

14 December 2009

Biotron (BIT)

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Recommendation

Spec Buy

Price

\$0.095

Target (12 months)

\$0.35

Biotron (BIT) is an early stage company developing new anti-viral drugs. We like the clinical data so far in Hepatitis C, the potential for a favourable clinical outcome in HIV, and the opportunity for early licensings of the BIT225 compound. We have a favourable regard for BIT management. With this note we are re-initiating coverage with a 12-month target price of 35 cents.

Expected Return

Capital growth	268%
Dividend yield	0%
Total expected return	268%

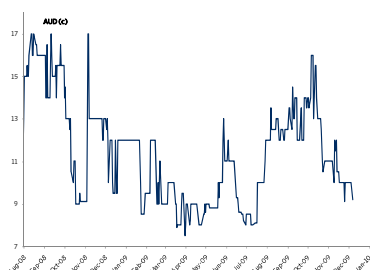
Company Data & Ratios

Enterprise value	\$10.4m
Market cap	\$10.9m
Issued capital	114.5m
Free float	100%
12 month price range	\$0.061-\$0.175

GICS sector

Healthcare Equipment and Services

Absolute Price



A compound with pre-clinical and clinical performance

Biotron's proprietary BIT225 compound has performed well in pre-clinical studies in Hepatitis C (HCV) and HIV, as well as shown encouraging early stage clinical data in HCV. The company is now preparing two clinical trials expected to be completed before the end of 2010 which we think will show strong efficacy in these conditions.

Strong markets and licensing opportunities

With the market for HIV and HCV drugs worth between US\$4bn and US\$5bn each, Big Pharma is interested in licensing compounds like those being developed by BIT. We see the company as well placed to license BIT225 after the two trials are completed in late 2010.

A well-managed company

Dr Michelle Miller has done an excellent job in focusing Biotron on anti-viral drug discovery, getting compounds ready for the clinic, and marketing the opportunity to potential licensing partners. Backing Michelle is a strong board chaired by the former Fairfax executive Michael Hoy that includes the well-regarded venture capitalist Dr Mike Hirshorn.

Biotron is inexpensive given the opportunity

On 10/12/2009 BIT announced a 1 for 1 new issue of listed 'jumbo' options at 2 cent per option to raise \$2.3m with which to fund the HCV and HIV trials it intends to conduct during the course of 2010. We value Biotron at \$0.37 base case and \$0.90 optimistic case, fully diluted for this options issue, which is currently in progress. Our target price of \$0.35 sits at our base case valuation. We see progress in BIT225's trials, set to be completed before Christmas 2010, as the catalyst to reprice BIT to at least our target and potentially beyond.

Disclosure of Interest: Biotron is a corporate client of Bell Potter Securities which is a related entity of Southern Cross Equities. Bell Potter will seek to earn corporate fees from Biotron.

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Biotron – Progress with HIV and HCV drugs¹

COMPANY DESCRIPTION

Biotron (BIT) is a Sydney-based early stage biotechnology company working on anti-viral drugs. The company’s lead compound, BIT225, has shown promise in pre-clinical work in HIV and Hepatitis C (HCV), while a small Phase I/IIa trial in Hepatitis C patients has shown efficacy with a dose response as a monotherapy. The company’s compounds tackle infection by new mechanisms of action. The company is currently planning two further human trials in 2010 - a Phase II trial for HCV and a Phase I/II trial for HIV, in order to demonstrate safety and clinical efficacy in small sample sizes.

INVESTMENT STRATEGY

We see a payoff to shareholders arising from partnering deals from 2011 for HIV and HCV as clinical data emerges from the 2010 trials. We expect a licensing deal will yield upfront and milestone payments as well as royalties.

VALUATION

We assume that BIT has value for both HCV and HIV. Our 35 cent target price for BIT is at the lower level of our base case \$0.37 / optimistic case \$0.90 per share probability-weighted DCF valuation, which fully dilutes for the current 1:1 jumbo options issue. We assume that BIT can be re-rated by the market as further clinical data emerges.

RISKS

We see the main risk in BIT as being clinical risk – ie that products fail to perform in human trials. Another major risk facing the company is that prospective licensing partners may drive too hard a bargain for BIT shareholders to enjoy a strong return. A third significant risk is burn rate. At 30 September BIT had \$516,000 cash but this company has burned around \$178,000 per month since late 2004. The company has raised \$21m in equity capital in an IPO and four subsequent rounds before the current \$2.3m raise. It may have to make further capital raisings to fund its burn rate in the future.

¹ Southern Cross previously published on BIT in a 13/6/2006 note headlined *Nearing the clinic with HIV and Hep C drugs*, recommending BIT as a Speculative Buy with a target price of \$1.60 per share. The share price at the time was 23 cents. With this note we are re-initiating coverage.

Ten reasons to look at Biotron

BIT225 is synergistic with existing HIV and HCV drugs

- 1 **Anti-viral drugs like Biotron's have traditionally enjoyed higher levels of clinical trial success.** While this factor does not eliminate the risk that Biotron's compounds will fail in the clinic, we have valued Biotron for its HIV programme using a higher success probability than we would use for comparable compounds. We also view Biotron as having employed good risk management strategies to minimise any potential downside in its drug development programmes.
- 2 **BIT225 has been carefully designed.** Biotron's lead compound, called BIT225, has been designed with other necessary drug-like properties in mind. Its toxicity profile is good. It is orally bioavailable. It is stable and has a reasonable half-life in the patient. It is easy to make. It appears to be active against hard to treat strains of HIV and Hepatitis C (HCV). It attacks the viruses by novel mechanisms of action (the VPU protein in HIV and the p7 protein in HCV). And it is synergistic with other anti-HIV and anti-Hepatitis C drugs. Consequently we think that BIT225's prospects are good with regard to attracting strong partnering interest subsequent to its Phase II (HCV) and Phase I/II (HIV) clinical trials in 2010.
- 3 **BIT225 has performed well against Hepatitis C.** In October 2009 Biotron reported highly encouraging data from an 18-patient randomised, placebo-controlled Phase I/IIa clinical trial of BIT225 in HCV patients, where viral loads were noticeably cut in the high dose group. We think this data bodes well for a second Phase II trial in which BIT225 will be combined with the standard of care in Hepatitis C, which is interferon plus ribavirin.
- 4 **Market demand for a Hepatitis C drug are high.** With HCV a large, US\$3bn+ market currently, and the existing drugs not very effective against the virus, any worthwhile anti-HCV data from BIT225 is likely to attract strong partnering interest.
- 5 **BIT225 is an attractive new generation anti-HIV drug candidate.** BIT225 seems to be able to attack HIV in the macrophage 'viral reservoirs' that have hitherto thwarted other anti-HIV drug strategies. This alone suggests that the drug is promising in the light of the vast, US\$5bn+ First World market for anti-HIV drugs.
- 6 **Results from the initial studies of BIT225 are likely to be available within the next twelve months.** BIT225 will enter the clinic in early 2010 for two post- Phase I trials in HIV (Phase I/II) and HCV (Phase II). The near-term nature of these milestones suggests the potential for an early re-rating of Biotron stock, helped by good news through the year, namely...

...in Hepatitis C

- Q1 CY10 – Initiation of Phase II clinical trial
- Q3 CY10 – Completion of dosing in trial
- Q4 CY10 – Availability of Phase II data

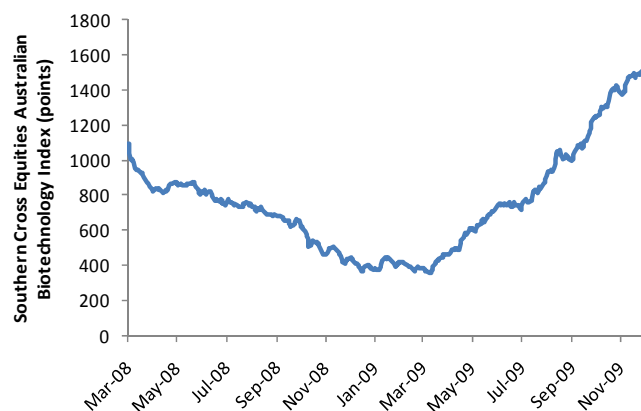
...in HIV

- Q1 CY10 – Regulatory approval for Phase Ib/IIa
- Q2 CY10 – Initiation of trial
- Q3 CY10 – Completion of dosing in trial
- Q4 CY10 – Availability of Phase I/II data

We have a high regard for Biotron CEO Dr Michelle Miller

- 7 **Biotron’s compounds are active against H5N1.** In March 2006 Biotron was able to announce that a number of its compounds had been tested against strains of influenza and that one compound had shown good activity against the H5N1 strain. What this announcement demonstrated was the power of the Biotron library. Not only did the company have a potential anti-influenza candidate, but it was able to quickly create an assay to do high-throughput screening to look for further drug candidates. We haven’t included any value for influenza in our valuation of Biotron but we think this programme represents a significant extra ‘blue sky’ element given the H1N1 pandemic of 2009.
- 8 **A good CEO and board.** Biotron’s CEO, Dr Michelle Miller, gained her PhD studying the molecular genetics of cancer, and then worked in Big Pharma developing gene therapy products for J&J. More importantly in terms of Biotron’s commercial prospects, Michelle spent the late 1990s and early 2000s heavily involved in the management of early stage biotech ventures through her role as Investment Manager at Start-up Australia, a venture capital company. Since joining Biotron in 2002 Michelle has brought discipline to the technology development process, overseeing the company’s transformation from an ANU-associated technology incubator into a focused drug developer (see Appendix V for more). She has also put in place the numerous building blocks to develop BIT225 and take it into the clinic. And she has done so while burning less than \$200,000 per month in capital, which has represented excellent value for money². We think Michelle has the skills to take Biotron to the next level of attracting licensing interest into the company and building the pipeline. Backing Michelle is a strong board chaired by the former Fairfax executive Michael Hoy that includes the well-regarded venture capitalist Dr Mike Hirshorn.
- 9 **Biotron is inexpensive given our valuation.** Based on the potential of BIT225 in HIV and HCV alone, we conservatively value the company at \$0.37 base case and \$0.90 optimistic case. Our 12-month share price target price of \$0.35 per share is at our base case valuation.
- 10 **Sentiment towards Australian biotech stocks has improved.** The end of the Global Financial Crisis came at a time when many Australian biotech companies had reached late stage maturity. Consequently at 11/12/2009 the Southern Cross Equities Australian Biotechnology Index was up 323% on the level of 9 March. We see Biotron benefiting from this improved sentiment.

Figure 1 – Sentiment toward Australian biotech stocks improved in 2009



SOURCE: IRESS, SOUTHERN CROSS EQUITIES

² Biotron’s historical underlying expenditure has been only A\$80,000 per month when costs associated with clinical trials etc are excluded.

Valuing Biotron – target price 35 cents

We value BIT at base case 37 cents and optimistic case 90 cents, fully diluted

We value BIT on the basis of a potential payoff in both HCV and HIV. To attempt a valuation of BIT we took BIT225 and assumed outlicensings after completion of the trials planned for 2010. We then conducted probability-weighted DCF valuations of the products should they gain regulatory approval using certain sales levels reached at the point of maximum sales growth in year 3, after which sales only rise 5% pa. We assumed royalties are collected for around 13 years after first sales. We valued this royalty stream using a 20% discount rate, a 30% tax rate, and a 0.90 AUD/USD exchange rate. And we also assumed a 35% chance of success in HIV and a 20% chance in Hepatitis C from Phase I to regulatory approval. The various valuation parameters are laid out in the table below.

Target price 35 cents. Our individual programme valuations plus our assumption of increased dilution from the current 1-for-1 jumbo options issue resulted in our valuing BIT at base case \$0.37 per share and optimistic case \$0.90 per share. Our 12-month target price sits at the base case valuation.

HCV value first, then HIV. The \$2.3m to be initially raised in the 1:1 jumbo options issue is not sufficient to do both the HCV and the HIV trials planned for 2010. The money will fund the HCV trial plus underlying expenses - the plan is that the HIV trial will be funded from funds received from early exercise of options (31/3/ 2010 deadline), and so won't commence until the company knows it has additional funds in early April. However Biotron will proceed with regulatory/ethics approvals for the HIV trial during 1Q10, on the assumption that it will get sufficient funds at the end of March.

Figure 2 – Key parameters for valuing BIT's products.

Product	Sales at maximum growth rate base (USDm)	Sales at maximum growth rate optimistic (USDm)	BIT remaining expenditure base (USDm)	BIT remaining expenditure optimistic (USDm)	Royalty base	Royalty optimistic	Start of Phase I	Upfronts and milestones base (USDm)	Upfronts and milestones optimistic (USDm)
BIT-225 in HIV	250	500	3	3	7%	14%	May-10	50	125
BIT-225 in HCV	500	1000	3	3	7%	14%	Feb-10	100	250

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Figure 3 - Our valuation of BIT.

	Base case	Optimistic case
BIT225 in HCV (\$m)	63.5	179.3
BIT225 in HIV (\$m)	28.8	98.7
Cash as at September 2009 (\$m)	0.5	0.5
Cash from options (\$m) ³	36.8	36.8
Total diluted value (\$m)	129.6	315.3
Total diluted shares	350.3	350.3
Value per diluted share	\$0.37	\$0.90
Share price target	\$0.35	

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

³ Assumes early exercise of jumbo options as well as exercise of the 20 cent options that arise from early exercise.

Biotron's powerful anti-HCV compound

Biotron is seeking to commercialise an anti-viral compound called BIT225.

The company initially developed BIT225 as an HIV treatment, but conducted its first clinical trial in patients as a Hepatitis C (HCV) therapy, where the drug performed well and where we think will be the initial commercial payoff. For background on the history of BIT225 since the mid-1990s, see Appendix I of this note.

BIT225 has performed well against HCV

A strong clinical performance. In October 2009 Biotron reported highly encouraging data from an 18-patient randomised, placebo-controlled Phase I/IIa clinical trial of BIT225 in HCV patients:

- BIT225 was safe and well tolerated;
- There was a modest but 'highly significant compared to placebo controls' reduction in viral load from baseline at Day 0 through to the end of the study at Day 21 at the highest of the two doses trialled, which was 200 mg twice daily;
- At this dose BIT225 reduced blood virus levels in three of the six subjects dosed.
- The drug proved active against the hard-to-treat genotype 1 of HCV, which is also the most common genotype in the US⁴;
- The trial outcome was achieved on dosing of only seven days, after which viral load was measured out to 21 days. This suggests potential for a better result over a more sustained dosing period⁵.

A dose response. With the other dosage in the trial, which was 35 mg twice daily, proving ineffective, there is potential for BIT to enjoy a 'dose response', meaning that it could be even better at dosages greater than 200 mg.

Encouraging pre-clinical evidence on drug synergy. Biotron has previously inferred, from pre-clinical work, that BIT225 is synergistic with both

- the current standard of care (ie interferon combined with ribavirin); and
- the emerging HCV polymerase inhibitor drugs that are in early stage clinical studies⁶.

We think this apparent multiple synergism, when combined with what we know from the Phase I/IIa clinical trial, suggests the likelihood for this drug to be highly effective against HCV in combination therapy, making it a potentially licensable candidate.

The market for HCV drugs is strong

HCV is a large market opportunity worth perhaps US\$10bn. In terms of patient numbers HCV is worth perhaps US\$10bn once the medical need has been met from a pharmaceutical perspective, with around 170 million people chronically infected worldwide. Currently the market is around US\$3bn and growing.

BIT225 performed well against the hard-to-treat genotype 1 of HCV

⁴ Genotype 1 affects 70- 90% of Americans with chronic HCV.

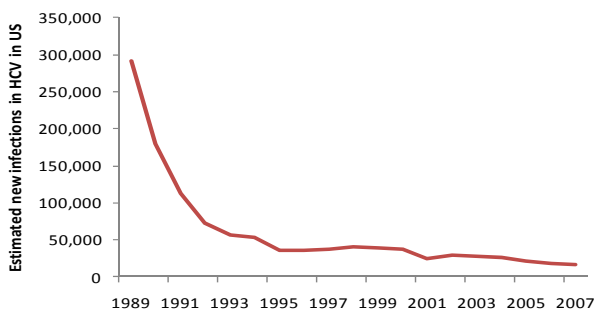
⁵ Biotron had initially intended to dose for 14 days but had difficulties in patient recruitment so after ethics approval the dose window was reduced to 7 days.

⁶ See BIT's 9/9/2008 ASX release.

Biotron (BIT)

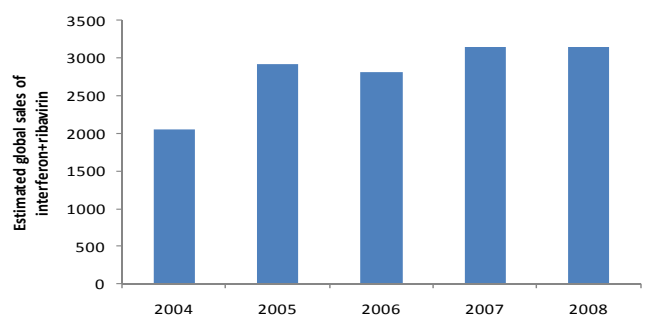
3 million chronically infected people in America alone. Hepatitis C is one of five viruses that infect liver cells (Hepatitis A to E). Like HIV the virus is passed from person to person by contact with infected blood, and there is no prophylactic vaccine⁷, but unlike HIV it's one of those viruses that some people's immune systems can actually defeat and clear from their systems. Not the majority, however. It is estimated that in the US alone some 4 million people have been infected with Hepatitis C, and that only around 30% of these people have seen the virus eliminated from their bodies. That leaves close to 3 million chronically infected Americans⁸, and even though the rate of new infection has been falling over the last twenty years, due mainly to changed behaviours among intravenous drug users, around 15,000-20,000 Americans annually are still newly infected with HCV.

Figure 4 - Around 15,000-20,000 new HCV infections are recorded in American each year.



SOURCE: CDC

Figure 5 - Interferon and ribavirin are a US\$3bn global market.



SOURCE: SCHERING-PLOUGH, ROCHE, SOUTHERN CROSS EQUITIES

HCV is a significant burden on the First World's health care systems. Not all of these 3 million are sick in bed. Indeed, many people can carry Hepatitis C in their bodies for years with no adverse health consequences. Others experience jaundice, a disease condition associated with too much bile in the blood⁹ and characterised by yellow skin, tiredness, fever and so on. And still others go on to contract more serious liver diseases. It's quite difficult to gauge the health care costs of Hepatitis C infection, however it is believed that perhaps 10-20% of chronically infected people will ultimately develop cirrhosis of the liver, and liver failure, while 1-5% will be victims of liver cancer. These estimates represent a large market opportunity.

HCV is an underserved drug market, for two reasons:

- 1) *Existing drugs to treat chronically infected HCV patients are considered woefully inadequate.* Currently the gold standard treatment regime consists of a pegylated version one of the 'interferon' drugs plus another anti-viral drug called ribavirin. Around US\$3bn of these drugs are sold annually around the world by Roche and Schering-Plough. The drugs come with a multitude of side effects, most notably mental problems and lowered white blood cell count. And they are considered by physicians to be not-so-hot in terms of efficacy. For example, the most favourable clinical data suggests that only

Hepatitis C infection is a seriously underserved pharmaceutical market

⁷ CSL and Chiron, now part of Novartis, had collaborated on one in the early 2000s without apparently much success. Chiron basically controls the HCV genome through key patents.

⁸ Around 10,000 Americans die annually from HCV infection.

⁹ Due to the inability of the liver to clear the bile.

Biotron (BIT)

around half of patients infected by the refractory 'genotype 1' of the virus will experience a 'sustained response' when treated with interferon/ribavirin¹⁰.

- 2) *There are only two new drugs at late stage of clinical development.* Currently only boceprevir, from Schering-Plough, and telaprevir, from the American biotech company Vertex, are nearing the end of clinical development. These drugs, both HCV protease inhibitors, are likely to help create some kind of HAART regime for the condition¹¹, thereby improving the treatment options available for HCV patients. They are not expected to be on the market, however, until 2011.
- 3) *The new drugs are likely to have inadequacies.* For example, both require a lot of tablets to be taken (6 a day for telaprevir and 12 for boceprevir, versus only two at this stage for BIT225), both come with side effects (up to one fifth of treated patients in the clinical trials to date have dropped out), and both are likely to be expensive. In addition, there are concerns that protease inhibitor drugs will quickly run up against viral resistance¹².

Big Pharma has been very active in licensing HCV compounds

Biotron's potential licensing demand is strong. The inadequacy of existing HCV drugs, and the likelihood of new drugs being necessary to treat 'non responders', has made Big Pharma particularly keen to introduce new HCV drugs. As proof of this, prospective licensees are paying up in a big way to access any promising drug candidates (see the table below), and even acquiring the owners of those candidates outright¹³. Typically a licensor will pay a certain amount upfront and the remainder over a period of time as key drug development milestones are met. In the light of deals like those that have been done internationally since 2004, we would argue that if BIT225 turns out to have strong efficacy against HCV the licensing interest for the product would be high.

Figure 6 - Recent deals in the anti-HCV drug space

Developer	Licensee	Upfront (US\$m)	Total deal value (US\$m)	Equity component (US\$m)	Date	Type of drug	Stage completed at time of license
Pharmasset (privately held at the time ¹⁴)	Roche	0	168	4	Oct-04	Nucleoside inhibitor	Pre-clinical
Achillion (Nasdaq: ACHN)	Gilead ¹⁵	5	110	5	Nov-04	Protease inhibitor	Pre-clinical
Medivir (STO: MVIR-B)	J&J	9	91		Nov-04	Protease inhibitor	Pre-clinical
Anadys (Nasdaq: ANDS)	Novartis	20	570		Jun-05	Toll-Like Receptor Agonist	Phase I
Idenix (Nasdaq: IDIX)	Novartis	25	525		Mar-06	Nucleoside inhibitor	Phase I
PTC Therapeutics (privately held)	Schering Plough	10	200		Mar-06	IRES Inhibitor	Pre-clinical
Human Genome Sciences (Nasdaq: HGS)	Novartis	45	552		Jun-06	Albumin/ interferon α 2b FP	Phase II
Vertex (Nasdaq: VRTX)	J&J	165	545		Jun-06	Protease inhibitor	Phase II
Genelabs (Nasdaq: GNLB)	Novartis	13	188		Jun-06	Polymerase inhibitor	Pre-clinical
Intermune (Nasdaq: ITMN)	Roche	60	530		Oct-06	Protease inhibitor	Pre-clinical
Biota (ASX: BTA)	Boehringer Ingelheim	0	103		Nov-06	Polymerase inhibitor	Pre-clinical
LG Life Sciences (privately held)	Gilead	20	212		Nov-07	Caspase inhibitor	Phase I
Santaris Pharma (privately held)	GSK	3	700	5	Dec-07		Pre-clinical
Medivir (STO: MVIR-B)	J&J	8	89		May-08	Polymerase inhibitor	Pre-clinical
Metabasis Therapeutics (Nasdaq: MBRX)	Roche	10	193		Aug-08	Prodrug to target liver	Pre-clinical
Zymogenetics (Nasdaq: ZGEN)	Bristol-Myers Squibb	85	1002	20	Jan-09	Pegylated interferon- λ	Phase I

SOURCE: COMPANY WEB SITES

¹⁰ Fried et. al., studying interferon plus ribavirin in HCV patients, found a 46% virologic response rate for genotype 1 patients. See N Engl J Med. 2002 Sep 26;347(13):975-82.

¹¹ The term HAART, short for 'Highly Active Anti-Retroviral Therapy', was coined in the late 1990s to describe the standard of care for HIV treatment. From the mid-1990s people with HIV had been living longer thanks mainly to the first three classes of anti-HIV drugs - the NRTIs, NNRTIs and the protease inhibitors. Around 1997 physicians figured out how to combine the various available drugs into a Highly Active Anti-Retroviral Therapy regime.

¹² Bristol-Myers Squibb's BMS-790052 polymerase inhibitor has generated excitement with early-stage clinical data showing it to be a once-a-day-tablet. However late stage trials of this drug are still some years away.

¹³ For example, GSK spent US\$57m in late 2008 taking over Genelabs Technologies, a hitherto publicly traded California company working on nucleoside and non-nucleoside inhibitors of HCV polymerase.

¹⁴ Pharmasset (Nasdaq: VRUS) did its IPO in 2007.

¹⁵ Gilead Sciences (Nasdaq: GILD, Foster City, California, www.gilead.com) is the world's leading specialist developer of HIV drugs, best known for the NRTI drugs Truvada and Viread.

Biotron (BIT)

BIT225 has a novel mechanism of action in treating HCV

Biotron's drug sits in a class of its own. Most anti-HCV drugs in development are designed to hit either

- NS5b, which is HCV polymerase – these drugs work in a similar fashion to the anti-HIV NRTIs and NNRTIs
- NS3, which is HCV protease - the above-mentioned boceprevir and telaprevir are protease inhibitors.

One of the attractive qualities of BIT225 is that this drug is the only one in the world so far that seems to be able to go after HCV's p7 protein as a target. HCV p7 is known to form ion channels in cells that assist in viral budding and release¹⁶, making it an attractive target for anti-HCV drug development (see Appendix I). We see BIT225's dominant position in the p7 area as helping it to attract licensing interest from companies looking for novel targets with the potential to further lower the level of non-responders in the HCV marketplace.

A second HCV trial to yield data before the end of 2010.

A larger trial than previously. Currently Big Pharma is looking for new HCV drugs that can work synergistically with interferon and ribavirin, since physicians have basically grown used to these two drugs as the 'standard of care'. Biotron has accordingly started work on the second clinical trial in HCV-infected patients for BIT225 where 24-30 patients will be randomised into three groups, one to receive placebo, one to receive a 50 mg twice daily dose of BIT225 and one to receive a 200 mg dose. The patients will be dosed for two for four weeks and then be measured for a comparable period of time, with additional follow-up for at least six months and possibly 12 months on just interferon and ribavirin. Basically the idea is to see if BIT225 firstly has an initial effect in eliminating free virus and reducing viral load, so that interferon and ribavirin then have a better chance of working.

BIT225's prospects are good. We like BIT225's prospects in this trial for three reasons:

- Recruitment is likely to be easier since treating physicians will likely be comfortable with the interferon/ribavirin inclusion;
- *In vitro* and *in vivo* data has already shown that BIT225 can work synergistically with interferon/ribavirin, suggesting the potential for a significant viral load reduction when all three drugs are used;
- The drug is likely to highlight the pivotal nature of BIT225 as priming the patient for success in conventional interferon/ribavirin therapy, setting BIT225 to enjoy premium pricing when it goes to market.

Data before the end of 2010. We expect that in addition to the abovementioned advantages, the near term nature of the trial, with data expected before the end of calendar 2010, may boost sentiment towards Biotron stock through the course of the year.

¹⁶ See, for example, PLoS Pathog. 2007 Jul;3(7):e103.

BIT225 has shown potential against HIV

The politics of HIV hasn't prevented the growth of a large First World drug market

What is HIV? AIDS, that is, Acquired Immune Deficiency Syndrome, is a disease in which the body's immune system is progressively shut down by infection with the insidious Human Immunodeficiency Virus. HIV, a retrovirus of which there are two types (HIV-1 and HIV-2), works by targeting certain of the body's white blood cells, which it gradually kills off until the infected person's immune system can no longer mount a response to other microbial infections. The unfortunate patient eventually dies from 'opportunistic infection' by another microbe perhaps a decade or so after the initial HIV infection. HIV has resisted all attempts to date to develop prophylactic or therapeutic vaccines.

Anti-HIV drugs constitute a large 'First World' market. It is estimated that for anti-HIV drugs the US market alone is worth north of US\$5bn, driven by the more than one million people who are HIV-positive and the more than 55,000 new cases diagnosed annually¹⁷. The European market is similarly large and growing. Good pricing and strong demand in these markets, combined with social consciousness regarding HIV issues, makes HIV a continued area of investment for Big Pharma in spite of intellectual property issues in Third World markets¹⁸.

Figure 7 - Leading anti-HIV drugs

Drug	Company	Style of drug	2008 worldwide sales (USDm)	Growth rate in 2008 ¹⁹
Truvada	Gilead Sciences	NRTI	2107	33.0%
Kaletra	Abbott Laboratories	Protease inhibitor	1474	11.2%
Reyataz	Bristol-Myers Squibb	Protease inhibitor	1292	15.0%
Sustiva	Bristol-Myers Squibb	NNRTI	1149	20.0%
Epzicom/Kivexa	GSK	NRTI	811	25.0%
Combivir	GSK	NRTI	794	-12.8%
Viread	Gilead Sciences	NRTI	621	1.3%
Trizivir	GSK	NRTI	389	-16.6%

SOURCE: COMPANY DATA

There is strong demand for new classes of anti-HIV drug. Because HIV eventually mutates around all the drugs and drug combinations that are sent against it, the search continues for drugs that can hit new targets in the structure of the virus, and that can be included in HAART regimes:

- Fuzeon, from Roche and the American biotech company Trimeris²⁰, gained FDA approval in early 2003 as the first 'fusion inhibitor' designed to prevent the virus from fusing with white blood cells;
- Selzentry, from Pfizer, which gained FDA approval in mid-2007, became the first 'entry inhibitor' drug. Entry inhibitors are designed to block the CCR5 and CXCR4 receptors on the surface of white blood cells, thereby making it more difficult for HIV to enter the cells;
- Insentress, from Merck, became the first integrase inhibitor with FDA approval in late 2007. Integrase is the HIV enzyme that integrates the viral genetic material into human chromosomes.

¹⁷ See www.cdc.gov/hiv/topics/basic.

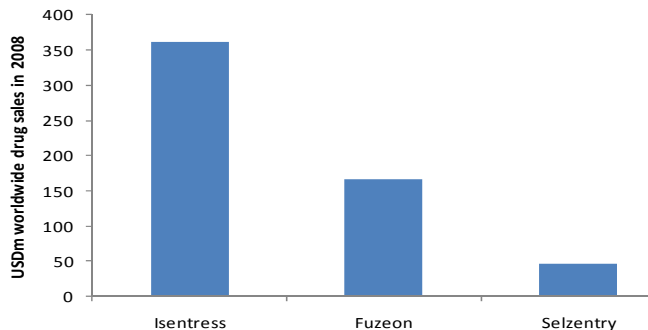
¹⁸ Where countries routinely tear up patents on HIV drugs in order to introduce generics so as to lower the cost of treatment.

¹⁹ The average growth in USD sales for these drugs in 2008 was 13.2%

²⁰ Nasdaq: TRMS, Morrisville, NC, www.trimeris.com.

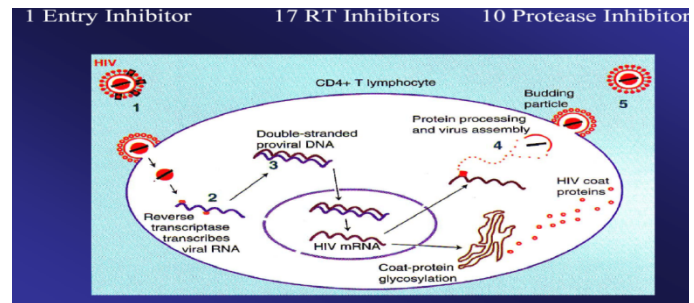
Biotron (BIT)

Figure 8 New HIV drugs - Commercial outcomes may vary



SOURCE: COMPANY DATA

Figure 9 - Biotron's compounds works at point 5 on the diagram below. Most compounds work at point 2, except the entry inhibitors which are at point 1



SOURCE: BIOTRON

There is evidence that BIT225 can hit HIV viral reservoirs

BIT225 represents another new class. This interest of Big Pharma in HIV innovation bodes well for Biotron as a prospective partner since BIT225, invented by the company's scientists around 2004/05, is a so-called 'VPU inhibitor'. 'Viral Protein U', like HCV p7, is a protein that HIV uses in the assembly of new virus particles, and in the 'budding' of new viruses from the host cell. Lack of VPU in HIV has been demonstrated to cut viral budding by 80-90%. And, *in vitro*, BIT225 has been able to markedly cut viral budding in VPU-positive HIV strains.

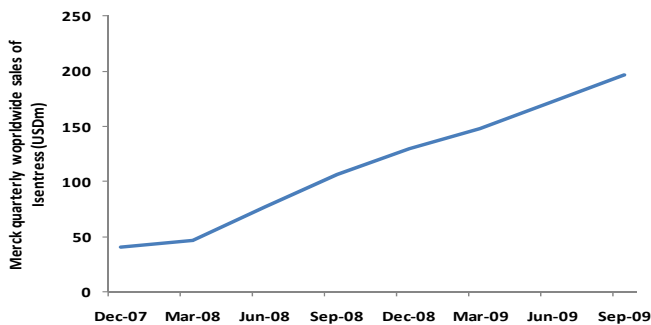
BIT225 may also be good at hitting HIV's favourite hideout. HIV researchers have grappled for some years with the problem of HIV 'reservoirs' – immune system cells where the virus 'hides' for long periods when the patient otherwise seems to be carrying negligible viral loads. Existing therapies are incapable of dealing with this issue, but Biotron believes that, in addition to BIT225's general anti-HIV properties, the drug is also good at hitting viral reservoirs.

Biotron will have to make sure its drug is really good. The potential downside of the market's hunger for new HIV drugs is that a drug has to perform well, be patient-friendly (ie, orally available with low side effects), and not be overpriced in order to be commercially successful. Isentress, which has been able to reduce virus to undetectable levels in patients, fitted all these qualities and is now on its way to blockbuster status. Selzentry hasn't grown strongly due to the need to take specialised tests before being prescribed the drug. And Fuzeon never really took off due to cost and the fact that the drug was injection-only. We think Biotron will not face these issues, since:

- The drug is orally available;
- It does not require specialised tests;
- We understand it is low-cost to manufacture and therefore would not warrant high pricing; and
- A Phase I safety study in healthy volunteers completed in August 2007 found the drug to be safe and well tolerated.

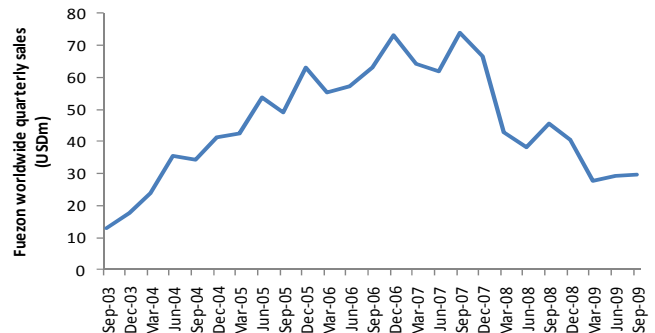
Biotron (BIT)

Figure 10 - Isentress has been a market success



SOURCE: MERCK

Figure 11 - Fuzeon has been in decline since 2007 due to the emergence of better drugs



SOURCE: TRIMERIS

Big Pharma is still licensing in HIV

The way forward for BIT225 in HIV

Getting ready for the clinic. Biotron has designed a small, 12 patient Phase Ib/Ia clinical trial in order to test the drug in treatment-naive HIV patients. A trial site has been selected in Argentina, where such patients are available, and the trial is currently awaiting local regulatory approval. The company expects it can launch the trial in April 2010, with results available around November 2010.

What happens after Phase Ib/Ia? As we noted above, the clinical demand for new anti-HIV drugs is strong. Consequently, if Biotron's Phase Ib/Ia data are particularly good, we would expect that licensing opportunities with Big Pharma for the drug to be forthcoming. Big Pharma has been less active on the licensing front in HIV in recent years, we believe because of

- the negative outcome of Fuzeon, which was the first significant HIV drug to be in-licensed from a biotech company by Big Pharma²¹;
- the Global Financial Crisis, which caused companies to be more cautious on licensing of all sorts of drugs, not just HIV drugs;
- The 2009 wave of pharma mergers²², which have distracted people within the companies concerned from licensing activity; and
- The decision by GSK and Pfizer, announced in April 2009, to pool their portfolios of approved HIV drugs into a new company to be owned 85% by GSK.

We believe that the end of the Global Financial Crisis, followed by the bedding down of the mergers and the new GSK/Pfizer company, will allow a new wave of partnering interest that Biotron can benefit from. Supporting this assertion is the fact that in 2009 GSK has concluded two significant deals in the space:

Figure 12 - Recent deals in the anti-HCV drug space

Developer	Licensee	Upfront (US\$m)	Total deal value (US\$m)	Equity component (US\$m)	Date	Type of drug	Stage completed at time of license
Medivir (STO: MVIR-B)	BMS	7.5	97		Sep-06	NNRTI	Pre-clinical
Ambrilia (TSX: AMB)	Merck	17	215		Oct-06	NNRTI	Pre-clinical
Idenix (Nasdaq: IDIX)	GSK	34	450		Feb-09	NNRTI	Phase II
Concert Pharma (Privately held)	GSK	18.3	>1000	16.7	Jun-09	Protease inhibitor	Pre-clinical

SOURCE: COMPANY WEB SITES

²¹ In July 1999 Trimeris was able to license Fuzeon to Roche with only Phase I/IIa results to hand. The licensee paid US\$10m up front and agreed to US\$68m in milestone payments. We believe the poor performance of Fuzeon was a factor in Roche's mid-2008 decision to suspend all internal HIV research.

²² ie Roche/Genentech, Pfizer/Wyeth, Merck/Schering-Plough and Gilead/CV Therapeutics.

Anti-HIV have a higher probability of success

Anti-infective drugs are generally easier to design. One of the factors working in Biotron's favour, as a developer of an anti-HIV drugs, is the higher 'success rates' that have prevailed since the 1980s in HIV drug development. Various studies have been done over the years concerning the chances of drug candidates to ultimately gain FDA approval. Historically, around 20% of all drug candidates are successful²³. However the record for different classes of drugs varies widely. One 2001 study²⁴ estimated that only 12% of candidates in the respiratory disease space had been successful, while for cardiovascular drugs the success rate was 18%. For anti-infective drugs, however, the odds were markedly better, with a success rate of 28% being one of the highest in the game. There are several reasons for these better odds. One is that safe and effective antibiotics have historically been relatively easy to develop. Another is that in certain relatively non-economic drug classes, such as anti-parasitics, where the success rate is believed to be north of 50%, fewer drugs are taken to the clinic, and, for those that do enter trials, the taxpayer has funded a good deal of pre-clinical work. And then there's the phenomenon of anti-HIV drugs.

The success rates for HIV drugs in development are high

Success rate 36%. A recent study²⁵ estimated the success rate for anti-HIV drugs at a very high 36%. Driving this has been the fact that no anti-HIV drug that entered Phase III trials has failed at this stage of development, and the majority of candidates make it through Phase II as well. In part the success rate of HIV drug candidates has to do with the virus's capacity to build resistance to drugs over time. This makes it a not-too-difficult task to develop new drugs that, while similar to existing drugs in the same class, have a reasonable chance of working. It also reflects the lower clinical hurdles that have tended to apply HIV over the years. And it may also be an outcome of ample taxpayer funding for drug development. Whatever the reason, we would argue that the statistics are in Biotron's favour as far as BIT225's chances of success are concerned.

Figure 13 - Anti-HIV drugs have a higher probability of success

Disorder targeted	% success rate	Disorder targeted	% success rate
Blood	25.0%	Musculoskeletal	22.0%
Cardiovascular	22.0%	Neurological	22.0%
Dermatological	29.0%	Antiparasitic	53.0%
Genitourinary	37.0%	Respiratory	16.0%
HIV/AIDS	36.0%	Sensory	40.0%
Cancer	20.0%	Weighted average	23.9%

SOURCE: HEALTH AFF (MILLWOOD). 2006 MAR-APR;25(2):420-8D

²³ J Health Econ. 2003 Mar;22(2):151-85.

²⁴ Clin Pharmacol Ther. 2001 May;69(5):297-307.

²⁵ *Estimating The Cost Of New Drug Development: Is It Really \$802 Million?* by Christopher Adams and Van Brantner. Health Aff (Millwood). 2006 Mar-Apr;25(2):420-8.

The risks

Biotechnology is risky

The stocks of biotechnology companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies in Australia fit this description, the speculative moniker also applies to the entire sector. The fact that biotechnology's intellectual property base lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology ought to be regarded. Investors are advised to be cognisant of this risk before buying any Australian biotech stock including BIT.

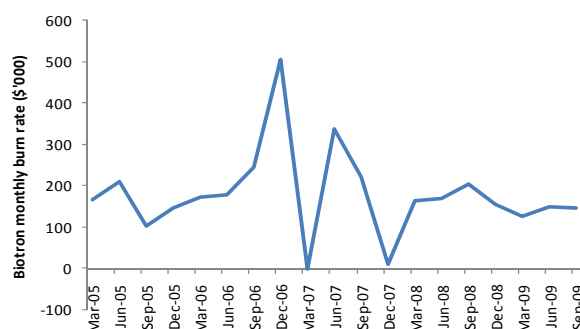
BIT is not without risk

We see seven major risks specifically related to BIT as a company and a stock:

- 1 **Clinical risk** – There is the risk that either of BIT's clinical trials could fail to reach their endpoints;
- 2 **Sentiment risk** – Biotech-oriented investors tend to prefer drug development stocks where the lead candidate is in Phase III rather than Phase II, where BIT is currently situated;
- 3 **Timing risk** – There is the risk that BIT could take much longer to organise its trials than the timing we have postulated in this note;
- 4 **Partnering risk** – There is the risk that BIT's prospective partners may strike too hard a bargain for BIT shareholders to enjoy a strong return;
- 5 **IP risk** – There is the risk that BIT could find itself locked in dispute over patent infringement should its science be found to lean too heavily on unrelated or unlicensed predecessor science;
- 6 **Burn rate** - At 30/9/2009 BIT had \$516,000 cash after burning around \$178,000 per month since late 2004. The company has raised \$21m in equity capital in an IPO and three subsequent rounds before the current \$2.3m raise. It may have to make further capital raisings to fund its burn rate in the future.
- 7 **Recruitment risk** – One of the reasons BIT stock has failed to perform since 2006 has been the slowness with which the company recruited for the HCV Phase I/II trial. While we think recruitment will be faster in the upcoming trial, recruitment remains a risk.

BIT has burned under A\$200,000 per month since 2004

Figure 14 – BIT's burn rate since 2004



SOURCE: BIT

Appendix I – Background to BIT225

Scientists associated with Biotron were the first to demonstrate that HIV VPU was druggable

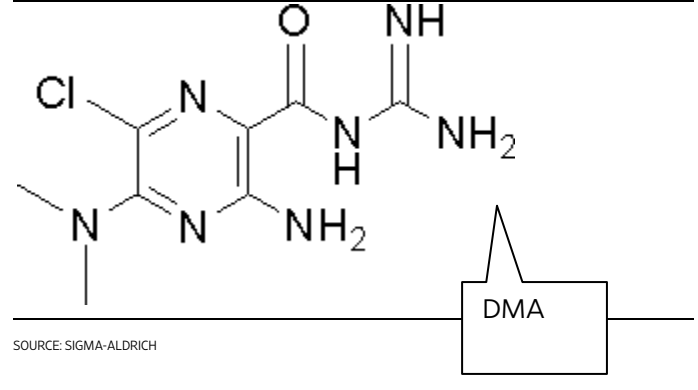
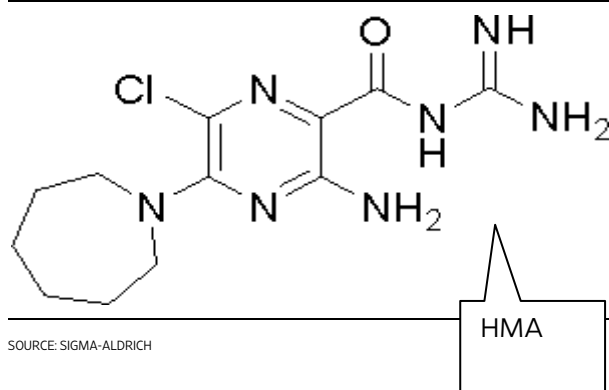
Initial work on the drug as an HIV inhibitor. BIT225 has its origins in work the late Professor Peter Gage (1937-2005²⁶) and some colleagues at the Australian National University (ANU) in Canberra did in the mid-1990s to demonstrate that VPU formed gates called ‘ion channels’ in the membrane of infected cells. They also showed that these channels, by allowing sodium to pass into and out of the cell, facilitated the viral budding process. The Gage lab invented a process of detecting VPU’s ion channel activity in cells, but more importantly, the team proved that VPU was potentially druggable²⁷. Using existing derivatives of a cardiovascular drug called amiloride²⁸, which is a sodium channel blocker, the team established two important points:

- That their compounds could block VPU’s ion channel activity, and thereby cut viral budding by up to 90%. This work was published in the *European Biophysics Journal* in its March 2002 edition.
- That the compounds could lower virus replication in the human form of a type of white blood cell called the macrophage, which is one of the main viral reservoirs in HIV-positive patients. This work was published in *Antimicrobial Agents and Chemotherapy* in June 2004.

We summarise these two papers in Appendix III of this note.

Figure 15 - HMA and DMA proved that VPU inhibition was possible...

Figure 16 - ...but they weren’t ideal compounds to take to the clinic



Drug development work since 2002. Biotron had initially expected to develop one of the above two amiloride analogues, and in particular one called hexamethylene amiloride, HMA or BIT009²⁹, as an anti-viral drug³⁰. However from

²⁶ See *Proceedings of the Australian Physiological Society* (2006) 37:29-30 for Gage’s obituary notice.

²⁷ The primary reason why the early Gage lab work was important had to do with VPU’s similarity to M2, an influenza protein. Amantadine, which in 1976 became the first anti-viral drug to gain FDA approval for treating influenza infection, works by hitting M2, which is an ion channel-forming protein. In effect Gage and his colleagues had re-discovered a way to therapeutically attack viruses. The amantadine/M2 phenomenon had established that the blockade of a virus-generated ion channel could prove a valid drug treatment. And then the Gage team established that HIV also generated ion channels. At the same time they had demonstrated that the VPU channels were sodium-permeable, which hinted at the possibility that a sodium channel blocking drug could become an anti-HIV drug, one that at the very least slowed down the rate of viral budding and therefore augmented the work of other anti-HIV drugs.

²⁸ Amiloride is a diuretic drug that has been used since the 1960s to treat hypertension and congestive heart failure.

²⁹ Biotron’s codename for the drug.

³⁰ The trouble with this approach was that the compounds that Gage et. al. used were somewhat deficient when it came to drug-like properties. That is, their half-life inside the body was too short; they weren’t all that bioavailable; and so on. Also, these other compounds were not novel so Biotron would not have any ownership over them.

Biotron built on the original science with a library of proprietary compounds

2002 the company embarked upon a rational drug design program that by 2005 had yielded BIT225, arguably a much better drug.³¹

BIT225 seems to have the right stuff in HIV. BIT225 is a good drug, in that it

- is around 68% orally 'bioavailable', meaning it can be taken in pill form and still get to where it needs to go in order to attack viruses;
- has proved in animal studies to be stable and have a reasonable half life (ie. it won't break down too quickly) as well as safe;
- is active, in low doses, against HIV and HCV, including drug-resistant strains of the viruses;
- is easy to make, with what we understand is relatively few steps in the manufacturing process³² and;
- is 'synergistic' with existing HIV and HCV drugs in terms of anti-viral activity, meaning that it has a good chance of fitting into existing treatment regimes.

There is potential for Biotron to develop other anti-viral drugs based on the 'Virion' concept. Beginning around 2003 the scientists associated with Biotron at ANU starting discovering and publishing on other viral proteins that have ion-channel-like properties and that are, apparently, good drug targets. Shortly after the 2002/2003 SARS epidemic Biotron found that the E protein of the SARS virus was druggable, and this was followed by successful discovery work on the M protein of Dengue virus. All this suggests the potential for a pipeline of anti-viral drugs to be built once BIT225 has been moved forward in HIV and HCV. Biotron calls its drug development platform 'Virion'.

Proof that Biotron can potentially drug Hepatitis C. Scientists working with Biotron demonstrated in 2003 that BIT009 was a potential Hepatitis C treatment via the p7 protein. This work was published in the European journal *FEBS Letters* in January 2004, which we summarise in Appendix III of this note.

BIT225 has proved to be a good HCV inhibitor. After developing its compound library BIT worked through it looking for a drug that best hit the HCV p7 protein while retaining good drug-like properties. In September 2006 BIT announced that it was getting *in vitro* hits in surrogate virus models with various compounds including BIT225³³. In February 2007 Biotron announced that BIT225 was able to inhibit virus-induced cell death in infected cells *in vitro*. In August 2007 the company reported that BIT225 was synergistic with interferon and ribavirin, increasing the level of inhibition of viral replication from 70% to 100% when BIT225 was added to the other two drugs. And in September 2008 the company announced that BIT225 was also synergistic with some of the new generation NS5b polymerase inhibitors in clinical trials.

³¹ By 2004 this programme, initially based on the amiloride derivatives, had yielded a proprietary drug library of around 200 compounds. During 2004 and 2005 this library was winnowed down to the best six compounds through various *in vivo* and *in vitro* tests that sought to maximise desired drug properties while maintaining anti-HIV efficacy. BIT225 was selected as the best of the best late in 2005. There are now in excess of 300 compounds in Biotron's library.

³² Biotron reported in July 2006 that with Dr Reddy's contract manufacture programme for the drug '*excellent results have been achieved in terms of product quality, and have demonstrated that BIT225 may be successfully scaled up from lab to commercial scale.*

³³ The viruses BVDV (Bovine Virus Diarrhoea Virus) and GBV-B (GB virus-B), are closely related to HCV and grow readily in cell culture. This allows them to be used as surrogate virus models for HCV, since at present there is no adequate viral culture system for HCV. That said, various scientists around the world are working on this problem. See, for example, Wakita et. al., *Nat Med.* 2005 Jul;11(7):791-6. Epub 2005 Jun 12.

Appendix II - Intellectual property

The intellectual property related to BIT225 is covered by five published patent applications. The intellectual property was transferred from ANU to Biotron in December 2006.

Method for Determining Ion Channel Activity of a Substance (WO/98/13514, priority date 27 September 1996). This patent, written by Peter Gage and his ANU colleagues Graeme Cox and Gary Ewart, covers assays devised by the Gage laboratory to determine the level of VPU inhibition by compounds. The work involved was basic to the development of BIT225. The WO/98/13514 application was granted in the United States as Patent No. 6,355,413 in March 2002.

A Method of Modulating Ion Channel Functional Activity (WO/00/21538, priority date 12 October 1998). Invented by Peter Gage, Graeme Cox and Gary Ewart. This patent covers the use of the Gage team's amiloride analogues, DMA³⁴ (BIT008) and HMA (BIT009) in antagonizing VPU and thereby cutting HIV viral budding.

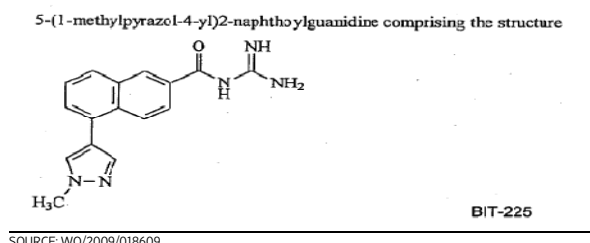
Antiviral Acylguanidine Compounds and Methods, WO/2004/112687, priority date 26 June 2003. Invented by ANU's Peter Gage and Anita Premkumar³⁵ as well as Gary Ewart and Lauren Wilson (Biotron employees at the time, working out of premises in Canberra) and Wayne Best of the Perth-based chemistry services firm EpiChem³⁶. This patent application, the first to be filed by Biotron rather than the ANU, covers the first of the anti-HIV compounds that the Biotron-associated scientists invented in 2003 and 2004. It also covers the use of Biotron's compounds in combating other viruses, notably Hepatitis C, SARS and other coronaviruses, and Dengue.

Antiviral Compounds and Methods, WO/2004/135978, priority date 24 June 2005. Invented by Gary Ewart and Wayne Best. This patent covers the second batch of anti-HIV compounds in Biotron's library, including BIT225. Given that patent life is 20 years from priority date, this gives Biotron patent protection for BIT225 until at least 2025³⁷.

Hepatitis C Antiviral Compositions and Methods, WO/2009/018609, priority date 3 August 2007. Invented by Gary Ewart, Carolyn Luscombe and Michelle Miller. This patent covers the use of the BIT compounds, including BIT225, in Hepatitis C therapy.

Biotron has patent protection over BIT225 to at least 2025

Figure 17 - Structure of the BIT225 molecule



³⁴ Short for dimethyl amiloride.

³⁵ The ANU staff were included due to their input in identifying ion channel properties of the various viruses covered in these applications, not from their input into designing and testing the compounds which are covered in these applications.

³⁶ See www.pharmaust.com/epichem_staff.asp. EpiChem is now part of PharmAust, ASX Code PAA. Best was a key player in the rational drug design programme that led to BIT225.

³⁷ We say 'at least' because of the provision of many jurisdictions for patent extension based on the time spent in clinical development.

Appendix III – The science behind Biotron

The 1996 *Journal of Virology* paper

In this paper³⁸ Ewart et. al. pointed to the potential of HIV to form ion channels in the cells that it infects, via VPU.

VPU can form ion channels. Ewart et. al. proved this by conducting an electrophysiological experiment³⁹. Taking a plastic cup that was divided into two chambers with a tiny hole in the middle, they painted a ‘lipid bilayer’ across the hole⁴⁰, and added solutions of potassium and sodium to the two chambers. They then measured electrical activity across the wall between the two chambers before and after the addition of purified VPU protein into one of the chambers. Before the addition of VPU there was no electrical conductance. Afterwards there was such conductance.

VPU’s ion channels are sodium-permeable. Ewart et. al. demonstrated this by expressing VPU into *E. coli* cells and using a ‘cross-feeding assay’. Cross-feeding assays are designed to detect the presence of a particular substance in one cell line by placing, in the same test tube, a second cell line that feeds off whatever is induced by the first cell line. Ewart et. al. hypothesised that if VPU formed sodium channels, then *E. coli*-expressing VPU would leak the amino acid proline but not another amino acid called methionine⁴¹. When they placed *E. coli* cells expressing VPU in the same minimal media (that is, media lacking any added proline) as cells that could not synthesise their own proline, the latter cells were able to grow, indicating that the proline they were getting was leaking from the former cells. A second experiment, this time with starved cells that could not synthesise their own methionine, saw those cells unable to grow in the presence of the VPU-expressing cells. Because the protein responsible for proline transport in *E. coli* cells is energised by the sodium ‘gradient’ normally maintained across the plasma membrane⁴², and the protein responsible for methionine transport is not sodium dependant, Ewart et. al. concluded that VPU formed sodium channels in the *E. coli* cells⁴³. The cross-feeding assay work provided the basis for Biotron’s WO/98/13514 patent application.

The 2002 *European Biophysics Journal* paper

In this paper⁴⁴ Ewart et. al. demonstrated that two amiloride derivatives – HMA and DMA – are able to inhibit VPU ion channel activity, and that HMA was able to inhibit viral budding. This work provided the basis for Biotron’s WO/00/21538 patent application.

HMA and DMA inhibit VPU activity. Ewart et. al. set up the same two-chamber electrophysiology experiment as that conducted for the *Journal of Virology* paper, only this time added HMA and DMA to the mix. HMA was the best inhibitor of VPU ion channel activity, with average conductance dropping from 14.1

Biotron’s development of BIT225 has been backed by some peer-reviewed papers

³⁸ Ewart et. al., *J Virol.* 1996 Oct;70(10):7108-15. Visit <http://jvi.asm.org/cgi/reprint/70/10/7108.pdf> for a full reprint.

³⁹ Electrophysiology is the study of the electrical properties of biological cells and tissues.

⁴⁰ Lipids are a class of compounds that include fats and waxes. The cell membrane is a lipid bilayer.

⁴¹ Since synthesis of proline required sodium to stay within the cell, and methionine did not.

⁴² That is, more sodium on one side of the cell wall than the other.

⁴³ Others researchers have since shown in ‘patch clamping’ experiments – where electrodes are placed on opposite sides of cell walls – that VPU can form ion channels in the plasma membrane of eukaryotic cells, that is, the cells of multi-cellular organisms. It is well known that VPU is membrane located (mainly in two structures called the ‘endoplasmic reticulum’ and the ‘Golgi apparatus’) in HIV infected mammalian cells. So with the Ewart et. al. work, it would now seem very likely that VPU is able to form ion channels in the cells of humans infected with HIV.

⁴⁴ Ewart et. al., *Eur Biophys J.* 2002 Mar;31(1):26-35

picoSiemens⁴⁵ to 0.9 picoSiemens (a 94% drop). For DMA the figure was a drop from 16.1 picoSiemens to 0.5 picoSiemens (97%). By contrast amiloride didn't depress ion channel activity at all, and neither did the anti-viral drug amantadine.

HMA cut Gag protein production. Ewart et. al. then expressed VPU and the 'Gag' protein of HIV inside HeLa cells⁴⁶ and found that the amount of Gag protein in the 'supernatant' (that is, released from within the cells to the outside culture medium in the form of virus like particles) dropped by more than 90% when HMA was added.

The 2004 *Antimicrobial Agents and Chemotherapy* paper

In this paper⁴⁷ Ewart et. al. demonstrated that HMA and DMA could inhibit HIV replication in human monocyte-derived macrophages (MDMs).

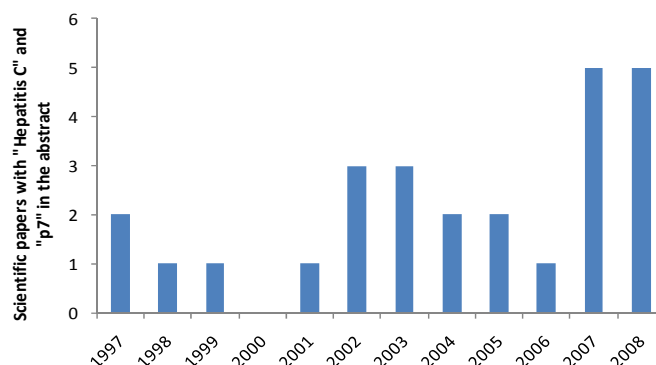
Ewart et. al. took some MDMs from healthy donors and infected them in the test tube with HIV. The supernatant was then tested for the presence of p24, the protein which makes up HIV's 'capsid' that is, protein coat, over a 28 day period. In the test tubes in which no DMA or HMA were subsequently added, p24 counts rose inexorably over that time, reflecting the normal process of virus replication and release. By contrast the drug-treated test tubes exhibited marked inhibition of virus release, as measured by p24. Ewart et. al. then tested for HIV DNA and RNA inside cells and found that drug treatment tended to reduce this as well, but not to the same extent as p24 release, suggesting that the drug's main effect was on viral budding.

BIT225 was designed as an anti-HIV compound but was found to be useful against HCV in some serendipitous science

The 2004 *FEBS Letters*⁴⁸ paper

In this paper⁴⁹ Premkumar et. al. demonstrated that the p7 protein of HCV was ion channel forming and that the ion channels could be blocked using HMA. Premkumar et. al. set up the same two-chamber electrophysiology experiment as that conducted for the *Journal of Virology* paper, only this time used p7 rather than VPU. They were able to demonstrate the presence of viral ion channels and then inhibition of the ion channels using HMA.

Figure 18 - Scientific interest in the p7 protein of HCV has been growing



SOURCE: PUBMED

⁴⁵ The siemens is the SI unit of electric conductance.

⁴⁶ HeLa is an 'immortal' cell line often used in cancer research, as the original cells were derived from a cervical cancer patient.

⁴⁷ Ewart et. al., *Antimicrob Agents Chemother.* 2004 Jun;48(6):2325-30. Visit <http://aacasm.org/cqi/reprint/48/6/2325> for a full reprint of this paper.

⁴⁸ FEBS is the Federation of European Biochemical Societies and *FEBS Letters* is one of its journals (www.febsletters.org).

⁴⁹ Premkumar et. al., *FEBS Lett.* 2004 Jan 16;557(1-3):99-103.

Appendix IV – Companies working on HIV and HCV drugs

At present the hot area of HIV research is 'entry inhibitors'

Companies working on anti-HIV entry inhibitor drugs

Myriad Genetics (NASDAQ: MGEN, Salt Lake City, Utah, www.myriad.com) acquired in early 2009 a drug called bevirimat, which is a 'maturation inhibitor' currently in Phase II. The drug works by inhibiting the final step in the processing of the HIV Gag protein.

Progenics Pharmaceuticals (Nasdaq: PGNX, Tarrytown, NY, www.progenics.com) is working on PRO-140m, a monoclonal antibody that functions as an entry inhibitor by binding to CCR5. PRO-140 has completed Phase II.

Samaritan Pharmaceuticals (OTCBB: SPHC, Las Vegas, Nevada, www.samaritanpharma.com) is in Phase IIb trials for SP-01A, an HIV entry inhibitor that can apparently block both CXCR4 and CCR5.

Sangamo Biosciences (Nasdaq: SGMO, Richmond, California, www.sangamo.com) is developing called SB-728-T, 'zinc finger DNA-binding protein nuclease' drug to disrupt the CCR5 receptor. This drug is in Phase I/II clinical trials.

Companies working on other kinds of anti-HIV drugs

Achillion Pharmaceuticals (NASDAQ:ACHN, New Haven, Connecticut, www.achillion.com). This company is in Phase II for Elvucitabine, an NRTI. It is also working on various HCV protease inhibitors.

Ambrilia Biopharma (TSX:AMB, Montreal, Quebec, www.ambrilia.com) has developed PPL-100, an anti-HIV protease inhibitor drug⁵⁰.

Ardea Biosciences, Inc. (Nasdaq: RDEA, San Diego, California, www.ardeabio.com) has done Phase II work on RDEA806, an NNRTI.

Avexa (ASX: AVX, Melbourne, www.avexa.com.au) has a completed Phase III trials of AVX-754, an NRTI drug which it in-licensed from Shire Pharmaceuticals in early 2005.

Idenix Pharmaceuticals (Nasdaq: IDIX, Cambridge, Massachusetts, www.idenix.com) partnered with GSK in early 2009 on IDC899, an NNRTI with Phase II data.

Pharmasset (Nasdaq: VRUS, Princeton, NJ, www.pharmasset.com) has done a Phase I study of Racivir, an NRTI.

Companies working on anti-HCV protease inhibitor drugs

Idenix Pharmaceuticals (Nasdaq: IDIX, Cambridge, Massachusetts, www.idenix.com) is in Phase II with IDX184, a nucleoside HCV polymerase inhibitor.

Intermune (Nasdaq: ITMN, Brisbane, California, www.intermune.com) is seeking to develop an HCV protease inhibitor drugs, ITMN-191, which is currently in Phase IIb clinical development in combination with interferon and ribavirin. Intermune

⁵⁰ It's also worked on an anti-HIV entry and integrase inhibitors, as well as anti-HCV entry and polymerase inhibitors.

has partnered this compound with Roche, which is significant given that Roche is a major supplier of interferon and ribavirin.

Medivir AB (STO: MVIR-B, Huddinge, Sweden, www.medivir.com) is seeking to develop an HCV protease inhibitor, in collaboration with Tibotec (a J&J subsidiary). The company's TMC-435 candidate is now in Phase II.

Pharmasset (Nasdaq: VRUS, Princeton, NJ, www.pharmasset.com) initially conducted a Phase I study of PSI-6130, a nucleoside HCV polymerase inhibitor before it partnered with Roche on RG7128, a prodrug of PSI-6130 that is now in Phase II.

Vertex Pharmaceuticals (Nasdaq: VRTX, Cambridge, Massachusetts, www.vrtx.com) received fast track designation for VX-950, a protease inhibitor, in December 2005. VX-950 is now in Phase III and has been partnered with Janssen, the J&J unit, as well as the Japanese drug company Mitsubishi Tanabe.

Companies working on other therapeutic approaches to HCV

Anadys Pharmaceuticals (Nasdaq: ANDS, San Diego, California, www.anadyspharma.com) gained favourable Phase I data with its ANA773 TLR agonist⁵¹. It is currently in Phase II with ANA598, a non-nucleoside polymerase inhibitor.

Benitec (ASX: BLT, Mountain View, California, www.benitec.com) has licensed its RNA silencing technology⁵² related to HCV to the privately-held Tacere Therapeutics (San Jose, California, www.tacerebio.com), which in turn has licensed Pfizer.

GlobeImmune (Privately held, Louisville, Colorado, www.globeimmune.com) has developed GI-5005, an anti-HCV therapeutic vaccine which performed well in pilot clinical trials reported in April 2009.

Inovio Biomedical (AMEX:INO, San Diego, California, www.inovio.com) has developed an anti-HCV DNA vaccine that generated favourable Phase I/II data.

Intercell (WBAG: ICLL, Vienna, Austria, www.intercell.com) has developed an HCV therapeutic vaccine which has performed well in a Phase II trial. The vaccine is partnered to Novartis.

Metabasis (Nasdaq: MBRX, San Diego, California, www.mbasis.com) has licensed its HepDirect liver-targeting technology, basically a prodrug which is activated in the presence of liver enzymes, to Roche, which had been interested in adapting the technology to a nucleoside-based drug to treat HCV.

Novelos Therapeutics (OTCBB: NVLT, Newton, Massachusetts, www.novelos.com) has conducted a Phase I/II trials for NOV-205, a 'hepatoprotective' agent based on oxidised glutathione⁵³. The product is already approved in Russia.

Zymogenetics (Nasdaq: NGEN, Seattle, Washington, www.zymogenetics.com) has licensed pegylated interferon lambda, a new kind of interferon product currently in Phase I, to Bristol-Myers Squibb.

⁵¹ Agonist drugs are designed to enhance the function of receptors, as opposed to antagonists, which are designed to block receptors. 'Toll-Like Receptors', or TLRs, are molecules on the surface of immune system cells that recognise foreign substances in the body and participate in an immune response. Toll-Like Receptor agonist drugs are designed to boost the body's immune response.

⁵² 'Gene silencing' involves compounds that bind to RNA but where the resulting nucleic acid complex is eaten up by enzymes in the cells.

⁵³ Glutathione is a tripeptide composed of three amino acids - glycine, glutamic acid, and cysteine. This compound is known to be an important component of the body's 'natural detoxification system'.

Appendix V – Non-core projects

Biotron has evolved from technology incubator to focused drug developer

When Biotron was formed in 2000 it was a biotech ‘incubation’ company, designed to work on a number of very early stage projects then emerging from the ANU’s John Curtin School of Medical Research. The VPU project was one of these projects, and it became the core project when Michelle Miller joined as CEO in 2002. There were three other projects:

- **C-Test** is designed to detect cancers at their early stages of development⁵⁴. The thinking is that cancers have a different glycolipid expression pattern in blood sera to ordinary sera. Scientists in the laboratory of Professor Chris Parish⁵⁵ have developed techniques for extracting certain carbohydrates from the blood and then analysing the expression profile of the carbohydrates using proprietary algorithms. The technology has been trialled using blood sera from patients with various kinds of cancers.
- **GeneTrans** is a test that can help predict the effect of new drugs. The technology is based on MRP2, a so-called ‘drug transport’ protein whose function, as the name suggests, is to move drugs across the walls of cells. Scientists in Professor Philip Board’s laboratory have created a cell line that expresses MRP2⁵⁶, and the rate at which these cells die when exposed to drug candidates can provide a good indication as to whether or not the drug is toxic to cells.
- **Muscion**, which emanates from Professor Angela Dulhunty’s lab⁵⁷, is a project focused on small molecule drugs that target calcium channels called ‘ryanodine receptors’⁵⁸. The thinking is that these drugs, by releasing calcium inside heart cells, can induce heart muscle to contract. This could lead to a new-generation drug to treat heart failure.

Biotron has retained ownership of C-Test although that project is currently on hold while the company focuses on BIT225. As for the other two projects, under a December 2006 deal with ANU Biotron received \$440,000 for relinquishing rights to the possible future intellectual property from the projects, but will receive a royalty from commercialisation should it occur. The development of GeneTrans and Muscion will not require any funding by Biotron.

⁵⁴ See *Method of identifying cancer markers and uses therefor in the diagnosis of cancer* (WO 02/087690, priority date 19 July 2000), and *A novel cancer marker and uses therefor in the diagnosis of cancer* (WO 03/014724, priority date 3 August 2001). The inventors in each case are Chris Parish and Dr Vivian Cabalda-Crane.

⁵⁵ Chris Parish was the principal inventor of PI-88, the carbohydrate-based cancer drug that the Brisbane-based Progen (ASX Code PGL) spent many years commercialising.

⁵⁶ See *Modified proteins, isolated novel peptides, and uses thereof* (WO 02/18438, priority date 31 August 2000), invented by Philip Board and PhD student Matt Harris.

⁵⁷ Professor Dulhunty is a major shareholder of Biotron with 8.7% of the ordinary shares on issue.

⁵⁸ See *Method of modulating the activity of calcium channels in cardiac cells and reagents therefor* (WO 02/092119, priority date 17 May 2001), invented by Angela Dulhunty and Dr Marco Casarotto.

Appendix VI – A Biotron glossary

AIDS – The Acquired Immune Deficiency Syndrome, a condition in which the immune system ceases to function effectively due to destruction of white blood cells by HIV.

Amiloride – A cardiovascular drug that is a sodium ion channel blocker. Biotron-associated scientists initially used amiloride analogues when searching for a VPU inhibitor drug. See *HMA* below.

Analogues – Chemical compounds that are based on a known substance but where various elements of the original compound have been changed. Scientists often create analogues of known compounds when looking for new drugs that have similar properties to the compound but are better as drugs.

Antibodies – Substances in the blood that can attach themselves to antigens, thereby neutralising them.

Antigen - The ‘bad guy’ substance that stimulates the immune system to respond to the perceived threat.

Assay – A test that allows the presence or absence of a substance in a test tube to be verified.

Baseline – The starting point for measurement in a scientific experiment or clinical trial.

Bioavailability – The quantity of a drug that is able to make it to its target once inside the body. High bioavailability is an important component in a drug’s prospects for commercial success. High oral bioavailability is even more desirable because then the drug can be administered in pill form. Some drugs have high bioavailability when injected intravenously but low bioavailability orally. BIT225 is considered to have good oral bioavailability.

Blockbuster – A drug that sells more than a US\$1bn worth of product annually.

BIT009 – Biotron’s initial proof-of-concept compound, based on HMA. BIT009 was superseded in 2005 by BIT225.

BIT225 – A rationally designed drug that Biotron has developed for the treatment of HCV and HIV infection.

CCR5 – A receptor on the surface of some immune system cells that HIV uses to enter the cell. Many ‘entry inhibitor’ drugs work by blocking CCR5 or its co-receptor, CXCR4.

CD4 cells - White blood cells that assist in the body’s immune response through the creation of antibodies. HIV uses the CD4 structure on the cell surface, as well as the co-receptors CCR5 and CXCR4, to enter and infect cells.

Compound library – A collection of proprietary chemical compounds that a drug developer uses when looking for a drug to hit a particular target. Biotron has over 300 compounds in its library.

Coronavirus – A virus with a halo or crown-like appearance mainly known for infections of the upper respiratory tract. SARS is a coronavirus.

CXCR4 – A receptor on the surface of some immune system cells that HIV uses to enter the cell. Many ‘entry inhibitor’ drugs work by blocking CXCR4 or its co-receptor, CCR5.

Dengue virus – The virus that causes Dengue fever, a disease characterized not only by fever but also rashes, headaches and muscle pain. Biotron has demonstrated that its compounds are capable of blocking the M protein in

Dengue virus.

DNA - Short for deoxyribonucleic acid, a complicated molecule that houses the body's operating instructions. It is made up of a long, long string of base pairs twisted around in a helical shape. Every living being has DNA, none as complicated as the human being's.

E coli - A bacterium typically used in laboratory experiments because of its ability to rapidly multiply.

Entry inhibitor - Anti-HIV drugs that prevent the entry of virus into cells, generally by blocking the cell surface receptors CXCR4 and CCR5.

Enzyme - A protein that helps speed up in biochemical reactions in the body. Enzymes generally have the suffix 'ase' in their name. Reverse transcriptase is an enzyme, as is protease.

E Protein - A protein in the SARS virus which Biotron's compounds seem to be able to block.

FDA - The Food and Drug Administration, the American government body which regulates the pharmaceutical industry and from whom approval must be received before a drug can be marketed in the US.

Fusion inhibitor - A drug that can prevent HIV from fusing with its target cell. Fuzeon is a fusion inhibitor.

Gag - Short for 'Group Antigens', Gag is one of three major proteins encoded within the HIV genome and represents the core structure of the virus

Genotype - A distinct genetic subtype of an organism. There are six genotypes of the Hepatitis C Virus with genotype 1 having historically proven hard to treat.

GMP - Short for Good Manufacturing Practice, GMP is the set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals.

H5N1 - The strain of influenza virus commonly known as 'bird flu'. Biotron compounds have been shown to be active against this strain of virus.

H1N1 - The 'swine flu' strain which has generated a human pandemic in 2009.

HAART - Short for Highly Active Anti-Retroviral Therapy, HAART is the regimes of 'drug cocktails' that physicians use to treat HIV infection. HAART is generally one three or more antiretrovirals, one of which has to be a protease inhibitor, one an NNRTI and one an NRTI. Integrase and entry inhibitors are now being included in HAART as well. Biotron considers BIT225 to be a good candidate to fit into HAART.

Hepatitis C - A virus that infects liver cells. Biotron's compounds including BIT225 are capable of blocking the p7 protein in Hepatitis C.

HCV - Short for Hepatitis C.

High-throughput screening - Running multiple compounds from a compound library past a drug target in order to determine if any are able to hit the target.

HIV - The Human Immunodeficiency Virus, which ultimately causes AIDS. BIT225 is an anti-HIV drug.

HMA - Short for hexamethylene amiloride, HMA was Biotron's BIT009 proof-of-concept compound. HMA was superseded by BIT225 in 2005.

IND - Short for Investigational New Drug, an application filed with the FDA to conduct human trials of a new drug in the United States.

Inhibitor - An anti-viral drug that can inhibit a particular viral action, thereby

slowing or stopping the rate of infection.

Ions - Atoms or group of atoms with an electrical charge.

Ion Channel - A 'tunnel' in a cell's membranes through which ions - mainly sodium, potassium, calcium, and chloride - travel in and out. Biotron's BIT225 drug inhibits HIV's VPU ion channel activity.

Integrase - HIV enzyme that integrates the viral genetic material into human chromosomes.

Interferon - One of suite of drugs currently used in the treatment of Hepatitis C infection, in conjunction with ribavirin.

In vitro - Testing in the test tube.

In vivo - Testing in live organisms including animal models and humans.

Macrophages - White blood cells involved in the immune system's response to infection. Macrophages are not found in the bloodstream but at locations where body organs interface with the environment or the bloodstream. They are often the 'reservoir' that allows HIV to hide in the body. BIT225 can hit HIV that is in danger of 'hiding' in macrophages.

Mechanism of action - The way in which a drug achieves its therapeutic effect. The mechanism of action of Biotron's BIT225 anti-HIV drug is to inhibit VPU.

Monoclonal antibodies - Antibodies cloned from a particular cell-making antibody that is highly specific for a particular antigen.

M Protein - A protein in the Dengue virus which Biotron's compounds seem to be able to block.

Monocyte - The class of white blood cells that includes the macrophages. BIT225 appears to be able to hit HIV in monocyte-derived macrophages.

Monotherapy - A treatment regimen in which only a single drug is used.

NNRTI - See Non-nucleoside reverse transcriptase inhibitor.

Non-nucleoside reverse transcriptase inhibitors - Drugs that interfere with HIV's reverse transcriptase by preventing that enzyme from binding to the nucleic acid that is going to be copied by the enzyme. The first such drug, Nevirapine, came on the market in 1996.

Non-responders - Patients that fail to enjoy a clinical response to a particular drug.

NRTI - See nucleoside reverse transcriptase inhibitor.

NS3 - HCV's protease protein

NS5b - HCV's polymerase protein

Nucleoside reverse transcriptase inhibitor - A drug that interferes with HIV's reverse transcriptase through a process whereby a nucleoside analogue causes the copying process of stop short. AZT, the first drug specifically approved as an anti-HIV treatment (in 1987), is a nucleoside reverse transcriptase inhibitor. Avexa's AVX-754 drug is an NRTI.

Nucleoside - Nucleotides without the phosphate groups.

Nucleotides - Combination of sugar, phosphate and one of four 'bases' that make up DNA and RNA. Nucleotides are genetic 'letters' in what is a four-letter alphabet.

Pharmacokinetics - The study of the time course of a drug's absorption, distribution, metabolism, and excretion from the body.

Phase I/IIa – An early-stage safety study (a Phase I study) but one conducted in patients rather than in healthy volunteers.

Phase IIb – A clinical trial to test the efficacy of a drug in a small number of patients.

Phase III – A. clinical trial to test the efficacy of a drug in a large number of patients.

Pegylation – Conjugation of polyethylene glycol to a drug to slow its release into the body. Often pegylated interferon is used to treat Hepatitis C infection.

Polymerase – An enzyme which viruses use to copy their DNA or RNA. Many HCV drug candidates are polymerase inhibitors. As with NRTIs and NNRTIs in the HIV field, HCV polymerase inhibitors can be nucleoside or non-nucleoside.

Pre-clinical – The stage of a drug's development in which a candidate drug has been selected and it is being tested for its safety ahead of human trials.

Prodrug – A drug that is administered in an inactive form and then metabolised into an active drug. Prodrugs are useful in targeting therapies to the right place in the body.

Prophylactic vaccine – A vaccine used to prevent disease, rather than treat existing disease (which is a therapeutic vaccine).

Protease – An enzyme which viruses use in virus assembly.

Protease inhibitors – Drugs that inhibit viral replication by hitting the enzyme that completes assembly of the virus. The first anti-HIV protease inhibitor was Roche's Saquinavir, approved in 1995. Protease inhibition is also widely regarded as a viable anti-HCV drug strategy.

Proteins - A class of fairly common molecules in the living things that includes antibodies and enzymes. Protein-based drugs have a high molecular weight compared to small molecules.

p7 – A protein in Hepatitis C which BIT225 seems to be able to block. HCV p7 is known to form ion channels in cells that assist in viral budding and release.

Refractory – A disease that does not respond to therapy very well.

Retrovirus - A virus whose method of replication is the reverse of the usual method used. Generally viruses have DNA cores and replicate via RNA. Retroviruses, by contrast, consist of only a single strand of RNA coated with protein and replicate via reverse transcriptase. The HIV viruses are retroviruses.

Reverse transcriptase – An enzyme used by retroviruses in their replication process, allowing viral RNA to be converted to DNA. The NRTI and NNRTI anti-HIV drugs work by impacting on reverse transcriptase.

Ribavirin – An anti-viral drug currently used in conjunction with one of the interferons to treat Hepatitis C infection.

RNA – The body's 'photocopier', in that it copies each individual strand of DNA for use in code the DNA into proteins.

SARS – Short for Severe Acute Respiratory Syndrome, a potentially fatal lung disorder resulting from infection with the SARS virus. SARS was first identified during its sole outbreak to date, in 2003. Biotron's compounds are capable of blocking the E protein in the SARS virus.

Small molecules – Drugs that have a low molecular weight, making them easier to penetrate cell membranes and the blood-brain barrier. All of Biotron's compounds are small molecules. Protein drugs are not small molecules.

Supernatant - Material floating on the surface of a liquid mixture.

Therapeutic Index – In pharmacology, the ratio of effective dose to minimum tolerated dose. The higher this number, the better. Biotron believes that BIT225 has a good Therapeutic Index.

Therapeutic vaccine – A vaccine used to treat an existing disease, rather than prevent that disease (which is a prophylactic vaccine).

Treatment-naive – A patient whom has yet to be treated with drugs for a particular disease.

Toxicology – Tests to see if a drug is harmful in the body.

Virion – The name of Biotron’s ‘platform’ technology, involving the blockage of viral ion channels in cells.

Viral budding – The process by which a newly created virus ‘buds’ off from an infected cell. BIT225 works to inhibit viral budding.

Viral load – The measure of the amount number of viruses that an infected individual is carrying.

Viral reservoirs – Cells in the body in which a virus such as HIV is able to ‘hide’ for long periods of time, out of the reach of drug therapy. BIT225 seems to be able to go after viral reservoirs.

Virologic response – The extent to which an anti-viral therapy lowers levels of virus in the bloodstream of patients.

Virus – A strip of DNA or RNA surrounded by a protein coat that is capable of replication only within human or animal cells. HIV is a virus as are Hepatitis C, Dengue and SARS.

VPU – Short for ‘Viral Protein U’, a protein in HIV that forms ion channels in the membrane of the cell that the virus has infected, thereby facilitating viral budding. BIT225 is a VPU inhibitor.

Appendix VII – Biotron’s capital structure

Fully diluted, Biotron will have 350 million shares on issue. In December 2009 BIT announced a 1 for 1 new issue of listed options at 2 cent per option to raise \$2.3m with which to fund the HCV and HIV trials it intends to conduct during the course of 2010⁵⁹. The new options, exercisable at 10 cents, are ‘jumbo options’, in that:

- if exercised before 31/3/2010, each option yields another option exercisable at 20 cents by 30/3/2012. We assume that the 20 cent options will be listed as well;
- if not exercised before 31/3/2010, the options expire on 30/12/2011.

Figure 19 - BIT’s current capital structure

Shares (ASX Code BIT)	114,537,315	Price (c)	10
Unlisted options	235,774,630	Undiluted cap (\$m)	11.5
Total diluted shares	350,311,945	F.D. cap (\$m)	35.0

OPTIONS	Number	Exercise price	Expiry date	Cash	Note
Listed	114,537,315	\$0.10	31/03/2010	11,453,732	'Jumbo options' Assumes early exercise of 'jumbo options'
	114,537,315	\$0.20	30/03/2012	22,907,463	
Unlisted	5,450,000	\$0.35	30-Sep-10	1,907,500	
	750,000	\$0.40	30-Sep-10	300,000	
	500,000	\$0.45	30-Sep-10	225,000	
Total listed and unlisted	235,774,630	\$0.010	22-Feb-03	36,793,695	

SOURCE: BIT. NOTE: THE JUMBO OPTIONS - IF NOT EXERCISED EARLY (IE BY 31/3/2010) ARE EXERCISABLE BY 31/01/2011 AND DO NOT YIELD THE 20 CENT MARCH 2012 OPTIONS LINE

Figure 20 - BIT’s share capital raising history

Date	Shares (million)	% of current shares on issue	Price	Amount raised (\$m)	Note
Jan-01	24.0	21.0%	\$0.50	12.0	IPO
Dec-04	5.7	5.0%	\$0.21	1.2	Share Purchase Plan
Mar-06	19.9	17.4%	\$0.23	4.6	2 for 7 rights
Dec-07	14.7	12.8%	\$0.17	2.5	Placement / Share Purchase Plan
Apr-09	10.1	8.8%	\$0.08	0.8	Placement / Share Purchase Plan
Total	74.5	65.0%	\$0.28	21.1	

SOURCE: BIT

Major shareholders. Currently the only substantial shareholders in the company are Professor Dulhunty with 8.7% and Peter Scott with 7.9%. Scott, a Biotron director, has had an entrepreneurial career centred on audio-visual technologies.

⁵⁹ This issue is partly underwritten by Bell Potter Securities, which is a related entity of Southern Cross Equities.

Recommendation structure

Spec Buy: Expect >30% total return on a 12 month view but carries significantly higher risk than its sector

Buy: Expect >15% total return on a 12 month view

Accumulate: Expect total return between 0% and +15% on a 12 month view

Reduce: Expect -15% and 0% total return on a 12 month view

Sell: Expect <-15% total return on a 12 month view

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Southern Cross Equities Ltd and its associates hold 790,545 shares in BIT as at the date of this report. This position is subject to change without notice.

Southern Cross Equities earned a 5% fee from underwriting a 2 for 7 rights issue for Biotron at 23 cents in March 2006. At that time Southern Cross was also granted 2.0 million Biotron options exercisable at 35 cents by September 2010. Southern Cross will earn a fee of 2 million 10 cent jumbo options for preparing this report.



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