR4) – A chemokine receptor that prompts the migration of white blood cells whose natural ligand is CXCL12 (SDF-1). CXCR4, a G Protein-Coupled Receptor, is the target of AdAlta's AD-114 i-body.

Fc – The region of an antibody at the bottom of the protein's 'Y' shape.

Fc-Fusion – Proteins made up of the Fc domain of a monoclonal antibody, linked to a peptide or protein of interest.

Fibroblast – A type of cell commonly present in tissues including skin that makes matrix components eg. collagen.

Fibrocyte - cells that circulate in the peripheral blood and produce connective tissue proteins such as vimentin and collagens I and III.

Fibrosis – Scarring and thickening of tissue, thereby weakening tissue function.

G Protein-Coupled Receptor (GPCR) – A protein on the surface if cells whose function is to transduce extracellular stimuli into intracellular signals.

i-body – AdAlta's fully human single-domain antibody-like scaffold.

Idiopathic Pulmonary Fibrosis (IPF) – A scarring of lung tissue that arises from unknown causes. IPF is an Orphan disease.

IgNAR – The 'new antigen receptor', an antibody unique to sharks which AdAlta adapted to create i-bodies.

Interstitial Lung Diseases (ILDs) – Any one of a number of disorders characterised by cells infiltrating the 'acini', the ending of a tiny airways in the lung, where the air sacs are located. Examples include Idiopathic Pulmonary Fibrosis and Chronic eosinophilic pneumonia.

In vitro – Latin for *'in glass'*, referring to data obtained through testing in a test tube.

In vivo – Latin for '*in life*', referring to data obtained through testing in live organisms including animal models and humans.

Intravitreal injection – Injection of a drug into the vitreous humour in the middle of the eye.

Ion channel – A 'tunnel' in a cell's membranes through which ions (molecules with an electrical charge) travel in and out. There are four main ion channels – sodium, potassium, calcium, and chloride.

I-SET – A type of immunoglobulin domain that includes the cell adhesion molecules. I-bodies use I-SET domains from human proteins as the scaffold onto which modified CDRs from shark antibodies are engineered.

Mozobil – A CXCR4 antagonist (generic name plerixafor) sold by Sanofi/Genzyme and indicated for the mobilisation of hematopoietic stem cells. In this indication Mozobil is useful in rebuilding the blood forming system after bone marrow transplantation.

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan Drug designation provides tax benefits as well as market exclusivity in both Europe and the US.

PBMC – Short for Peripheral Blood Mononuclear Cell, which is any cell having a round nucleus. Most white blood cells are PBMCs.

Peptide – Two or more amino acids linked by chemical bonds.

Phage display – A tool for drug discovery in which a library of variants of a peptide or protein are expressed on the outside of small viruses called bacteriophages.

Phase – A stage of the clinical trialling process for a drug candidate. Phase 1 tests for safety. Phase 2 tests for efficacy in a small sample. Phase 3 tests for efficacy in a large sample.

Pre-IND meeting – A meeting with the FDA where drug developers can discuss with the Agency what the Agency will be requiring before it approves the drug in question.

Protease – An enzyme which breaks down protein.

Scaffold – A protein onto which antigen-binding sub-units can be engineered.

Statistical significance – The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone. Generally, p-values below 0.05 are taken as markers of statistical significance.

VNAR – A single variable domain of IgNAR.

Appendix II - AdAlta's IP position

AdAlta's core intellectual property is covered by two patent families:

WO/2016/109872, *CXCR4 binding molecules*, priority date 9 January 2015, invented by Mick Foley, Andrew Pow, Katherine Griffiths, Samantha Cobb and Katerina Viduka.

- This patent family covers AdAlta's AD-114 i-body targeting CXCR4. This patent has been granted in the US as No. 10,538,596 (January 2020).

WO/2005/118629, *Binding moieties based on shark IgNAR domain* priority date 2 June 2004, invented by Stewart Nuttal, Victor Streltsov, Katherine Griffiths, Jennifer Carmichael, Peter Hudson, Robert Irving, Joseph Varghese, Miles Barraclough, David Simmons and Kylie Henderson.

- This patent family covers AdAlta's i-body platform. This patent has been granted in Europe as EP1751181 (August 2012) and EP2330121 (September 2014) and in the US as No. 7,977,071 (July 2011).

Appendix III – AdAlta's capital structure

Class		% of fully diluted	Note
Ordinary shares, ASX Code 1AD (million)	163.9	84.1%	
Listed options (million)	23.3	12.0%	Exercise price 25 cents, average expiry date 30-Jun-2021
Unlisted options (million)	7.7	4.0%	Weighted average exercise price 24.8 cents, weighted average expiry date 16-Jun-2024
Fully diluted shares	195.0		

Current market cap:	A$18 million (US$12.8 million)
Current share price	$0.110
Twelve month range	$0.22 - $0.041
Average turnover per day (last three months)	275,300

Appendix IV – AdAlta's major shareholders

AdAlta currently has only two substantial shareholders with >5% that we can identify:

- **Yuuwa Capital** (33%), a A$40 million venture capital fund founded by James Williams and Liddy McCall in 2009 which provided seed capital in previous funding rounds.
- **Platinum Asset Management** (8.5%), the Sydney-based fund manager.

Appendix V – Papers relevant to AdAlta

There are seven peer-reviewed papers that are relevant to AdAlta:

Nuttall et. al. (2004), *Selection and affinity maturation of IgNAR variable domains targeting* Plasmodium falciparum *AMA1*, Proteins. 2004 Apr 1;55(1):187-97 (full text available at AdAlta's web site).

- This paper shows how IgNAR variable domain could be used to treat a serious infectious disease, in this case malaria, through a VNAR specific to the AMA1 protein of *Plasmodium falciparum*.

Henderson et. al. (2007), *Structure of an IgNAR-AMA1 complex: targeting a conserved hydrophobic cleft broadens malarial strain recognition*, Structure. 2007 Nov;15(11):1452-66 (full text available at AdAlta's web site).

- This paper demonstrates the binding capability of the IgNAR variable domains used in i-bodies. In the paper Nuttall, Foley and others showed that the long CDR3 loop in the VNARs they selected to go after AMA1

worked against the malaria parasite because it could penetrate deep into a hydrophobic cleft on the target and hit residues conserved across parasite species.

Walsh et. al. (2011), *Targeting the hepatitis B virus precore antigen with a novel IgNAR single variable domain intrabody*, Virology. 2011 Mar 1;411(1):132-41. Epub 2011 Jan 15 (full text available at AdAlta's web site).

- This paper demonstrates that IgNAR variable domains could be used to go after intracellular targets.

Griffiths et. al. (2013), *Shark Variable New Antigen Receptor (VNAR) Single Domain Antibody Fragments: Stability and Diagnostic Applications*, Antibodies 2013, 2(1), 66-81 (full text available at AdAlta's web site).

- This paper demonstrates the stability of IgNAR variable domains.

Griffiths et. al. (2016), *i-bodies, Human Single Domain Antibodies That Antagonize Chemokine Receptor CXCR4.*, J Biol Chem. 2016 Jun 10;291(24):12641-57. Epub 2016 Apr 1 (full text available at AdAlta's web site).

- This paper demonstrates that an i-body to CXCR4 could inhibit cell migration and leukocyte recruitment but would not affect the mobilisation of hematopoietic stem cells. This paper also demonstrates the stability of the i-body and describes how the i-body libraries were made.

Griffiths et. al. (2018), *Anti-fibrotic Effects of CXCR4-Targeting i-body AD-114 in Preclinical Models of Pulmonary Fibrosis*. Sci Rep. 2018 Feb 16;8(1):3212.

- This paper summarises the pre-clinical data which AdAlta's scientists collected on AD-114 to show that it would work in IPF.

Griffiths et. al. (2019), *Half-life Extension and Non-Human Primate Pharmacokinetic Safety Studies of I-Body AD-114 Targeting Human CXCR4* MAbs . 2019 Oct;11(7):1331-1340. Epub 2019 Aug 23.

- This paper demonstrates that i-bodies are amenable to various half-life extension approaches.

Appendix VI – Companies to watch

Antibody and scaffold platform companies

argenx. This company's antibody platform, which was based on antibodies from llamas, takes advantage of the fact that the variable regions of conventional llama antibodies are virtually identical to human, even though llama target proteins are different to human proteins. In March 2020 the company's lead product, efgartigimod, generated favourable topline data in Phase 3 in an autoimmune disorder called generalized myasthenia gravis. Efgartigimod is also in Phase 3 in Primary Immune Thrombocytopenia. The

company has other autoimmune and cancer programmes in Phase 2 and early stage partnerships with AbbVie and LEO Pharma among others.

BioInvent. This cancer antibody drug developer uses its 'F.I.R.S.T' platform to select antibodies that bind specifically to cancer tissue rather than healthy tissue. It also has an antibody library called n-CoDeR containing 30 billion functional human antibody genes assayed using phage display. The company is currently in Phase 1/2 with an antibody called BI1206 in haematological malignancies and solid tumours.

Genmab. This company's original technology was the UltiMab, a transgenic mouse for the creation of human antibodies. The first drug to make it to the market sourced from this model was Arzerra (ofatumumab, now marketed by Novartis), FDA approved in 2009 for the treatment of Chronic Lymphocytic Leukemia[96]. Its second approved product, Darzalex (daratumumab) for the treatment of Multiple Myeloma gained FDA approval in 2015, having been partnered to J&J in 2012. A third product, Tepazza (teprotumumab) gained FDA approval for Roche in January 2020 for the treatment of adults with an eye condition called Graves ophthalmopathy. Genmab has clinical-stage partnerships with AbbVie, J&J and Novartis, among others.

ImmunoGen. This company is a player in antibody-drug conjugates (ADCs) through its Targeted Antibody Payload technology, which was the basis of Roche's Kadclya (trastuzumab emtansine), where the antibody is Roche's earlier blockbuster Herceptin. Kadclya gained FDA approval in 2013. The company's Mirvetuximab soravtansine ADC, for the treatment of folate receptor alpha positive cancer, is in Phase 3 in ovarian cancer.

Immunomedics. This company was originally built on an antibody humanisation platform that allowed the creation of epratuzumab, which is now in Phase 3 in acute lymphoblastic leukemia. The company also has a proprietary ADC linker technology. The lead programme here is Sacituzumab govitecan, which has completed Phase 3 in triple negative breast cancer. This product received a Breakthrough Therapy Designation from the FDA in February 2016. Immunomedics has filed for approval based on the Phase 2 response rate, which was ~30%[97]. The initial filing received a Complete Response Letter[98] due to CMC matters[99], but Immunomedics refiled in December 2019.

Innate Pharma. This company, focused on antibody modulators of the innate immune system, has particular expertise in the creation of bispecific antibodies and ADCs[100]. Monalizumab, which targets NKG2A, a checkpoint receptor on some NK cells and CTLs, was partnered to AstraZeneca in April 2015 for US$250m upfront and a total deal value of US$1.275bn. This antibody is now in Phase 2 in a couple of cancer indications.

MacroGenics. This company can create bispecific and Trispecific antibodies using its DART (Dual-Affinity Re-Targeting) and Trident platforms, and more effective antibodies using its Fc Optimization Platform. The company is in Phase 3 with Margetuximab, an Fc-optimised HER-2-binding monoclonal antibody that has better HER-2 binding than Herceptin. Flotetuzumab is in Phase 3 in AML. And Retifanlimab is a PD-1 antibody in three registration-directed studies being run by Incyte in endometrial cancer.

[96] GSK licensed this drug in late 2006 in a deal worth US$2.1bn, including US$102m upfront and GSK agreeing to invest US$357m to buy 10% of Genmab.
[97] J Clin Oncol. 2017 Jul 1;35(19):2141-2148. Epub 2017 Mar 14.
[98] A letter issued by the FDA explaining why it won't yet approve a particular drug.
[99] CMC is short for Chemistry, Manufacturing, and Control, the description of a how a drug is manufactured..
[100] An important drug for Innate between 2011 and 2017 was lirilumab, which targets KIR (Killer-cell immunoglobulin-like receptors. BMS licensed this antibody in June 2011 when it was still in Phase 1 for US$35m upfront and US$430m in milestones. The drug subsequently failed studies in acute myeloid leukaemia and squamous cell carcinoma of the head and neck.

MorphoSys. This antibody company was pioneer of phage display technology. The company contributed to the development of J&J's Tremfya (guselkumab) for moderate to severe plaque psoriasis, which gained FDA approval in June 2017. Today its lead antibody is tafasitamab , partnered to Incyte and in Phase 3 for diffuse large B cell lymphoma. Other partners for MorphoSys programmes include Bayer, Boehringer Ingelheim, GSK, Novartis and Pfizer.

Pieris Pharmaceuticals. This company has been built on a family of small extracellular proteins called the lipocalins, which often play a transporter role in cells. Pieris has used the basic structure of lipocalins and phage display to create a large library of 'Anticalin' proteins with drug-like qualities. Among the benefits of Anticalins in that they are small enough to be manufactured in bacterial expression systems. The company's lead Anticalin product is PRS-343, a bispecific which targets the immune checkpoint 4-1BB as well as HER2. Pieris has partnerships with AstraZeneca, Seattle Genetics and Servier

Seattle Genetics. This company was the original pioneer of antibody drug conjugates. The company's first product, Adcetris (brentuximab vedotin), gained FDA approval for two lymphoma indications in August 2011. Padcev (enfortumab vedotinm) gained FDA approval in January 2020 for urothelial cancer. SeaGen has clinical-stage partnerships with Astellas and Genmab among others.

Sorrento Therapeutics. This company, perhaps best known for its CAR-T programmes, has an antibody platform called 'G-MAB' based on genetic sequencing of the variable regions of antibodies sourced from healthy donors. The resulting antibody libraries are reportedly vast enough to include antibodies that can drug GPCRs. Sorrento has used the platform to identify antibodies to 'clinically-relevant high-impact oncogenic targets'.

Xencor. This company's XmAb antibody platform allows better Fc regions to be engineered, improving potency, half-life and stability. The company's lead proprietary antibody, called XmAb5871, is in Phase 2 for IgG4-related disease and lupus.

Companies with fibrosis programmes

Galectin Therapeutics. This company is being built around carbohydrate-based drugs that bind to proteins called galectins, known to play a role in fibrosis. Galectin's GR-MD-02 compound, a galectin-3 inhibitor, is in Phase 2 in NASH. The company is evaluating its potential in kidney fibrosis.

Intercept Pharmaceuticals. This company, whose focus is non-viral liver diseases, gained FDA approval in May 2016 for Ocaliva (obeticholic acid), for the treatment of primary biliary cholangitis (PBC). This drug targets the farnesoid X receptor (FXR), highly relevant in inflammatory disorders and fibrotic disease. Ocaliva has completed Phase 3 in NASH and approval is being sought.

Regulus Therapeutics. This company, one of the pioneers of RNA-based therapeutics is focused on microRNAs, which small naturally occurring non-coding RNAs 20-25 nucleotides in length. The company is in Phase 1 with RG-101, which targets a microRNA in liver cells called miR-122 that Hepatitis C Virus uses to replicate. A product for the Orphan kidney disease Alport syndrome has been partnered with Sanofi's Genzyme unit and is in Phase 2.

Companies with IPF programmes

Bridge Biotherapeutics. This company's BBT-877 drug targets autotaxin, an enzyme known to contribute to IPF by generating lysophosphatidic acid[101]. This drug is now in Phase 2 under the Boehringer Ingelheim partnership we noted above.

FibroGen. This company's work on Connective Tissue Growth Factor (CTGF) has led to Pamrevlumab, an anti-CTGF antibody that in in Phase 3 in pancreatic cancer and IPF. FibroGen is also interested in the therapeutic potential of hypoxia-inducible factor (HIF). Roxadustat, an inhibitor of HIF prolyl hydroxylases, has completed Phase 3 for anemia arising from Chronic Kidney Disease.

Galapagos. This company is one of the pioneers of drugs that work through the JAK1 pathway. Its partner, Gilead, filed for approval of filgotinib, a JAK1 inhibitor, in Rheumatoid Arthritis in December 2019. Galapagos's Ziritaxestat (GLPG1690) autotaxin inhibitor completed a Phase 2a study in IPF in August 2017, showing a stabilisation of Forced Vital Capacity[102] in the lungs of treated patients over a 12-week treatment period. This programme has now fast tracked to Phase 3.

Liminal BioSciences. This drug developer, formerly Prometic, is in Phase 3 with Ryplazim, a plasminogen replacement product for patients suffering a deficiency. Fezagepras (PBI-4050), a synthetic analogue of a medium-chain fatty acid, is in Phase 2 in Alström syndrome and in Phase 1 in IPF. In Phase 2 data released in November 2016 Prometic was able to show stabilisation of lung function in IPF patients with PBI-4050 over 12 weeks, whether the drug was used alone or in addition to either nintedanib or pirfenidone. The current Phase 1 is being used to evaluate multiple ascending doses of Fezagepras in healthy volunteers, at higher doses than that Phase 2.

MediciNova. In April 2018 this company announced that a Phase 2 study of MN-001 (tipelukast), a leukotriene receptor antagonist, in IPF patients had terminated early due to significant positive results from an interim analysis. MediciNova has completed Phase 2 for MN-166 (ibudilast) in MS and ALS.

Pliant Therapeutics. This company is in Phase 2 with PLN-74809, a small molecule which inhibits both αVβ1 and αVβ6, two integrins which cause upstream activation of TGF-β1 in actively fibrotic tissue.

[101] Am J Respir Cell Mol Biol. 2012 Nov; 47(5): 563–565.
[102] Forced Vital Capacity is the amount of air which can be forcibly exhaled from the lungs after taking a deep breath.

Risks related to AdAlta

Risks specific to AdAlta. We see four major risks for AdAlta as a company and as a listed stock:

- **Timing risk.** There is the risk that the progression of AD-214 from the current Phase 1 study may take longer than expected.
- **Regulatory risk**. There is the risk that the FDA and other regulators may decline to approve AD-214, even if AdAlta considers the data submitted to be adequate.
- **Commercial risk**. There is the risk that AdAlta may fail to find commercial partners for AD-214.
- **Uptake risk**. AD-214 may not find significant usage in IPF as other therapies come onto the market between now and the end of AD-214's clinical development.

Risks related to pre-revenue Life Science companies in general.

The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the 'term' speculative can reasonably be applied to the entire sector.

The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including AdAlta.

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