NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

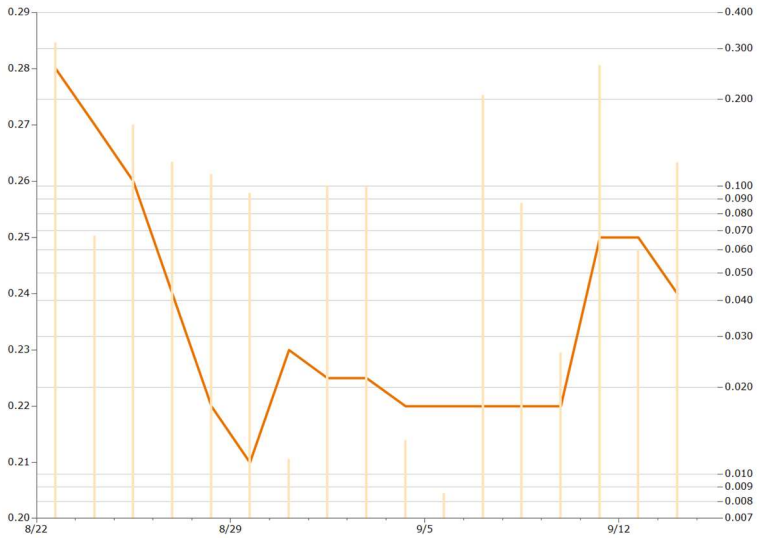
AdAlta (ASX: 1AD)

Initiation of Coverage – Tuesday 13 September 2016

Smaller, smarter antibody-like drugs

Monoclonal antibodies are a workhorse of modern medicine with global sales of >$US70bn 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 is developing an antibody-like drug called the i-body 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's first clinical product from its platform will be AD-114, initially for the treatment of Idiopathic Pulmonary Fibrosis. We see considerable upside for AdAlta given the high valuation that validated antibody and antibody-like platforms tend to trade for, the early focus on fibrosis and the demonstrated ability to hit targets that have proved extremely difficult to drug with antibodies, such as GPCRs. We value AdAlta at 38 cents per share base case and 89 cents optimistic case. Our target price of 60 cents per share sits around the midpoint of our DCF range.

Rating	**Risk**	**Current price**	**Target price**
Buy	Speculative	$0.024	$0.60



Stock details

Daily Turnover: ~A$27,000
Market Cap: A$24.0m
Shares Issued: 100m
52-Week High: $0.28
52-Week Low: $0.21

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

Please note: Please refer below for risks related to AdAlta as well our General Advice Warning, disclaimer and full disclosures. Also please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX). This Exchange hosts one of the world's premier equity markets for biotech and medical device companies, and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit ndfresearch.com.

Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Financial summary

Code	1AD
Analyst	Stuart Roberts
Date	13 September, 2016
Share price	$0.2400
Market capitalisation	$24m
Year end	30 June

Rating	BUY
Price target	$0.600
Upside/downside	150.0%
Valuation	$0.375 / $0.894
Valuation method	Probability-weighted DCF
Risk	Speculative

PROFIT AND LOSS (A$m)

Y/e June 30 (A$m)	FY15A	FY16A	FY17E	FY18E	FY19E
Revenue	0.8	0.7	0.9	0.9	15.5
EBITDA	**-1.4**	**-1.2**	**-4.1**	**-5.4**	**8.0**
D&A	0.0	0.0	0.0	0.0	0.0
EBIT	**-1.4**	**-1.2**	**-4.1**	**-5.4**	**8.0**
Net interest	0.0	0.0	0.0	0.0	0.0
Pre-tax profit	**-1.4**	**-1.2**	**-4.1**	**-5.4**	**8.0**
Tax	0.0	0.0	0.0	0.0	0.0
NPAT	-1.4	-1.2	-4.1	-5.4	8.0
Minority interests	0.0	0.0	0.0	0.0	0.0
Net profit after minorities	-1.4	-1.2	-4.1	-5.4	8.0

BALANCE SHEET (A$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Cash	0.0	0.5	6.2	1.2	8.9
Current receivables	0.1	0.9	0.9	0.9	1.5
Inventories	0.0	0.0	0.0	0.0	0.6
Other current assets	0.0	0.0	0.0	0.0	0.0
Current assets	**0.1**	**1.4**	**7.1**	**2.1**	**10.9**
PPE	0.0	0.0	0.0	0.0	0.0
Intangible assets	0.0	0.0	0.0	0.0	0.0
Other non-current assets	0.0	0.0	0.0	0.0	0.0
Non-current assets	0.0	0.0	0.0	0.0	0.0
Total assets	0.1	1.4	7.1	2.1	10.9
Payables	0.3	0.2	0.2	0.2	0.6
Debt	0.0	0.0	0.0	0.0	0.0
Other liabilities	0.0	0.0	0.0	0.0	0.0
Total liabilities	0.3	0.2	0.2	0.2	0.6
Shareholders' equity	-0.2	1.2	6.9	1.9	10.3
Minorities	0.0	0.0	0.0	0.0	0.0
Total shareholders funds	**-0.2**	**1.2**	**6.9**	**1.9**	**10.3**
Total funds employed	**0.1**	**1.4**	**7.1**	**2.1**	**10.9**
W/A shares on issue	2	8	100	100	101

CASH FLOW (A$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
NPAT plus discontinued ops.	-1.4	-1.2	-4.1	-5.4	8.0
Non-cash items	0.0	0.0	0.4	0.4	0.4
Working capital	0.0	0.0	0.0	0.0	-0.7
Other operating cash flow	0.0	0.0	0.0	0.0	0.0
Operating cashflow	**-1.4**	**-1.2**	**-3.8**	**-5.0**	**7.6**
Capex	0.0	0.0	0.0	0.0	0.0
Investments	0.0	0.0	0.0	0.0	0.0
Other investing cash flow	0.0	0.0	0.0	0.0	0.0
Investing cashflow	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Change in borrowings	0.0	0.0	0.0	0.0	0.0
Equity raised	1.0	1.6	9.5	0.0	0.0
Dividends paid	0.0	0.0	0.0	0.0	0.0
Other financing cash flow	0.0	0.0	0.0	0.0	0.0
Financing cashflow	**1.0**	**1.6**	**9.5**	**0.0**	**0.0**
Net change in cash	**-0.3**	**0.5**	**5.8**	**-5.0**	**7.7**
Cash at end of period	0.0	0.5	6.2	1.2	8.9

EARNINGS (A$m)

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Net profit ($m)	-1.4	-1.2	-4.1	-5.4	8.0
EPS (c)	-66.2	-14.1	-4.1	-5.4	8.0
EPS growth (%)	N/A	N/A	N/A	N/A	N/A
P/E ratio (x)	-0.4	-1.7	-5.8	-4.5	3.0
CFPS (c)	-66.9	-14.2	-3.8	-5.0	7.6
Price/CF (x)	-0.4	-1.7	-6.4	-4.8	3.2
DPS (c)	0.0	0.0	0.0	0.0	0.0
Yield (%)	0.0%	0.0%	0.0%	0.0%	0.0%
Franking (%)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA	-17.4	-20.1	-4.3	-4.2	1.9
EV/EBIT	-17.4	-20.1	-4.3	-4.2	1.9

PROFITABILITY RATIOS

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
EBITDA/revenue (%)	N/A	N/A	N/A	N/A	51.6%
EBIT/revenue (%)	N/A	N/A	N/A	N/A	51.6%
Return on assets (%)	-1536.0%	-84.1%	-57.6%	-249.8%	73.4%
Return on equity (%)	790.2%	-99.6%	-59.4%	-277.6%	77.6%
Return on funds empl'd (%)	790.2%	-99.6%	-59.4%	-277.6%	77.6%
Dividend cover (x)	N/A	N/A	N/A	N/A	0%
Effective tax rate (%)	0.0%	0.0%	0.0%	0.0%	0.0%

LIQUIDITY AND LEVERAGE RATIOS

Y/e June 30	FY15A	FY16A	FY17E	FY18E	FY19E
Net debt/(cash) ($m)	0	0	-6	-1	-9
Net debt/equity (%)	20.2%	-41.6%	-90.2%	-64.6%	-86.2%
Net interest cover (x)	N/A	N/A	N/A	N/A	N/A
Current ratio (x)	0.3	6.4	33.2	10.0	18.6

INTERIMS

Y/e June 30 ($m)	2H15A	1H16A	2H16A	1H17F	2H17F
Revenue	0.8	0.2	0.6	0.4	0.5
EBITDA	**-0.4**	**-0.7**	**-0.5**	**-2.1**	**-2.0**
D&A	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
EBIT	**-0.4**	**-0.7**	**-0.5**	**-2.1**	**-2.0**
Net interest	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Pre-tax profit	-0.4	-0.7	-0.4	-2.1	-2.0
Tax	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
NPAT	-0.4	-0.7	-0.4	-2.1	-2.0
Minority interests	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Net profit after minorities	-0.4	-0.7	-0.4	-2.1	-2.0

VALUATION

	Base	Optimistic
Value of AdAlta technology	31.8	84.8
Value of tax losses	2.1	2.1
Corporate overhead	-5.7	-5.7
Cash now (A$m)	10.0	10.0
Cash to be raised (A$m)	0.0	0.0
Option exercises (A$m)	0.1	0.1
Total value (A$m)	38.3	91.3
Total diluted shares (million)	102.1	102.1
Value per share	$0.375	$0.894
Valuation midpoint	$0.635	
Share price now (A$ per share)	$0.240	
Upside to midpoint	164.4%	

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 and 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 lead candidate, AD-114, which targets a GPCR called CXCR4, is being prepared for a Phase I study in the Orphan lung disorder Idiopathic Pulmonary Fibrosis, with multiple large market indications potentially to follow.
- **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$70bn drug class today.
- **Why the need for new, antibody-like drugs?** The trouble with monoclonal antibodies is that they are large molecules[2]. 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[3]. 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 late 2006) and Ablynx (now capitalised on Euronext at ~US$770m) that have created such scaffolds and started taking the Monoclonal Antibody Revolution to the next stage.

MONOCLONAL ANTIBODIES ARE A >US$70BN DRUG CLASS TODAY

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

- **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[4] 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 is 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.

I-BODIES FUNCTION LIKE ANTIBODIES BUT HAVE MANY OF THE GOOD DRUG QUALITIES OF SMALL MOLECULES

- **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 had joined AdAlta's board, AdAlta began to focus, at Williams' suggestion, on applying i-bodies to an important class of drug target, the G Protein-Coupled Receptors (GPCRs)[5]. GPCRs have frequently been targeted by small molecules over the years, in many cases resulting in blockbusters, but the complicated nature of these receptors means that they have never been hit by an approved monoclonal antibody[6]. Williams was convinced, and the *in vivo* evidence for AD-114 has since backed him up, that GPCRs could be drugged with an i-body due to the i-bodies 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. 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 in affects around 100,000 people annually. AdAlta chose this disease as the initial indication for AD-114 because, as 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 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.

[4] 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.
[5] This is the main focus of another Yuuwa-backed company, Dimerix (ASX: DXB), whose story is the subject of an NDF Research note dated 25 August 2016 and headlined '*Hitting the GPCR spot*'.
[6] 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. That said, there is strong research interest today in developing anti-GPCR monoclonals – see, for example, Sci Rep. 2015 Jun 10;5:11333.

- **If AdAlta is this good, why is it only capitalised on ASX at A$24m?** AdAlta is only a newly listed company, the company having commenced trading on ASX on 22 August 2016, after raising A$10m in an IPO at 25 cents per share. Consequently, the market has yet to get to know AdAlta well. In addition, the company has yet to go to the clinic with AD-114 so there are certain risks related to the pre-clinical development of i-bodies, and there are no pharma partners or collaborators. We see this changing over time as AdAlta executes on its development plans for both AD-114 and for its i-body platform.

Ten reasons to consider AdAlta

1. **Booming monoclonal antibodies**. Monoclonal antibodies have over the past two decades boomed into a >U$$70bn 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.
2. **The success of other scaffold companies**. We see the clinical and commercial success of companies like Ablynx (market cap ~US$770m) as pointing to the upside for successful scaffold companies. We list a number of scaffold companies with market capitalisations in the hundreds of millions in Appendix VI of this note.
3. **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.
4. **Data on AD-114 looks good**. 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. We think this bodes well for AD-114's future clinical experience.
5. **Choice of Orphan indication**. While there are two existing drugs to treat Idiopathic Pulmonary Fibrosis, this disease alone is potentially a 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. The benefits that come from being an Orphan Drug developer will also help AdAlta quickly build value.
6. **The upside from fibrosis is strong**. With many diseases have a fibrosis element to them there are potentials to take AD-114 and other anti-fibrotic i-bodies into large market opportunities such as NASH, wet-AMD and renal fibrosis.
7. **Potential upside from first commercial collaborations from recent science.** AdAlta has yet to attract pharma partners to work with it on collaborations. Given the high demand in Big Pharma for access to

I-BODIES ARE AROUND ONE-TENTH AS BIG AS MONOCLONAL ANTIBODIES

antibody-like scaffolds, we see potential for early collaborations to emerge arising from a key *Journal of Biological Chemistry* paper on i-bodies which was published in April 2016.

8. **Potential to quickly build a pipeline**. AdAlta intends to build a pipeline from its i-body platform but has yet to announce new candidates beyond AD-114. We see any moves in this regard as signalling a de-risking of the i-body opportunity.
9. **Great management team**. CEO Sam Cobb has built the AdAlta platform over a nine-year period to the point where i-bodies are credible in terms of the *in vitro* and *in vivo* data. Backing Sam is an experience board Chaired by the Life Sciences veteran Dr Paul MacLeman and that includes the US bio-entrepreneur Dr John Chiplin.
10. **AdAlta is undervalued on our numbers**. We value AdAlta at 38 cents per share base case and 89 cents optimistic case. Our target price of 60 cents per share sits around the midpoint of our DCF range. We see AdAlta being re-rated by the market on the back of Orphan drug status for AD-114 in IPF as well as various scientific publications, a build-out in the pipeline, and a favourable outcome on drug manufacturing.

ADALTA HAS YET TO BUILD ITS PIPELINE OF I-BODIES

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.

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[7]. HER-2-positive breast cancers tend to be more aggressive and the prognosis for patients is poor[8]. By hitting only those cells that overexpress HER-2 – something that a monoclonal antibody can easily achieve, but would be difficult with a small molecule – Herceptin is able to extend the life of HER-2-postive breast cancer patients[9] without some

[7] 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.
[8] 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.
[9] In the Phase III 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).

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' came on the market.

Why monoclonal antibodies are a >US$70bn 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[10]. Once the tools became available, and the first more-or-less human monoclonal antibody gained FDA approval in 1997[11], the result was what we called 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 by 2015 this class was worth more than US$70bn, constituting around 6% of all drug sales worldwide. The reason for this growth is that the right target, hit with a monoclonal antibody, is inevitably better than the existing standard of care.

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:

ANTIBODIES WILL BE A MAINSTAY OF THE PHARMA INDUSTRY FOR YEARS TO COME

- The critical mass of products in development – in late 2015 there were around 500 antibodies in various stages of development and over 50 in Phase III, more than double the number from 2010[12]. This in turn is a function of the fact that antibodies have historically enjoyed higher success rates in clinical development[13];
- 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[14], 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.

[10] 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.

[11] 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.

[12] MAbs. 2016;8(2):197-204. Epub 2015 Dec 14.

[13] 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*').

[14] 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.

- 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[15] so as to improve their cancer-killing abilities[16].

- The ability of antibodies to interact with other elements of the immune system[17]. 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, for another transgenic mouse called the 'HuMAb-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. 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:

DOMANTIS SHOWS THE POTENTIAL FUTURE 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[18].

- 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, c. BiTE antibodies are ideal for the treatment of cancer. Micromet was in Phase II in Acute Lymphoblastic Leukemia before it was acquired by Amgen for US$1.2bn in January 2012.

[15] Afucosylated monoclonal antibodies are antibodies where the oligosaccharides in the Fc region lack fucose sugar units, which increases ADCC.
[16] See Expert Opin Biol Ther. 2006 Nov;6(11):1161-73.
[17] 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 signalling 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.
[18] Domantis had had early funding from Peptech, an Australian antibody developer which later became Arana Therapeutics. AdAlta director Dr John Chiplin was Arana's CEO and also briefly served on the Domantis board.

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$8.9bn company[19] while MorphoSys is worth US$1.1bn;
- Seattle Genetics, the pioneer of the antibody-drug-conjugate, current market capitalisation US$7.2bn;
- Ablynx and argenx, two Belgian companies which have pioneered the concept of antibody-like scaffolds derived initially from antibodies unique to camels and llamas; these companies are now capitalised at ~US$770m and ~US$320m respectively.

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' once it can demonstrate that it can make its i-bodies under GMP and that these i-bodies have clinical utility.

ADALTA CAN POTENTIALLY GO ONE BETTER THAN ABLYNX

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 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[20]. 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[21]. 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[22].

- 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

[19] Thanks in part to its second drug, Darzalex (daratumumab) for the treatment of Multiple Myeloma.
[20] The term 'peptide' is generally used in biology to refer to amino acid strings of less than 30 'residues', that is, individual amino acids.
[21] They are joined by various disulphide 'bridges'.
[22] 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.

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.

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[23]. 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[24] and showed that this variable region or VNAR could be used as a scaffold for an antibody library accessible using phage display[25]. In 2002 Nuttall et. al. showed that this library could select antibodies that would effectively bind target antigens[26], 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[27], demonstrated the power of this library by raising VNARs that, after affinity maturation (ie optimisation of the antibodies to improve binding power), could kill malarial parasites *in vitro* through targeting AMA1, a protein which facilitates malaria's invasion of red blood cells[28]. Around the time of this work, the Nuttall group published an important paper in the influential journal PNAS[29] demonstrating that the variable domain in an IgNAR was structurally similar to the 'I-Set' family of immunoglobulin domains[30]. 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 the Neural Cell Adhesion Molecule 1 as the scaffold. The result was the first i-body, for which patent protection was sought by the CRC for Diagnostics in 2005[31].

I-BODIES GOT THEIR ORIGINAL INSPIRATION FROM SHARKS

[23] Nature. 1995 Mar 9;374(6518):168-73.
[24] The spotted wobbegong, *Orectolobus maculatus.*
[25] Mol Immunol. 2001 Aug;38(4):313-26.
[26] FEBS Lett. 2002 Apr 10;516(1-3):80-6.
[27] Because of Foley's involvement La Trobe currently owns around 3% of AdAlta stock.
[28] See Proteins. 2004 Apr 1;55(1):187-97.
[29] Proc Natl Acad Sci U S A. 2004 Aug 24;101(34):12444-9. Epub 2004 Aug 10.
[30] A large group of proteins in the human body, called the 'Immunoglobulin superfamily', have in common a structure called the immunoglobulin domain. The common characterising of 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.
[31] See *Binding moieties based on shark IgNAR domain*, WO/2005/118629, priority date 2 June 2004.

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 shown 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. Sam Cobb, then Business Development Director of the CRC for Diagnostics, became its foundation CEO.

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 2 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 or yeast systems.

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. 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. AdAlta announced in September 2016 that it had retained Fujifilm Diosynth Biotechnologies to manufacture AD-114 using its pAVEway bacteria-based system[32].
- Being based on a cell adhesion molecule, they are very stable to proteases, high temperatures and low pH. The only downside is that they lack the three-week half-life of IgG monoclonals, so AdAlta has chosen to formulate them with a recombinant half-life extension technology called PASylation[33] to improve half-life with its lead candidate[34].
- 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 CAN BE MADE IN BACTERIA

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:

[32] See www.fujifilmdiosynth.com.
[33] This technology, developed by a German company called XL-protein GmbH (Friesing, Germany, privately held, www.xl-protein.com), involves a long sequence of the small amino acids proline, alanine, and serine. This 'PAS' sequence, by adopting a random coil structure in aqueous solution, generates the kind of hydrodynamic volume that allows for extensions of protein half-lives. Originally AdAlta had used PEG. The company now uses PAS because the latter technology provides the extended half-life of PEG, but, being a single recombinant protein, does not require multiple conjugation/purification steps.
[34] AdAlta may use other half-life extension technologies for future i-bodies, or simply develop an i-body that binds to serum albumin or FcRN and create a bi-specific (as Ablynx have done) where one i-body binds to the target of interest and the other binds to albumin, thereby extending the half-life.

- i-bodies, with their long loop and small shape, have the ability to go after diverse targets in a similar fashion on the aforementioned Ablynx and argenx, as well as two other notable companies – Ossianix, a shark antibody company[35] and VH Squared, a camelid antibody company[36], but AdAlta beats these 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[37] and the so-called 'Ankyrin Repeat Proteins' used by Molecular Partners[38].

AD-114 - AdAlta's proof-of-concept molecule

AD-114 targets CXCR4. As we noted above, AdAlta chose a GPCR called CXCR4 as their 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[39]. However, this could lead to cytopenias (low red blood cell counts) with prolonged use[40]. 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 success in this regard with an important publication in the *Journal of Biological Chemistry*[41] in April 2016[42].

- The binding action 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[43]);
- 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.

AD-114 HAS EXQUISITE TARGETING FOR CXCR4

Idiopathic Pulmonary Fibrosis– AdAlta's first potential indication. Following selection of AD-114 as its optimum CXCR4 antagonist[44], 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

[35] Stevenage, UK privately held, www.ossianx.com.
[36] Babraham, UK, privately held, www.vhsquared.com.
[37] 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.
[38] Zurich, Switzerland, SIX: MOLN, www.molecularpartners.com
[39] Generic name plerixafor, see www.mozobil.com.
[40] 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.
[41] Impact Factor 4.573.
[42] J Biol Chem. 2016 Jun 10;291(24):12641-57. Epub 2016 Apr 1.
[43] See Future Microbiol. 2010 Jul;5(7):1025-39.
[44] See *CXCR4 binding molecules*, WO/2016/109872, priority date 9 January 2015 for *in vitro* data.

recently, a lack of treatment options meant that patients' lung function declined quickly, with median survival of only around two or three years after diagnosis[45]. 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[46];
- IPF is an Orphan Disease, with an estimated US patient population of 100,000 IPF patients in the US[47]. Orphan Drug status brings developers of such drugs substantial benefits in terms of the path to market[48].
- 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 last two years have seen strong pharma interest in new anti-fibrotic drugs

AD-114 looks promising in IPF[49]:

- In the standard Bleomycin mouse model of IPF[50], 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)[51].

AD-114 SEEMS TO WORK FOR BOTH FAST AND SLOW IPF PROGRESSORS

IPF is probably a US$1-3bn market opportunity. The two drugs which gained FDA approval for the treatment of IPF in 2014[52] are Roche's Esbriet[53] and Boehringer Ingelheim's Ofev[54]. AdAlta sees room for another drug, since AD-114 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). We estimate that the global market opportunity for IPF is probably US$1-3bn so commercially there is room for other drugs. More importantly 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[55].

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

[45] Am J Respir Crit Care Med. 2011 Feb 15;183(4):431-40. Epub 2010 Oct 8.
[46] 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.
[47] See Eur Respir Rev. 2012 Dec 1;21(126):355-61.
[48] 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.
[49] See *CXCR4 binding molecules*, WO/2016/109872, op. cit.
[50] 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).
[51] 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.
[52] Indeed, both drugs were approved on the same day – 15 October 2014.
[53] Generic name pirfenidone, see www.esbriet.com, This drug is understood to work by interfering with the production TGF-β and TNF–α,
[54] Generic name nintedanib, see www.ofev.com. Ofev is a tyrosine kinase inhibitor that inhibits pathways involved in fibrosis.
[55] N Engl J Med. 2014 May 29;370(22):2083-92. Epub 2014 May 18.

- **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[56]. AdAlta has *in vivo* evidence that inhibition of CXCR4 can prevent choroidal neovascularisation[57]. AdAlta has indicated that it intends to pursue a Wet-AMD indication for AD-114.
- **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[58]. CXCR4 is known to be a key player in NASH[59].
- **Renal fibrosis.** CXCR4 significantly upregulates after renal injury, with sustained activation known to lead to kidney fibrosis. Notably, reducing CXCR4 also brings down kidney TGF-β[60]. Currently around 12% of the US population has CKD and the European experience is probably similar[61]
- **Cardiac fibrosis**. CXCR4 antagonism is known to attenuate the development of diabetic cardiac fibrosis in animal models of this condition[62]. 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[63]. Systemic sclerosis, in which there is fibroblast-driven abnormal growth of connective tissue throughout the body and is potentially a second Orphan indication for AdAlta with perhaps 20,000 patients in the US[64].

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:

FIBROSIS IS GENERATING BILLION DOLLAR PHARMA DEALS THESE DAYS

- Bristol-Myers Squibb paid US$150m upfront and agreed to US$1.25bn in milestones in August 2015 to acquire Promedior[65]. This US company was in Phase II in myelofibrosis with a recombinant version of the endogenous human protein Pentraxin-2, known to have anti-fibrotic properties.
- Gilead Sciences paid US$400m upfront and agreed to US$800m in milestones in April 2016 to acquire the NASH programme of Nimbus Therapeutics.
- Shire acquired Fibrotech Therapeutics in May 2014 for US$75m upfront and US$482.5m in milestones. At the time Fibrotech was in a Phase 1b study in diabetic nephropathy with an anti-fibrosis small molecule FT011[66]
- **Cancer may be the next indication for AD-114**. CXCR4 has long been known as a cancer target, mediating tumour metastasis among other things[67], and AdAlta has favourable pre-clinical data on AD-

[56] Estimated from Invest Ophthalmol Vis Sci. 2011 Aug 29;52(9):6842-8.
[57] Invest Ophthalmol Vis Sci. 2010 Jul;51(7):3666-72. Epub 2009 Dec 30.
[58] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.
[59] Clin Sci (Lond). 2015 Feb;128(4):257-67.
[60] Am J Physiol Renal Physiol. 2015 Mar 1;308(5):F459-72. Epub 2014 Dec 23.
[61] J Am Soc Nephrol. 2006 Aug;17(8):2275-84. Epub 2006 Jun 21.
[62] PLoS One. 2015 Jul 27;10(7):e0133616. eCollection 2015.
[63] Arthritis Rheum. 2006 Sep;54(9):3022-33.
[64] Arthritis Rheum. 2003 Aug;48(8):2246-55.
[65] See www.promedior.com.
[66] The drug appears to work partly by attenuating TGF-ß induced collagen synthesis.
[67] See Pathol Int. 2010 Jul;60(7):497-505).

114 as an anti-cancer molecule[68] It's interesting, therefore, to note two collaborations announced in 2016 by the Israeli drug developer BioLineRx[69]. That company's lead compound is BL-8040, a peptide antagonist to CXCR4. BioLineRx announced in September 2016 that BL-8040 will be studied in combination with Genentech's anti-PDL1 monoclonal antibody atezolizumab[70]. This follows the announcement in January 2016 of a similar collaboration with Merck & Co. related to Keytruda (pembrolizumab), the PD-1 inhibitor which gained FDA approval in September 2014[71]. With *in vivo* evidence now suggesting that CXCR4 inhibition in the tumour microenvironment is synergistic with the checkpoint inhibitors[72], 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[73].

The path forward for AdAlta

We believe that potential pharma partners will want to see two qualities in i-bodies before they seek access AdAlta's platform:

- Early clinical data, showing that i-bodies have the combination of antibody and small molecule qualities which AdAlta claims for them; and
- Manufacturing data, showing that i-bodies can be made at scale under GMP.

We believe both pieces of evidence will be in place by 2018 once the Phase I of AD-114 in IPF is recruiting patients. AdAlta intends to spend the remainder of 2016 mainly on scaling up for manufacturing of AD-114, after which it will undergo toxicology studies in mid-2017 and then enter a Phase I in patients in early 2018.

Valuing AdAlta

We valued AdAlta at $0.38 per share base case and $0.89 per share optimistic case using a probability-weighted DCF approach. Our approach was as follows:

- Our WACC was 14.5% (Speculative)[74].
- We modelled a payoff only for AD-114 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 VALUE ADALTA AT 38 CENTS BASE CASE AND 89 CENTS OPTIMISTIC CASE

[68] 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.
[69] Tel Aviv, Israel, Nasdaq: BLRX, www.biolinerx.com.
[70] See the BioLineRx press release dated 7 September 2016 and headlined '*BioLineRx Announces Clinical Research Collaboration to Investigate Combination of BL-8040 with Atezolizumab in Multiple Oncology Indications*'.
[71] 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*'.
[72] Hepatology. 2015 May;61(5):1591-602. Epub 2015 Mar 20.
[73] Oncotarget. 2016 Jan 19;7(3):2809-22.
[74] 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 1.9%; 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'.

- We assume another US$5-10m in expenditure for AdAlta to further develop AD-114;
- We model around 14 years of commercial exclusivity for AD-114.

Risk weighting

- We modelled AD-114 with a 20% probability of clinical success, which is roughly what its chances would be at Phase II. 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.

Commercial outcomes

- We assume that the product can license to a pharma partner in FY20 (base case) or FY19 (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 FY23 (base case) or FY22 (optimistic case) in the US and FY24 (base case) or FY23 (optimistic case) in Europe.
- We assume peak sales for AD-114 of US$300-600m, initially from in IPF and Wet AMD. We believe this assumption is conservative given the market opportunity in both indications.

Further capital

- We assume no further capital needs to be raised, but that partnership and collaboration deals from 2018 can fund the company on an ongoing basis.

Re-rating AdAlta

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

- Gaining of Orphan Drug status for AD-114 in IPF;
- Publication of further *in vitro* and *in vivo* data showing the therapeutic of i-bodies in IPF and other fibrosis indications;
- Development of new i-body candidates;
- Potential partnerships or evaluation agreements around i-bodies.

ADALTA WILL APPLY FOR ORPHAN DRUG STATUS FOR AD-114

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:

Sam Cobb (CEO), who joined AdAlta in 2007 shortly after its founding, brought to the company technology development and commercialisation skills initially gained at Uniquest, the University of Queensland's tech transfer arm, and honed through roles such as Business Development Director at the Co-operative Research Centre for Diagnostics. Under Sam's leadership AdAlta has refined its position as a next generation antibody-type platform play and, notably, showed that i-bodies can be used for hitting targets that are yet to be drugged with antibodies.

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. 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.

ADALTA'S CHIEF SCIENTIFIC OFFICER IS AN AUTHORITY ON PHAGE DISPLAY

The AdAlta board 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[75], Genetic Technologies[76] and IDT Australia[77], the pharmaceutical manufacturing company where he is currently CEO.
- **Dr James William** runs Yuuwa Capital, the A$40 million venture capital fund which currently owns 54% of AdAlta. 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[78].
- **Liddy McCall,** who co-owns Yuuwa Capital with James Williams, brings corporate advisory and legal smarts to AdAlta.
- **Dr John Chiplin,** AdAlta's San Diego-based director, knows the antibody space well, having run the antibody company Arana Therapeutics from 2006 until its sale to Cephalon in 2009. In that role he also served on the Domantis board just prior to its being bought by GSK. Chiplin is well connected in both US and European biotech circles.

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** and **Dr David McGibney,** formerly of Pfizer. John Westwick brings a background in respiratory medicine, Brian Richardson in musculoskeletal disease and David McGibney in CNS and cardiovascular drugs.

[75] 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.
[76] Melbourne, Australia, ASX: GTG, www.gtgcorporate.com. On MacLeman's watch this company was developing molecular diagnostics.
[77] Melbourne, Australia, ASX: IDT, www.idtaus.com.au.
[78] The Philadelphia-based Iroko Pharmaceuticals – see www.iroko.com.

Risks related to AdAlta

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

- Manufacturing risk. There is the risk that AdAlta may take longer to manufacture AD-114 than the time we have postulated in this note, particular given that PASylation is a relatively new modality for extending the half-life of protein therapeutics.
- Timing risk. There is the risk that the intended Phase I study of AD-114 may not happen as early as the beginning of 2018.
- Regulatory risk. There is the risk that the FDA and other regulators may decline to approve AD-114 even if AdAlta considers the data submitted to be adequate.
- Commercial risk. There is the risk that AD-114 may not find significant usage in IPF as other therapies come onto the market between now and the end of AD-114'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.

General Advice Warning, Disclaimer & Disclosures

The information contained herein ("Content") has been prepared and issued by NDF Research the business name of Stuart Dean Roberts, ABN 11 209 563 517) ("NDF Research"), an Authorised Representative (no: 1242594) of Bellmont Securities ABN 47 119 852 890 AFSL 331625. All intellectual property relating to the Content vests with NDF Research unless otherwise noted.

Disclaimer

The Content is provided on an as is basis, without warranty (express or implied). Whilst the Content has been prepared with all reasonable care from sources we believe to be reliable, no responsibility or liability shall be accepted by NDF Research for any errors or omissions or misstatements howsoever caused. Any opinions, forecasts or recommendations reflect our judgment and assumptions at the date of publication and may change without notice. NDF Research will not accept any responsibility for updating any advice, views, opinions or recommendations contained in this document.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by NDF Research, and under no circumstances will any of NDF Research, its officers, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the Content.

General advice warning

The Content has been prepared for general information purposes only and is not (and cannot be construed or relied upon as) personal advice nor as an offer to buy/sell/subscribe to any of the financial products mentioned herein. No investment objectives, financial circumstances or needs of any individual have been taken into consideration in the preparation of the Content.

Financial products are complex, entail risk of loss, may rise and fall, and are impacted by a range of market and economic factors, and you should always obtain professional advice to ensure trading or investing in such products is suitable for your circumstances, and ensure you obtain, read and understand any applicable offer document.

Disclosures

NDF Research has been commissioned to prepare the Content. From time to time, NDF Research's representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned herein. NDF Research and its associates, officers, directors and employees, may, from time

to time hold securities in the companies referred to herein and may trade in those securities as principal, and in a manner which may be contrary to recommendations mentioned in this document.

NDF Research may receive fees from a company referred to in this document, for research services and other financial services or advice we may provide to that company. The analyst has received assistance from the company in preparing this document. The company has provided the analyst with communication with senior management and information on the company and industry. As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in the report. Diligent care has been taken by the analyst to maintain an honest and fair objectivity in writing this report and making the recommendation.

Where NDF Research has been commissioned to prepare Content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the Content provided. Buy/Hold/Sell recommendations or price targets will NOT be published in respect of companies for which we receive a fee to provide research or analysis.

Recommendations

NDF Research issues a BUY recommendation in case of an expected total shareholder return (TSR, share price appreciation plus dividend yield) in excess of 25% within the next twelve months, an ACCUMULATE recommendation in case of an expected TSR between 5% and 25%, a HOLD recommendation in case of an expected TSR between -5% and +5% within the next twelve months and a SELL recommendation in case of an expected total return lower than -5% within the next twelve months.

Appendix I – An AdAlta glossary

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 signalling 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.

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.

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.

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 I tests for safety. Phase II tests for efficacy in a small sample. Phase III tests for efficacy in a large sample.

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:

- *CXCR4 binding molecules*, WO/2016/109872, 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.

- *Binding moieties based on shark IgNAR domain* WO/2005/118629, 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). The patent is also granted in Australia, Canada and Japan.

Appendix III – AdAlta's Capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code 1AD (million)	100.0	88.8%	
Unlisted options (million)	2.1	6.7%	Average exercise price 4.6 cents, average expiry date 03-Apr-2019
Fully diluted shares	102.1		

Current market cap:	A$24.0 million (US$18 million)
Current share price	$0.24
Twelve-month range	$0.21 - $0.28
Average turnover per day (since listing)	108,000

Appendix IV – AdAlta's major shareholders

AdAlta currently has only three substantial shareholders:

- **Yuuwa Capital (54.1%),** 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%),** the Sydney-based fund manager.
- **Leon Serry (5.3%),** a Melbourne bio-entrepreneur, through Citycastle Pty Ltd. Serry was the founder of Circadian Group, now Opthea Ltd (ASX: OPT), which over the years has created various other biotech companies including Metabolic Pharmaceuticals and Antisense Therapeutics (ASX: ANP).

Appendix V – Papers relevant to AdAlta

There are five 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.

Appendix VI – Companies to watch

Company	Location	Code	Market cap (USDm)	Website
Genmab	Copenhagen, Denmark	Nasdaq Copenhagen: GEN	8,945	www.genmab.com
Seattle Genetics	Bothell, Wa.	Nasdaq: SGEN	7,237	www.seattlegenetics.com
Intercept Pharmaceuticals	New York, NY	Nasdaq: ICPT	3,572	www.interceptpharma.com
Galapagos	Mechelen, Belgium	Euronext Brussels: GLPG	2,536	www.glpg.com
FibroGen	San Francisco, Ca.	Nasdaq: FGEN	1,137	www.fibrogen.com
MorphoSys	Munich, Germany	Xetra: MOR	1,123	www.morphosys.com
MacroGenics	Rockville, Md	Nasdaq: MGNX	973	www.macrogenics.com
Xencor	Monrovia, Ca.	Nasdaq: XNCR	864	www.xencor.com
Ablynx	Ghent, Belgium	Euronext Brussels: ABLX	773	www.ablynx.com
Global Blood Therapeutics	South San Francisco, Ca	Nasdaq: GBT	671	www.globalbloodtx.com
Innate Pharma	Marseilles, France	Euronext Paris: IPH	659	www.innate-pharma.com
Molecular Partners	Zurich, Switzerland	SIX: MOLN	532	www.molecularpartners.com
Sorrento Therapeutics	San Diego, Ca.	Nasdaq: SRNE	392	www.sorrentotherapeutics.com
argenx	Ghent, Belgium	Euronext Brussels: ARGX	323	www.argen-x.com
Immunomedics	Morris Plains, MJ	Nasdaq: IMMU	253	www.immunomedics.com
Curis	Lexington, Ma.	Nasdaq: CRIS	242	www.curis.com
MediciNova	La Jolla, Ca.	Nasdaq: MNOV	232	www.medicinova.com
ImmunoGen	Waltham, Ma	Nasdaq: IMGN	222	www.macrogenics.com
Regulus Therapeutics	San Diego, Ca.	Nasdaq: RGLS	168	www.regulusrx.com
Xoma	Berkeley, Ca.	Nasdaq: XOMA	78	www.xoma.com
BioInvent	Lund, Sweden	Nasdaq Stockholm: BINV	72	www.bioinvent.se
Pieris Pharmaceuticals	Boston, Ma.	Nasdaq: PIRS	68	www.pieris.com
BioLineRx	Jerusalem, Israel	Nasdaq: BLRX	52	www.biolinerx.com
Tobira Therapeutics	South San Francisco, Ca	Nasdaq: TBRA	52	www.tobiratx.com
iBio	New York, NY	NYSE MKT: IBIO	51	www.ibioinc.com
Galectin Therapeutics	Norcross, Ga.	Nasdaq: GALT	48	www.galectintherapeutics.com
Conatus Pharmaceuticals	San Diego, Ca.	Nasdaq: CNAT	38	www.conatuspharma.com
Pulmatrix	Lexington, Ma.	Nasdaq: PULM	25	www.pulmatrix.com

Antibody and scaffold platform companies

- **Ablynx**. This company, which originates from the finding that llamas can produce 'heavy chain only' antibodies, is built around 'nanobodies', which are basically single-domain antibody fragments. The company's lead product is Caplacizumab anti-vWF Nanobody to treat acquired Thrombotic Thrombocytopenic Purpura (aTTP) that is in Phase III. The company has various partnerships with AbbVie, Boehringer Ingelheim, Merck & Co., Merck KGaA, Novartis, Novo Nordisk, and Sanofi/Genzyme.
- **argenx**. This company's antibody platform, also a llama platform, 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. The company has pre-clinical partnerships with AbbVie and Shire among others. Early programmes in cancer and autoimmune disease are in Phase I.
- **BioInvent**. This cancer antibody drug developer uses its 'F.I.R.S.T' platform to selects 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 current in Phase I/II in Multiple Myeloma with BI-505, an antibody targeting ICAM-1.
- **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) from GlaxoSmithKline, FDA approved in 2009 for the treatment of Chronic Lymphocytic

Leukemia that gained FDA approval in 2009[79]. 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. Genmab has clinical-stage partnerships with Amgen, Bristol-Myers Squibb, J&J and Novartis.

- **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 being moved into Phase III in ovarian cancers.
- **Immunomedics**. This company was originally built on an antibody humanisation platform that allowed the creation of epratuzumab, which is now in Phase III in acute lymphoblastic leukemia. The company also has a proprietary ADC linker technology. The lead programme here is Sacituzumab govitecan, which has completed Phase II in triple negative breast cancer. This product received a Breakthrough Therapy Designation from the FDA in February 2016.
- **Innate Pharma**. This company, focused on antibody modulators of the innate immune system, has particular expertise in the creation of bispecific antibodies and ADCs. BMS has taken Innate's lirilumab antibody, which targets KIR (Killer-cell immunoglobulin-like receptors) into Phase II. BMS licensed this antibody in June 2011 when it was still in Phase I for US$35m upfront and US$430m in milestones. 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 I/II in various indications.
- **MacroGenics**. This company can create bispecific and Trispecific antibodies using its DART (Dual-Affinity Re-Targeting) and Trident platform[80] and more effective antibodies using its Fc Optimization Platform. The company is in Phase III with Margetuximab, an Fc-optimised HER-2-binding monoclonal antibody that has better HER-2 binding than Herceptin. The company has partnerships over bispecific antibodies with Servier and Janssen.
- **Molecular Partners**. This company has been built around 'DARPins, short for 'Designed Ankyrin Repeat Proteins'. Ankyrin Repeat Proteins are a common binding proteins in nature, and Molecular Partners design their drugs around DARPins that a specific for a single disease target and responsible for diverse functions, such as cell signalling and receptor binding. The company's lead DARPin is Acibipar, partnered to Allergan and now in Phase III for the treatment of wet AMD. Under Molecular Partners' 2011 partnership with Allergan the company has received combined upfront payments of US$107.5m and can receive up to $1.7bn in milestones.
- **MorphoSys**. This antibody company was pioneer of phage display technology. Today its lead antibody is Gantenerumab, an anti-amyloid beta antibody partnered with Roche and in Phase III for the treatment of Alzheimer's. Guselkumab is a Janssen-licensed antibody in Phase III for psoriasis. Other partners for MorphoSys programmes include Bayer, Boehringer Ingelheim, Celgene, GSK, Novartis and Pfizer.

[79] 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.
[80] Short for 'Dual-Affinity Re-Targeting'.

- **Pieris Pharmaceuticals**. This company has been built on a family of small extracellular proteins called the lipocalin, 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-080 for the treatment of anemia. Pieris has partnerships with Daiichi Sankyo, Roche and Sanofi.
- **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. SGN-CD33A (vadastuximab talirine) is in Phase III in Acute Myeloid Leukemia. SeaGen has partnerships with AbbVie, Astellas, Bayer, Genentech, and GSK among others.
- **Sorrento Therapeutics**. This company's G-MAB platform is 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 is developing a number of biosimilar antibodies to existing blockbusters.
- **Xencor**. This company's XmAb antibody platform allows better Fc regions to be engineered, improving potency, half-life and stability. The company's lead XmAb5871 antibody is in Phase II for IgG4-related disease and lupus.
- **Xoma**. This company owns phage display and other antibody optimisation platforms. Currently its two leading antibodies, both in Phase II, are XOMA 358 for the treatment of hyperinsulinism and XOMA 213 for hyperprolactinemia

Companies with fibrosis programmes

- **BioLineRx**. This drug developer's lead programme is BL-8040, a peptide antagonist to CXCR4. BL-8040 completed a Phase 2 clinical trial for the treatment of relapsed or refractory Acute Myeloid Leukemia. BioLineRX have also done recent deals in 2016 with Merck & Co. and Genentech to collaborate on checkpoint inhibitor drugs with their CXCR4 peptides. In August 2016 BioLineRx announced that it was in-licensing a liver fibrosis drug candidate from Hadassah Medical Centre[81]. We believe this candidate targets NLGN4, the overexpression of which seems to result in the exhaustion of NK cells[82].
- **Conatus Pharmaceuticals**. This company's lead compound is emricasan, a small molecule caspase protease inhibitor. This product is in Phase II in liver cirrhosis and NASH cirrhosis.
- **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 II in NASH. The company is evaluating its potential in kidney fibrosis.
- **iBio**. This company is being built on a plant-based protein expression system. The company's lead product, manufactured using the protein expression system, is BIO-CFB03, which is a peptide derived from endostatin useful in the treatment of fibrotic disease. iBio intends to go after systemic scleroderma and IPF with BIO-CFB03. Current programmes are pre-clinical.

[81] See the BioLineRx press release dated 1 August 2016 and headlined '*BioLineRx Announces In-licensing of Liver Fibrosis Project Under Strategic Collaboration*'
[82] See US Patent 9,243,294.

- **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 is now in Phase III in NASH.
- **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 II with RG-101, which targets a microRNA in liver cells called miR-122 that Hepatitis C Virus uses to replicate. It is in Phase I, in partnership with AstraZeneca, with RG-125, which targets the miR-103/107 microRNA precursor and is being looked at for the treatment of NASH patients with Type II Diabetes or pre-diabetes. A product for the Orphan kidney disease Alport syndrome has been partnered with Sanofi's Genzyme unit.
- **Tobira Therapeutics**. This company, whose main focuses are liver disease and inflammation, is in Phase II with Cenicriviroc, a dual inhibitor of the CCR2 and CCR5 pathways known to be relevant in both inflammation and fibrosis. The first two indications are NASH and another disease of the bile ducts of the liver called primary sclerosing cholangitis (PSC)[83].

Companies with IPF programmes

- **Curis**. This company, which is mostly focused on new cancer drugs, developed Genentech's Erivedge (vismodegib) for the treatment of advanced Basal Cell Carcinoma. Genentech has now taken Erivedge into the clinic as a potential IPF treatment. Erivedge works by targeting the Hedgehog signaling pathway, and Hedgehog is understood to play a role in IPF as well.
- **FibroGen**. This company's work on Connective Tissue Growth Factor (CTGF) has led to Pamrevlumab, an anti-CTGF antibody that performed well in an open-label Phase II study in IPF[84]. A placebo-controlled Phase 2 trial has completed enrolment. FibroGen is also interested in the therapeutic potential of hypoxia-inducible factor (HIF). Roxadustat, an inhibitor of HIF prolyl hydroxylases, in Phase III for anemia arising from Chronic Kidney Disease.
- **Galapagos**. This company is one of the pioneers of drugs that work through the JAK1 pathway. Its filgotinib JAK1 inhibitor is in Phase III in Rheumatoid Arthritis. Its GLPG1690 autotaxin inhibitor is in Phase I in IPF. Autotaxin is an enzyme which generates lysophosphatidic acid (LPA), known to be a mediator of fibroblast recruitment in IPF.
- **Global Blood Therapeutics**. This company, focused on blood-based disorders, is in Phase III in sickle cell disease and IPF with GBT440, a haemoglobin modifier.
- **MediciNova**. This company is in Phase II in Multiple Sclerosis with a neuroprotective small molecule called ibudilast) and in Phase II in NASD and IPF with tipelukast, a leukotriene receptor antagonist.
- **Pulmatrix**. This company is a developer of pulmonary therapeutics based on a platform called ISPERSE for engineering inhaled small particles. PUR1900 is an ISPERSE formulation of an anti-fungal for cystic

[83] This is where the large bile ducts are scarred. In primary biliary cholangitis it is the small bile ducts that are affected.
[84] Eur Respir J. 2016 May;47(5):1481-9. Epub 2016 Mar 10.

fibrosis patients. PUR1500, for IPF, is an iSPERSE formulation of a 'kinase inhibitor with established anti-angiogenesis activity'.