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Bioshares

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Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - May '15)	23.0%
Year 15 (May '15 - May '16)	33.0%
Year 16 (May '16 - current)	17.3%
Cumulative Gain	**765%**
Av. Annual gain (14 yrs)	**18.7%**

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Extract from Bioshares –

Adalta Fibrosis Symposium

Last month, single domain antibody (i-body) company Adalta held a symposium dedicated to discussion of the opportunities and problems in developing therapies for the treatment of different fibrotic conditions, including fibrosis occurring in the lung, eye, liver and kidneys.

The symposium opened with a talk by Robert Peach, a director of Adalta (and also Innate Immunotherapeutics), who was a co-founder and Chief Scientific Officer of Receptos. His experiences gained at Receptos and from the development of RPC1063 were the subject of his talk. His talk offered many lessons for drug developers and investors, including what it takes to achieve an US$7.2 billion acquisition figure.

The Receptos Story

San Diego-based drug developer Receptos was acquired by Celgene in 2015 for US$7.8 billion or $7.2 billion net of cash. The acquisition was priced at $232 per share, a 12% premium to the share price at the time, in July 2015. However, its share price had risen strongly during the year, from $124 at the beginning of January, 2015.

Receptos had taken a compound, RPC1063 (ozanimod) for the treatment of multiple sclerosis, through to Phase III, as well as advancing the drug as a treatment for inflammatory bowel disease. However, what marked RPC1063 out as a drug candidate of great commercial interest was that it was an orally available, once a day formulation that offered potential benefits over existing oral MS drugs, which had been steadily taking market share away from injectable MS drugs.

Robert Peach completed his PhD in Biochemistry at the University of Otago (NZ). He commenced his post-doctoral studies at Bristol-Myers Squibb in 1991, where he worked on the development of the rheumatoid arthritis drug Orencia and the kidney transplant rejection drug Nulojix. He regarded working in an industry setting (as opposed to an academic research institute) as a "tremendous experience".

From 2000 to 2003 he directed antibody drug discovery at IDEC, and after that company's merger with Biogen in 2003, he worked on developing new approaches for auto-immune therapies.

IDEC was a US West Coast company which had been based in San Diego, whereas Biogen was headquartered at the time in Boston, on the East Coast. Peach observed that the cultural differences between the East Coast and the West Coast were pretty significant, which meant that people drifted away from merged entity.

However, Biogen had a VC arm with which Peach became involved. This allowed him to "really understand assets".

Cont'd over

In 2007 Peach co-founded Apoptos, licencing in oncology assets from the Burnham Institute in conjunction with a US$28 million capital raising. The company floundered because the assets were not good enough, he said.

In 2009 Peach founded Receptos with William Rastetter and Marcus Boehm, based on compounds licensed from the Scripps Institute.

2009 proved to be a difficult year for accessing funding with the raising of US$25 million taking a long time. Peach said that it was very hard for West Coast companies to get East Coast VC investment.

In its first phase of existence Receptos had staff of 20 scientists, one business development staffer, one accountant and one admin person. The company did not hire a CEO, CFO, or CMO until much later, around the time the company commenced a Phase I trial.

The founders hired people with multiple skills, deep experience and "cultural fit". "There was no deadwood in the company from day one," stated Peach. The VCs were very comfortable with that approach. The company was "completely science driven."

There were several facets to the organisation of Receptos' work environment: medicinal chemists and biologists worked alongside each other; the company had an in-house animal facility, which enabled rapid compound testing; and the company mostly used second hand equipment.

Scientific Focus

Receptos' scientific focus was on lymphocyte (white blood cell) trafficking and a cell membrane receptor called $S1P_{1,5}$ R , from the sphingosine 1-phosphate (S1P) receptor family.

The company had licensed molecules from the Scripps Institute which were capable of halting lymphocyte trafficking, and thereby modulating the inflammation processes associated with MS and IBS.

The company was not the first to target SP1 receptors. It followed the lead from Novartis' Gilenya (fingolomid). However, Gilenya had safety issues, notably a drop in heart rate occurring after the first dose, which required patients to sit in a neurologist's office for six hours.

Therefore, Receptos' goal was to develop a best-in-class drug in an oral daily formulation. At the time MS was dominated by injectable drugs, so there was a major need for a developing an oral form. However, as Peach stated "in chronic diseases you need a clean drug," in other words a drug with a very good safety profile.

Rapid Clinical Development

It took the company juts one year to identify a compound because the starting compounds from the Scripps Institute were really good and because Receptos had employed a highly functional team of medicinal chemists who could make compounds quickly.

The IND for RCP1063 was compiled in 10 months, and cleared by the FDA in November 2010, allowing the drug candidate to commence an ascending dose Phase I trial in January 2011. Peach himself managed the IND process but brought in consultants to assist when needed.

There were no hitches in the Phase 1 trial, according to Peach. "The drug didn't show any warts– it just kept going through the ascending doses." A lot of drugs fail because they are underdosed, he said.

Phase II/III Trial Design

The company designed its Phase II trial so that it included an interim analysis at 12 weeks (in November 2013). This was agreed to in the Special Protocol Assessment (SPA) reached with the FDA. The relevance of the interim analysis was that it triggered the Phase III component. This meant all the study sites could continue to enrol new patients into the trial since they were up and running.

According to Peach, this strategy saved 18 months in development time.

The data from the Phase II trial showed a dramatic drop in brain lesions in MS patients, between week 12 and week 24, with both doses (0.5mg and 1 mg) recording 86% fewer lesions compared to placebo.

However, of equal interest was the cardiovascular safety profile of RCP1063. Phase II data showed that RCP1063 did not decrease or suppress the heart rate in the first 6 hours after dosing. Indeed, the drug appeared to increase the heart rate. "If Celgene can get a drug label that excludes 6 hour monitoring it will be a big deal," said Peach.

Celgene is currently overseeing two Phase III trials of RCP1063, each with 1,200 subjects and with each trial costing $130 million. The trials are expected to be completed this year, with an NDA scheduled for 2018.

The potential benefits of RCP1063 are not confined to MS. The compound has potential to treat patients with inflammatory bowel disease (IBD), where it could be prove to be superior to the anti-TNF drugs (e.g. Remicade, Enbrel, Humira)

When Receptos received data from its Phase II ulcerative colitis trial in April 2015 it was a big day. "We knew we had the tiger by the tail because we knew we could treat multiple auto-immune diseases," said Peach.

The data showed that RCP1063 delivered remission in 14% of patients (at 8 weeks) at the 0.5mg dose and 16% of patients on the 1.0mg dose, compared to 6% of patients on placebo.

These data helped confirm the MS results.

The problem the company wanted to solve was how much of its drug could it sell.

It could sell more drug by moving into other indications. It esti-

Cont'd over

mated it could achieving peak sales in MS of US$1 billion a year, but it could achieve three times that in IBD.

MS Market Analysis

The first oral MS drug, Gilenya, was launched in Q4 2010, followed by Aubagio in Q4 2012 and Tecfidera in Q2 2013. These drugs now account for almost 40% of the market, having taken market share away from Avonex, Betaseron, Copaxone and Rebif.

This market trend showed that the rationale for a once a day oral drug was very strong.

RPC1063 has been positioned to go head-to-head against Tecfidera, to serve the newly diagnosed MS patient and as a first line and second line treatment but not as a salvage treatment.

Receptos conducted market research with neurologists, because as Peach stated "you need get a sense of what your drug is worth if someone comes knocking."

This survey of 75 neurologists showed that RCP1063 was viewed more favourably than Tecfidera on efficacy and tolerability and viewed more favourably than Gilenya on safety.

Acquisition by Celgene

By July 2015 when Receptos was acquired the company had grown to 110 employees. However, two years prior it had listed on the Nasdaq raising US$83 million at US$14 a share. It then went on to raise ~US$700 million through three capital raisings in 2014.

It had two Phase III trials underway in MS, Phase II trials underway in ulcerative colitis and Crohn's disease, another Phase II underway in Eosinophilic Esophagitis (EoE), as well as a pre-clinical program in Type 2 diabetes and NASH, and a discovery program underway with chemokine receptors.

Lessons Learnt

Peach concluded his talk with a summary of lessons learnt from his career at Apoptos and later at Receptos.

First, it was important to hire the right people but on an 'as needed' basis. Staff should be capable of dealing with different tasks in the business.

Second to this was the building of a productive, creative and rewarding culture. At Receptos, staff could leave at lunch on Friday, giving them more time with their families and for recreational pursuits.

Peach said that focus was also very important and that it was important to understand critical path activities.

Peach noted that many companies aim to partner their assets early. The problem with doing this he said, was that you end up owning half the drug. It's better to not partner early and to own 100%, he argued. One issue with the early partnering strategy was that a lot of time of staff and management is consumed by joint steering committees.

Among other pieces of advice he offered were that companies should enact bold, but not reckless clinical development plans, as well as developing an understanding of the competition and where a drug would fit in the market place.

He also said that a company should raise money when it can, indeed raise a 'war chest'. "We were able to say we can do this ourselves," said Peach

Peach said that the reason Receptos was sold to Celgene was that "the offer was too good to turn down.". "We didn't actively pursue the acquisition, we let them come to us," he said.

Adalta's AD-114

Michael Foley, Adalta's founding scientist, said that antibodies have incredible specificity and affinity.

Shark antibodies, on which Adalta's technology is based, have evolved to function as single domain antibodies.

The long loop on these antibodies, which are about 10% of the size of human antibodies, allows these drug candidates to access areas in the body where traditional antibodies can not reach whilst maintaining high specificity and affinity. The long loop binds deep into the GPCR pocket said Foley.

While shark antibodies would potentially be seen as foreign by the human system, Adalta's technology uses human proteins that mimic the shape of the shark antibody binding domain.

Adalta's lead program with AD-114 (which is due to move into clinical studies this year) is in the treatment of idiopathic pulmonary fibrosis (IPF), which affects more than 135,000 people in the US alone.

The target for this program is CXCR4 which is involved with different fibrosis-driven diseases.

In IPF, patients with up-regulated CXCR4 in the lungs are known to see more rapid disease progression.

AD114 is has been shown to bind to lung tissue and significantly reduce the migration of fibrotic cells into the lungs.

Foley said that AD-114 outperformed the only two drugs on the market for IPF, nintedanib (Boehringer Ingelheim) and pirfenidone (Roche), in preclinical studies with respect to efficacy.

If Adalta can show that AD-114 can work in the lungs, then one of the next applications will be in the treatment of NASH (non-alcoholic steatohepatitis).

Adalta has already shown its drug candidate has anti-fibrotic and anti-inflammatory effects in the liver in preclinical studies. AD-114 may also have an application in the treatment of eye diseases, with positive preclinical results also in the treatment of wet AMD.

Cont'd over

Foley said that AD-114 is a potential first-in-class therapy that has shown anti-inflammatory and antifibrotic effects in several pre-clinical disease models.

Idiopathic Pulmonary Fibrosis

Associate Professor Glen Westall is the head doctor of the Pediatric Lung Transplant program at the Alfred Hospital in Melbourne. Westall set up the IPF registry in Australia.

While it is not known exactly what causes IPF, in around 70% of cases it is linked to smoking. It is a terminal disease with life expectancy being around three years following diagnosis.

Westall said that patients can lose a lot of lung tissue and not be aware of it. As such patients can present with very advanced symptoms when they realise there is an issue.

Lung diseases account for over 200 different types of disorders. Fibrosis is a scarring of the lungs. With fibrosis, the lungs stiffen and lung size can be reduced by about half.

IPF represents around 50% of all fibrotic lung diseases. It is termed 'idiopathic' because it is still not known precisely what causes it.

However, it is believed to be a result of continuous injury to the lung tissue that eventually causes different healing processes resulting in fibrosis.

The average age at diagnosis is 66 years with around 10,000 cases in Australia.

Two drugs were approved by the FDA to treat IPF in 2014, being nintedanib and pirfenidone although both have limited efficacy and side effects said Westall.

In clinical studies, pirfenidone reduced IPF deaths by 68%. However 36% of patients experienced nausea, 25% had headaches and 22% reported diarrhea. Nintedanib also reduces mortality but is not curative. And 61% of patients experience diarrhea.

Westall said that better drugs are still required for IPF which remains a terminal disease. In clinical development for IPF, Westall listed four programs in Phase I trials, seven in Phase II and five in Phase III.

Westall confirmed the target that Adalta is working on, CXCR4, which Westall says has very limited expression in healthy lung tissue.

The Alfred Hospital conducts around 90 lung transplants a year. Westall said that IPF does not recur after transplant, and as such, the disease is likely due to lung resident fibroblasts.

Worldwide drug sales are expected to reach US$4.2 billion by 2020 said Michael Foley.

Chronic Kidney Disease

Dr Muh Geot Wong is a renal physician at the Royal North Shore Hospital in Sydney. Dr Wong said that by 2030, it is expected that 5.4 million people worldwide will be on kidney dialysis.

The chronic kidney disease (CKD) market is expected to reach US$11.7 billion by 2022. One of the big drivers of this disease is escalation in numbers of people with Type 2 diabetes.

One of the problems with developing drugs to treat CKD is the lack of clarity in intermediate endpoints that should be used to satisfy regulatory drug bodies.

There is a high drug failure rate with a need to find a marker for early stage disease. Approaches being taken in drug development include LOX and SSAO/VAP1 inhibitors (which are areas Pharmaxis is focusing on) and CXCR4 antibodies (Adalta).

Eye Fibrosis

A third area where Adalta has developed positive preclinical data in fibrosis treatment is in eye diseases. Professor Erica Fletcher heads up the Visual Neuroscience laboratory at The University of Melbourne and discussed drug treatment around eye diseases and the role that fibrosis plays in these areas.

Since the introduction of VEGF inhibitors in 2006, the incidence of blindness has fallen by 47%. However, Fletcher said there is a sting in the tail of these treatments for wet AMD, with VEGF therapies providing respite and improvement for four years, however at 7.3 years after first treatment, around 50% of patients are legally blind. Fletcher said the issue is scarring (fibrosis), with scarring occurring in 45% of eyes treated with Lucentis.

Wet AMD occurs as a result of abnormal blood vessel growth from under the retina into the retina. Scars occur in places that control central vision said Fletcher.

Fletcher highlighted that effective treatment for wet AMD requires co-treatments, addressing fibrosis as well which is the leading cause of blindness.

Approaches such as Adalta's CXCR4 inhibitor is one such approach to address fibrosis in the eye. Addressing fibrosis is also important in treatment resistant AMD, end stage diabetic retinopathy and following repair of retinal detachment said Fletcher.

Panel Discussion on Fibrosis

Stuart Roberts from NDF Research chaired a panel discussion with Adalta's non-executive director Robert Peach and two members of its scientific advisory board, John Westwick (14 years at Novartis Institutes for Biomedical Research) and Brian Richardson (42 years at Novartis Institutes for Biomedical Research/Sandoz).

NASH is a difficult disease and one where Novartis had no expertise said Richardson (it now has two Phase II programs).

Cont'd over

One of the problems is that there are no good animal models. And it is not just fibrosis that needs to be addressed, but also metabolic processes that result in insulin resistance and fatty liver.

Animal models reflect early stage insulin disease but not later stage fibrosis. Fibrosis is a long term disease and there is a lot of work required to find an accurate biomarker that can reduce clinical trial length.

Biopsies are also not great as they can be hit or miss. However, pharmaceutical companies are interested in fibrosis because there is a lot of crossover between diseases.

At Novartis two of the key requirements were an understanding of the molecular mechanism and whether the program was tackling an unmet clinical need.

John Westwick said that the Adalta technology allows the antibodies to get into ion channels with selectivity and specificity that opens up a phenomenal area. “Previously antibodies could not target ion channels or GPCRs. But these small i-bodies seem to be able to do that.”

Robert Peach said that there are not many great targets for drug developers. “Adalta allows undruggable targets to be targeted.”

Adalta in Brief

Sam Cobb, CEO of Adalta, gave a brief overview of the company summarising some of the above points. Cobb said that in transactions in the fibrosis space, an upfront payment of around $100 million was common.

Adalta is seeking to move into the clinic (Phase I trials) in early 2018. Safety will be very important not just for the company's lead program but for the platform.

Key milestones for this year are to complete manufacturing, and obtain toxicology data at the end of the year. This will be with an extended half-life formulation of AD-114 which gives the drug a 20-30 fold increase in half-life.

The first indication for Adalta will be in IPF, followed by investigating the treatment of fibrosis in eye diseases. Earlier this year Adalta was granted Orphan Drug Designation by the FDA for its IPF program after presenting its preclinical data to the regulator.

Adalta is capitalised at $16 million. The company raised $10 million (at 20 cents a share) in an IPO in August last year. It had $8.8 million in cash at the end of December.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

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