

30 September 2009

Prana Biotechnology (PBT)

Unforgettable opportunity

Analyst

Stuart Roberts 612 8224 2871

Authorisation

Jonathan Snape 613 9235 1601

Recommendation

Spec Buy

Price

\$0.23

Target (12 months)

\$1.10

Prana Biotechnology (PBT) is developing the Alzheimer's drug PBT2, which did well in a Phase IIa trial. We expect a strong Phase IIb result in late 2011 to generate a valuable licensing deal. We like PBT's science, its drug pipeline and its commercially-oriented management team. We are initiating coverage with a target price of \$1.10 per share based primarily on our valuation of PBT2 but also PBT's pipeline.

Expected Return

Capital growth	378%
Dividend yield	0%
Total expected return	378%

Company Data & Ratios

Enterprise value	\$43m
Market cap	\$54m
Issued capital	232.9m
Free float	100%
12 month price range	\$0.125-\$0.50

GICS sector

Healthcare Equipment and Services

Absolute Price



SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Alzheimer's is a significant opportunity

Prana Biotechnology (PBT) is an early stage company developing the Alzheimer's drug PBT2. This compound performed well in a Phase IIa clinical trial completed in early 2008. We regard PBT2 as valuable because of a strong demand for new Alzheimer's compounds by Big Pharma, seeking to address a market where existing drugs are not very effective but still sell around US\$6bn worth of product.

PBT2 has performed well in the clinic

In PBT2's Phase IIa trial the drug was able to improve Executive Function in the treated patients, based on elements of the so-called Neuropsychological Test Battery used to assess the mental state of Alzheimer's patients. We think this suggests the potential for PBT2 to ultimately be a commercial success. We see a Phase IIb trial of PBT2 due for completion in late 2011 as the likely catalyst to unlock a significant partnering deal with Big Pharma that would yield strong commercial value to PBT.

PBT is a well managed company

We have a high regard for PBT's management led by CEO Geoffrey Kempler. We like the science that Kempler and his colleagues have helped foster, the pipeline of compounds that have been built around that science, and the commercial approach that the company has taken towards realising value from it.

Target price \$1.10 per share

We assume both PBT2 and the PBT pipeline has value. Our \$1.10 target price for PBT is at the midpoint of our base case \$0.83 / optimistic case \$1.47 per share probability-weighted DCF valuation range. We assume that PBT can be re-rated by the market as the quality of the PBT2 work and the PBT science comes to be more appreciated by the market.

Contents

Eight reasons to own PBT	3
Valuing PBT and realising that value	4
The market for Alzheimer's drugs is strong	6
Why we think PBT2 will be successful	9
PBT's solid pipeline	16
Strong leadership	18
The risks	19
Appendix I - A PBT glossary	20
Appendix II - PBT's capital structure.....	23

Prana Biotechnology - Unforgettable opportunity

COMPANY DESCRIPTION

The Melbourne-based Prana Biotechnology (PBT) is an early stage drug development company focused on PBT2 for the treatment of Alzheimer's disease. This drug candidate worked well in a Phase IIa clinical trial completed in early 2008. PBT is preparing to take the drug into a Phase IIb trial expected to complete in late 2011. We expect that success in this Phase can lead to a valuable licensing deal for the drug with a Big Pharma (ie large pharmaceutical company) partner. PBT was built on science that elucidated the role of metals in loss of brain function. Over the last nine years that science has helped build a large compound library that PBT has used to develop a pipeline of drug candidates to treat not only Alzheimer's but also Parkinson's and Huntington's disease and brain cancer.

INVESTMENT STRATEGY

We see a payoff to shareholders in PBT arising from a partnering deal for PBT2 with Big Pharma once PBT2 completes a Phase IIb clinical trial due for commencement in late 2009 or early 2010. Given the strong demand by Big Pharma for Alzheimer's drug candidates the up-front and milestone payments associated with a partnering deal could reasonably be in the hundreds of millions of US dollars, even before a double digit royalty on sales. We expect PBT2 can complete Phase IIb by late 2011.

VALUATION

We assume both PBT2 and the PBT pipeline has value. Our \$1.10 target price for PBT is at the midpoint of our base case \$0.83 / optimistic case \$1.47 per share probability-weighted DCF valuation range. We assume that PBT can be re-rated by the market as the quality of the PBT2 work and the PBT science comes to be more appreciated by the scientific and pharmaceutical communities.

RISKS

We see the main risk in PBT as being clinical risk - ie that PBT2 fails to perform well in its Phase IIb trial. Another major risk facing the company is that its preferred Big Pharma partner may drive too hard a bargain for PBT shareholders to enjoy a strong return. A third significant risk is burn rate. At present PBT has around \$10m cash and has burned around \$600,000 per month since 2000. It will likely have to make further capital raisings to fund this burn rate as well as the Phase IIb trial of PBT2. We expand on these risks on page 19 of this report.

Eight reasons to own PBT

- 1 Alzheimer's is a large market of unmet medical need.** It is estimated that around one in eight people over the age of 65 has Alzheimer's disease. Existing drugs to treat Alzheimer's are poor at improving cognition beyond about a year but still sell around US\$6bn worth of product annually. Consequently Big Pharma has strong licensing demand for new compounds like PBT2 that have shown promise in the clinic against Alzheimer's.
- 2 The science behind PBT2 is solid.** In a series of peer-reviewed papers over the last decade scientists associated with PBT have demonstrated that Alzheimer's can be treated by preventing metals in the brain from causing the amyloid plaques and associated neurotoxicity characteristic of the disease. This science has allowed PBT to create the PBT2 compound as well as other drugs in the PBT pipeline.
- 3 PBT2 has worked well in the clinic.** In its Phase IIa clinical trial, conducted in 2006 and 2007 with results in early 2008, PBT2 demonstrated that it was able to modify the course of Alzheimer's disease by 1) reducing the patient's levels of amyloid beta, a protein understood to be a significant factor in Alzheimer's and 2) improving Executive Function in those patients, as measured by elements of the so-called Neuropsychological Test Battery commonly used to assess the mental state of Alzheimer's patients.
- 4 The upside for PBT2 is significant.** Given the abovementioned demand by Big Pharma for an Alzheimer's compound we expect any licensing deal for PBT2 after a Phase IIb trial from late 2011 onwards would be lucrative, with the Medivation/Pfizer partnering deal of 2008 a good guide to the potential outcome.
- 5 PBT is a well managed company.** We have a high regard for PBT's management led by CEO Geoffrey Kempler. We like the science that Kempler and his colleagues have helped foster, the pipeline of compounds that have been built around that science, and the commercial approach that the company has taken towards realising value from it.
- 6 PBT has developed a valuable pipeline.** Using its solid scientific base PBT has developed drugs for the treatment of Parkinson's disease as well as brain cancer which are now at the pre-clinical phase of development. Meanwhile PBT2 has also shown promise in the treatment of Huntington's disease. Early *in vitro* and *in vivo* success allows us to be optimistic about the pipeline's prospects.
- 7 PBT's news flow is fairly strong.** While the end of the PBT2 Phase IIb trial is two years away, PBT's capacity to generate progress with its technology and pipeline on a regular basis makes for a news flow favourable for sentiment. We estimate that in the twelve months to September 2009 PBT made around eight significant announcements to the market related to developments that enhanced the value of its intellectual property.
- 8 Our target price for PBT is \$1.10 per share,** which is significantly above the share price and reflects the high potential payoff from clinical success. We assume both PBT2 and the PBT pipeline has value. Our \$1.10 target price for PBT is at the midpoint of our base case \$0.83 / optimistic case \$1.47 per share probability-weighted DCF valuation range. We assume that PBT can be re-rated by the market as the quality of the PBT2 work and the PBT science comes to be more appreciated by the scientific and pharmaceutical communities.

Valuing PBT and realising that value

We value PBT at \$0.83 per share base case and \$1.47 per share optimistic case

Our valuation of PBT

We value PBT on a lead-product basis. To attempt a valuation of PBT we took PBT2 plus a notional pipeline of three earlier stage products – an Alzheimer’s vaccine, a Parkinson’s drug and a brain cancer drug. We assumed that PBT2 is outlicensed after completing Phase IIb in 2012, while we assumed that the other drugs are outlicensed prior to being taken by others into Phase I. 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 an 0.87 AUD/USD exchange rate. And we also assumed a 35% chance of success from Phase I to regulatory approval for PBT2 and a 4% chance of success for the other three pipeline elements. The various valuation parameters are laid out in the table below.

We assume a further \$20m capital raising. With the forthcoming PBT2 trial expected to cost \$20m we assume that this is fully funded via a further equity raising at 19 cents per share that increases the fully diluted shares on issue to 373 million. We further assume that a partnering deal for PBT-2 after late 2011 can provide further funding after this point.

Target price \$1.10. Our individual programme valuations plus our assumption of increased dilution resulted in our valuing PBT at base case \$0.83 per share and optimistic case \$1.47 per share. Our 12-month target price sits at the midpoint of this range.

Figure 1 – Key parameters for valuing PBT’s products

Product	Sales at maximum growth rate base (USDm)	Sales at maximum growth rate optimistic (USDm)	PBT remaining expenditure base (USDm)	PBT remaining expenditure optimistic (USDm)	Royalty base	Royalty optimistic	Start of Phase I	Upfronts and milestones base (USDm)	Upfronts and milestones optimistic (USDm)
PBT-2	1500	2000	15	20	10%	15%	2005	200	300
Alzheimer's vaccine	750	1200	6	7	4%	6%	2012	50	100
Parkinson's drug	1200	1500	6	7	5%	7%	2012	75	150
Brain cancer drug	1000	2000	6	7	6%	8%	2013	60	100

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

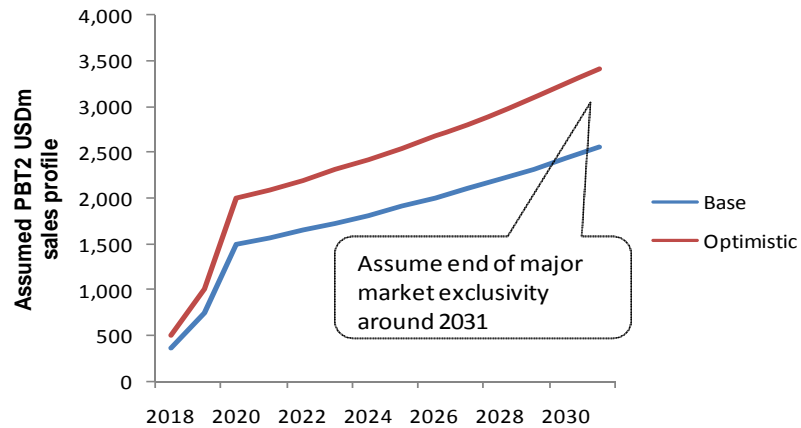
Figure 2 - Our valuation of PBT

	Base case	Optimistic case
PBT2 (A\$m)	226.3	424.2
PBT pipeline (A\$m)	44.1	88.7
Cash on hand at Sept 09 plus \$20m raise (A\$m)	30.3	30.3
Cash from options (A\$m)	13.2	13.2
Total diluted value (\$m)	313.9	556.3
Total diluted shares	377.3	377.3
Value per diluted share	\$0.83	\$1.47
Valuation midpoint	\$1.15	
Share price now	\$0.23	
Premium / Discount to share price	401.4%	

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Strong potential upside. We regard the current (ie 29 September) market capitalisation of Medivation on Nasdaq of US\$928m as indicative of the potential upside from PBT2 once PBT begins to gain in sentiment terms.

Figure 3 - Assumed sales profile for PBT2



SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

PBT benefits from being an Alzheimer’s ‘pure play’

The Path to \$1.10 per share

We see a number of catalysts emerging to drive a re-rating of PBT stock over the next 12 months:

- 1) **Increased interest in Alzheimer’s.** With public awareness of Alzheimer’s growing¹, PBT is likely to benefit as the world’s only ‘pure play’ when investors are looking to capitalise on the rise in disease incidence.
- 2) **Commencement of the Phase IIb trial.** We expect that PBT will dose the first patient in the Phase IIb trial by early in 2010. We see the publicity this trial is likely to garner as attracting new investor interest in the stock.
- 3) **Scientific validation of PBT’s scientific approach.** The publication of papers related to the relationship between metals and proteins in Alzheimer’s has been increasing in recent years, and we expect that some of these papers may contribute to an improvement in PBT’s standing in the Alzheimer’s field.
- 4) **Progress with PBT-proprietary drugs.** We expect any favourable developments with PBT’s pipeline to help focus investor interest on the potential of PBT2.

¹ For an example of this growing awareness, consider the 23/9/2009 address at the National Press Club in Canberra entitled *Dementia: Facing the Epidemic* by Professor Constantine Lyketsos, an authority on Alzheimer’s at Johns Hopkins University.

The market for Alzheimer’s drugs is strong

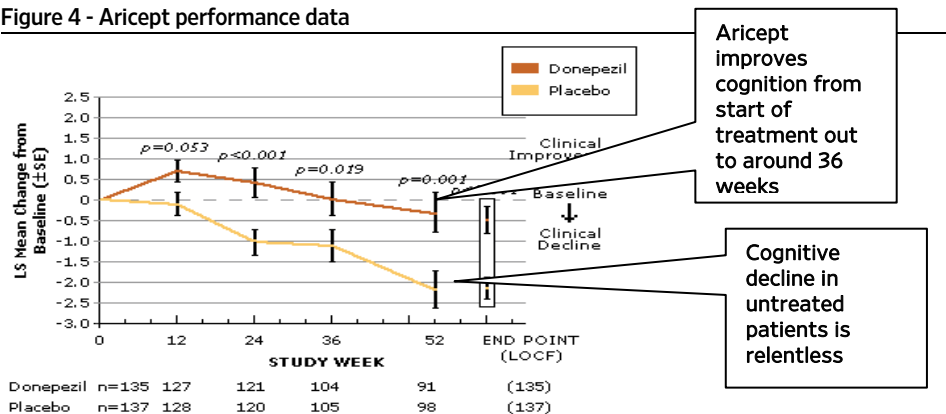
With Alzheimer’s disease rapidly becoming a serious healthcare issue in the Western world due to the aging of the population, the potential market for PBT2 is large and growing.

Four reasons why Big Pharma wants more Alzheimer’s drugs

- 1) **Patient numbers are large.** It is estimated that around one in eight people over the age of 65 in the United States have Alzheimer’s disease, making for 5 million patients in that country alone². Around the world the patient population may be 36 million once other forms of dementia are included³.
- 2) **The cost of care is expensive.** In the US alone the cost of care for Alzheimer’s patients is estimated to be US\$148bn, since it largely involves high-intensity personal care in a home or institutional setting rather than drugs or physician visits.
- 3) **Existing drugs are inadequate.** A problem with existing drugs to treat Alzheimer’s is that, while they’re better than nothing, they do not appear able for most patients to prevent declines in cognition beyond about 9-12 months. The typical profile of such a drug is Pfizer’s Aricept, where cognition returns to baseline at around the 36 week mark. The drugs also come with various side effects⁴.
- 4) **Alzheimer’s is a huge drug market even without cognition stabilisation.** The inadequacy of existing drugs hasn’t prevented Alzheimer’s establishing itself as a >US\$5bn drug market. This is not only because the patient community is large but because the drugs are still cost-effective for Western world healthcare systems given the high cost of care related to Alzheimer’s. In effect the drugs pay for themselves by allowing a lower level of nursing care for a while, as well as less use of hospital beds and other parts of the medical system. For example, a 2005 study of Aricept found that treated patients cost one particular HMO US\$2,500 less over a twelve month period after costs of the drug were factored in, compared to the controls⁵.

Most Alzheimer’s drugs can only improve cognition for around one year

Figure 4 - Aricept performance data



SOURCE: NEUROLOGY. 2001 AUG 14;57(3):489-95. NOTE: THE CHART SHOWS LEAST-SQUARES MEAN CHANGE FROM BASELINE IN MINI MENTAL STATE EXAMINATION SCORE FOR PATIENTS TREATED WITH DONEPEZIL OR WITH PLACEBO.

² US figures come from The Alzheimer’s Association, *2009 Alzheimer’s Disease Facts and Figures*.

³ Source: Alzheimer’s Disease International, *World Alzheimer’s Report 2009*.

⁴ Such as nausea, diarrhoea, vomiting, indigestion, abdominal pain, loss of appetite and weight loss.

⁵ Am J Geriatr Pharmacother. 2005 Jun;3(2):92-102.

Figure 5 - Sales of existing Alzheimer's drugs

Drug	Maker	USDm global sales (08/09)	Generic name	Drug goes off US patent
Aricept	Pfizer	3,021	donepezil	2010
Namenda / Ebixa ⁶	Forest / H. Lundbeck	1,319	memantine	2015
Exelon	Novartis	815	rivastigmine	2014
Razadyne	J&J	541	galantamine	2008
Total		5,696		

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

A thinning out of the Alzheimer's drug field has improved PBT2's chances

PBT can look forward to an attractive licensing climate

Available drug candidates are scarce. As a result of the abovementioned factors Big Pharma has been highly interested since the 1990s in new Alzheimer's drugs to add to their pipelines via partnering deals. However, in recent years there has been a thinning out in the Alzheimer's development field, with various clinical failures leaving only a handful of late stage drug candidates still standing. Another effect of these failures appears to have been the deterrence of earlier stage development by companies at a similar stage of maturity to PBT, with only a few having done serious Phase II work lately. All of this is good for PBT in that it raises the price for clinical candidates with good performance data, which we argue PBT2 has generated.

Figure 6 - Recent Alzheimer's clinical failures

Company	Drug	Mechanism of action	Date
Forest Laboratories	Neramexane	NDMA-receptor antagonist	Sep-04
Axonix	Phenserine	Acetylcholinesterase inhibitor	Mar-05
Neurochem	Alzhemed	Glycosaminoglycan inhibitor	Aug-07
Myriad Genetics	Flurizan	Secretase inhibitor	Jun-08

SOURCE: SOUTHERN CROSS EQUITIES

Figure 7 - Current late stage Alzheimer's candidates

Company	Drug	Mechanism of action
Baxter	IVIG	Auto-antibodies' to amyloid beta? ⁷
Elan / Wyeth	Bapineuzumab	Antibodies to amyloid beta
Medivation / Pfizer	Dimebon	Improving mitochondria function
Eli Lilly	Semagacestat	Secretase inhibitor
Eli Lilly	Solanezumab	Antibodies to amyloid beta

SOURCE: SOUTHERN CROSS EQUITIES

Figure 8 - Companies that have done Phase II work on Alzheimer's in recent years

Company	Location	Code	Drug	Mechanism of action
Allon Therapeutics	Vancouver	TSX: NPC	Davunetide	Microtubular network strengthening
Cortex Pharmaceuticals	Irvine, Ca	AMEX: COR	CX717	Glutamate receptor potentiation
Transition Therapeutics	Toronto	Nasdaq: TTHI	AZD-103	Defibrilisation of amyloid beta

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Licensing deals for Alzheimer's involve large numbers. Consider four recent examples:

⁶ Namenda is memantine's brand name in the US while Ebixa is used in Europe. Forest is a US specialty pharma company (www.frx.com) while Lundbeck is a Danish company specialising in CNS drugs (www.lundbeck.com).

⁷ IVIG's exact mechanism of action is unclear at this stage.

Medivation's licensing to Pfizer in 2008 indicates the huge potential upside to PBT from PBT2

Medivation⁸. In September 2008 Pfizer partnered with this company to get hold of an old Russian antihistamine called Dimebon, which had performed well in Alzheimer's patients in a Phase IIb trial in 183 Russian patients. The performance data for this drug was particularly strong, with a 9.7 point drug-placebo difference in ADAS-cog in moderately affected patients after 12 months of treatment ($p < 0.0001$)⁹, although this was achieved using controls who were not being treated with any other standard Alzheimer's drug. The Pfizer deal was lucrative nonetheless, with US\$225m in an upfront payment followed by US\$500m in milestone payments. Pfizer and Medivation will share development costs 60/40, but Medivation will then receive a 40% royalty on US sales of the drug.

Elan¹⁰. In July 2009 Johnson & Johnson unveiled a deal which would see it sink US\$1bn into this Irish biotech company, in a deal that will see J&J take 18% of Elan. In addition, for a further US\$500m, J&J gains 49.9% of all Elan's Alzheimer's pipeline including bapineuzumab, an antibody-based Alzheimer's drug now in Phase III¹¹. This deal is all the more interesting because of the controversial nature of bapineuzumab:

- In 18-month Phase II results released in July 2008 the drug didn't seem to work overall, but it did work in the one-third of Alzheimer's patients who didn't have a gene mutation called APOE4 – here the ADAS-cog improvement was a creditable 5 points ($p = 0.026$ – controls were on existing Alzheimer's drugs) over placebo. This is the group that Elan and its partner Wyeth (soon to be acquired by Pfizer) are focusing on in Phase III;
- bapineuzumab had a problem in that the highest dose of the drug had caused some brain swelling, leading Elan and Wyeth to drop that dose in its trial protocols from April 2009.

What the J&J/Elan deal suggests is that even drugs that don't work for all Alzheimer's patients can attract strong valuations so long as the Phase II data is good for the relevant target market.

Vitae Pharmaceuticals¹². In June 2009 this unlisted American company partnered with the German drug company Boehringer Ingelheim on some early stage technology in a deal potentially worth US\$250m.

Comentis¹³. In April 2009 this company persuaded the Japanese drug company Astellas to pay US\$80m and agree to milestone payments of US\$660m related to some very early stage Alzheimer's drug candidates. Astellas also made an equity investment in Comentis of US\$20m.

What the above four deals indicate is that Alzheimer's drug candidates at all stages of development are of interest to Big Pharma, while clinical data in particular can generate outstanding commercial returns for their developers prior to Phase III. Consequently we're confident that PBT will ultimately generate a large licensing deal, potentially on the scale of Medivation, should Phase IIb for PBT2 work out as planned.

⁸ Nasdaq: MDVN. San Francisco, Ca. www.medivation.com.

⁹ See Medivation release, 30/7/2008.

¹⁰ NYSE: ELN. Dublin, Ireland. www.elan.com.

¹¹ The pipeline also includes a subcutaneous formulation of bapineuzumab, administered once a week, which is now in Phase II, as well as ACC-001, a vaccine for Alzheimer's disease.

¹² Philadelphia, Pa. www.vitaepharma.com

¹³ San Francisco, Ca. www.comentis.com

Why we think PBT2 will be successful

We see five reasons why PBT2 will be a successful drug candidate in terms of its future performance in the clinic.

1. The peer-reviewed science behind the PBT2 concept is of long standing and has been growing;
2. The proof of concept trial that preceded PBT2, which involved an earlier compound called PBT1, demonstrated the validity of the science in a clinical sense;
3. PBT2's performance in Phase IIa demonstrated improvements in 'Executive Function' in Alzheimer's patients;
4. PBT2's trial in Phase IIb is powered to succeed across a range of cognition and Executive Function measures;
5. PBT have continued to gather pre-clinical data on PBT2's effectiveness since the Phase IIa work.

The science behind PBT2 has been growing for years

PBT2 potentially attacks the metals which causes amyloid plaques. The principle pathology of Alzheimer's is the presence in the brain of 'plaques' of a starch-like protein called amyloid beta. PBT2 is based on a scientific concept, first enunciated in the mid-1990s by Professors Ashley Bush, Rudy Tanzi and Colin Masters, that Alzheimer's disease is a function of neurotoxicity associated with the interaction of metals and amyloid beta that causes the amyloid plaques to form. The thinking goes roughly as follows:

- Free-radical copper and zinc ions agglomerate with amyloid beta to cause the plaques;
- Those plaques generate chemicals which result in brain cell death and impaired brain cell connections, which in turn manifests itself in impaired brain function;
- Alzheimer's is therefore treatable by preventing the metals from wreaking this havoc by redistributing them within the central nervous system to places of need, using drugs that have an affinity to the metals. We call this concept the 'MPAC approach', MPAC standing for 'Metal-Protein Attenuating Compound', since the drug merely attenuates the interaction between the metal ions and amyloid beta to detoxify it, rather than removing the amyloid from the body as some competing treatment approaches attempt to do.

The MPAC approach that allowed the creation of PBT2 is backed by a large body of published work. The above concept has been developed by Bush and his collaborators, as well as other scientific workers, in a series of groundbreaking peer-reviewed papers. PBT's own web site lists around fifty that have been published since 1998. However in terms of establishing the basic PBT science before it was taken to the clinic, we think three papers in particular have been important.

- **Science, 1994:** Here Bush et. al. demonstrated that zinc could cause soluble amyloid beta (the kind that easily removed itself from the brain) to turn into an insoluble form of amyloid beta that then aggregated into amyloid plaques.¹⁴

PBT scientists have published intensively on their work

¹⁴ See Bush et. al., *Rapid induction of Alzheimer Aβ amyloid formation by zinc*, *Science*. 1994; 265, 1464-1467.

- **Biochemistry, 1999:** This paper demonstrated that positively charged iron and copper ions, when interacting with amyloid beta, caused the protein to become a catalyst for the production of hydrogen peroxide¹⁵, which proved to be poisonous to brain cells¹⁶.
- **Neuron, 2001.** When clioquinol, an old anti-amoebic drug whose chemistry was known to be able to bind to copper and zinc, was tested in transgenic mouse models of Alzheimer's disease, the result was a marked reduction in 'Alzheimer brain pathology within nine weeks', with amyloid accumulation 50% lower than that of controls¹⁷.

PBT2's origins are in the 'amyloid hypothesis', but not of the amyloid hypothesis. From the 1980s through to around the present the dominant paradigm in Alzheimer's research was the so-called 'amyloid hypothesis', which holds that amyloid beta is solely responsible for Alzheimer's and that Alzheimer's is potentially treatable by drugs that break up amyloid the plaques and remove the protein from the body. In more recent years the amyloid hypothesis has been challenged, with various studies suggesting that the insoluble plaques are merely a symptom of Alzheimer's and that only soluble oligomeric forms of the protein are toxic or that other proteins such as Tau are the real culprit. Probably the best evidence to date of the amyloid hypothesis's weakness has been data from the abovementioned Medivation drug Dimebon, where the drug markedly improved cognition in treated patients while increasing levels of amyloid beta in animal experiments. We think PBT2 fits well in the 'post amyloid hypothesis' world, since it is able to treat the conditions under which plaques and oligomers form, without seeking to remove amyloid protein from the body.

The 'PBT1' proof of concept trial was successful

PBT1 generated strong lifts in cognition in the treated patients

PBT1 proved that the MPAC approach was a valid one. Following on from the work that led to the abovementioned *Neuron* paper, PBT tested the MPAC approach in a 36-patient double-blind, placebo-controlled clinical trial in moderate-to-severe Alzheimer's patients in 2000 and 2001. PBT used clioquinol, which it renamed PBT1, as the proof-of-concept compound, fully expecting that were the clinical trial successful, the company would develop its own proprietary compounds based on PBT1 but with improved pharmaceutical properties. Success with this trial was announced in April 2002 and the arising peer-reviewed paper was published in December 2003¹⁸. There were four noteworthy aspects to this trial;

1. **A marked improvement in cognition in the treated patients.** By week 36 of the trial the average treated patient had registered a 7 point improvement in a common test of cognition called 'ADAS-cog' whereas with the placebo group the improvement was only 4, meaning significant outperformance by PBT1¹⁹. While this difference was not statistically significant due to small sample size ($p=0.08$), the result was important because a 3 point difference between drug and placebo was enough to get FDA approval for Aricept in

¹⁵ Chemical symbol H_2O_2 - it's one of the active ingredients in bleaches for the alteration of hair colour.

¹⁶ See Huang et. al. *The A β Peptide of Alzheimer's Disease Directly Produces Hydrogen Peroxide Through Metal Ion Reduction*. *Biochemistry* 1999; 38, 7609-7616.

¹⁷ See Cherny et. al. *Treatment with a Copper-Zinc Chelator Markedly and Rapidly Inhibits β -Amyloid Accumulation in Alzheimer's Disease Transgenic Mice*. *Neuron* 2001;30:665-676.

¹⁸ See Ritchie et. al. *Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting A β amyloid deposition and toxicity in Alzheimer's Disease*, *Archives of Neurology (Arch Neurol)*. 2003;60:1685-1691.

¹⁹ Short for 'Alzheimer's Disease Assessment Scale - Cognitive Subscale', ADAS-Cog test is a battery of individual tests of such abilities as word recall and recall of test instructions etc. The ADAS cog score range is from 0 to 70 - the higher the score, the greater the cognitive impairment.

1996, and that drug has since gone to blockbuster status in spite of the relatively narrow period of efficacy²⁰ we noted above.

2. **Strong cognition jumps in severely affected patients.** For severely affected Alzheimer's patients the ADAS-Cog improvement with PBT1 was a massive 6 points, with a p-value of 0.016, suggesting that the drug was particularly powerful in that sub-group.
3. **The mechanism of action worked.** With amyloid beta levels in the blood plasma falling, pointing to elimination of plaques, it was reasonable to suggest that the MPAC approach to disease treatment was working. This allowed PBT to suggest that PBT1 was 'disease modifying' in terms of tackling an underlying cause of the Alzheimer's rather than simply improving cognition ability.
4. **The outperformance of PBT1 continued well beyond one year.** An open-label extension study beyond the original 36 week trial period studied patients out to week 84, with results announced by PBT in October 2004. By this stage the notional ADAS-cog gap between treated and untreated had widened to 10 points, so that while the treated patients were still declining cognitively, PBT1 appeared to have cut the expected rate of disease progression in half.

PBT1's performance was long-lasting

PBT2 was based on PBT1, but is much better. With data from the PBT1 trial PBT was able to proceed with its own drug design programme aimed at coming up with a proprietary, patent protected compound²¹ based on the chemical properties of PBT1 but significantly improved²². The result by 2003 was a large library of proprietary MPACs, of which the best candidate, PBT2, entered the clinic in early 2005²³. This drug generated favourable Phase IIa data in early 2008²⁴ which was subsequently published in *The Lancet Neurology* in July 2008²⁵.

The Phase IIa trial of PBT2 was also successful

PBT2 passed the test. PBT2's Phase IIa trial was a success, in our view, because the drug outperformed placebo, with statistical significance, in a couple of neuropsychological tests administered to the patients during the course of their treatment, meaning that overall Executive Function - which as we'll see is an important emerging concept in Alzheimer's therapy - was significantly improved. We think that this outperformance, when combined with the drug's favourable safety profile²⁶ and demonstrated mechanism of action²⁷, makes PBT2 a licensable product.

Phase IIa was a tough test to pass. So the drug worked. However, as we explain below, the overall trial data at first glance seems ambiguous. Consequently since early 2009 PBT has come to the view that before a licensing

²⁰ When Aricept was trialed in a 30-week study in 473 patients, the patients on the drug were '2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively' better off than the placebo group.

²¹ Patent grants for '*8-Hydroxyquinoline derivatives*'; the key composition of matter patent related to PBT2, was announced by PBT for both Europe and the US in August 2009.

²² Studies both *in vitro* and *in vivo* have shown PBT2 to be better than PBT1. Probably the most important measures are 'brain amyloid solubility', which shows PBT2 to be 5 times better at reducing the levels of soluble amyloid plaques in the brain over a 24-hour period. It also performed well on 'inhibition of peroxide', where PBT2 is 1.6 times better at holding back H₂O₂ production than its predecessor compound.

²³ PBT had initially anticipated conducting a pivotal trial of PBT1 in order to gain an Alzheimer's indication for this compound, and announced moves to that end in October 2004 however these were scrapped in April 2005 after it was found that it was difficult to remove di-iodo impurities from the manufacturing process.

²⁴ Randomised, placebo controlled, n=78.

²⁵ See *Lancet Neurol.* 2008 Sep;7(9):779-86. Epub 2008 Jul 30.

²⁶ Consider, for example, that bapineuzumab has registered oedema and haemorrhaging issues.

²⁷ The mechanism of action first demonstrated with PBT1 was successfully demonstrated again in the PBT2 trial.

of PBT2 can take place a Phase IIb trial is necessary to gather the data that was lacking in the IIa work. To understand the issues involved, it's important to keep two factors in mind:

- 1) **The patient group in this trial was more challenging** – PBT1 was trialled in moderate-to-severe Alzheimer's patients, whereas PBT-2 was tested only in mild patients²⁸ where short term memory isn't as badly affected, so improvement is more difficult to measure. This raised the performance bar for PBT2²⁹.
- 2) **The trial ran for only twelve weeks**, which was significantly shorter than the 36 weeks over which PBT1 data was gathered³⁰. Since loss of mental function in Alzheimer's patients tends to accelerate over time, there wasn't as much time for PBT2 to gain ground on placebo as was the case with PBT1.

Basically the main issue that PBT faces coming out of the Phase IIa is that the trial was designed to track changes in the levels of amyloid protein in the cerebrospinal fluid and was not designed or powered sufficiently in this mild patient group to assess cognitive improvement. Although the drug performed surprisingly well in elements of a testing mechanism known as NTB that is used to assess the mental state of Alzheimer's patients, there were insufficient patients to assess if the drug could perform well in overall measures of NTB and in ADAS-cog terms.

PBT used two tests to evaluate the effectiveness of PBT2. Over the years neurologists have developed a number of tests of mental function in order to evaluate whether a patient has Alzheimer's and how severe the disease has become. These tests include ADAS-Cog as well as others such as MMSE, CDR-SB and the abovementioned NTB. In trialling PBT-2, PBT used NTB as well as ADAS-cog for three reasons:

- **ADAS-Cog is considered the 'gold standard'** in terms of measuring 'cognition', a term which covers multiple aspects of mental function such as a memory, language, praxis³¹, orientation³² and so on. It's been around a long time, having first been published in 1984. It was used to achieve marketing approval for all symptomatic drugs such as Aricept. And because of its widespread use in the Alzheimer's field today the ADAS-Cog measure remains the common primary endpoint in terms of determining clinical efficacy of new Alzheimer's drugs.
- **NTB is important because of what ADAS-cog doesn't measure.** Short for Neuropsychological Test Battery, NTB was developed in order to address what was considered a shortcoming of ADAS-Cog – that there was no measure of 'Executive Function', that is, a patient's skill with attention, concentration, planning, and working memory. Basically Executive Function is the brain's ability to organise itself to get things done. A person with poor memory but good Executive Function might forget what day it is but be able to perform everyday tasks like dressing and feeding himself, which would reduce the level of care required for that person. Consequently most

PBT2 works well in boosting Executive Function

²⁸ Alzheimer's patients are typically segmented by the Mini-Mental State Examination, where a patient is given a score out of 30, with the lower numbers representing greater levels of cognitive impairment. PBT considers an MMSE score between 27 and 30 to represent a person without cognitive impairment, 20-26 represents "mild" impairment, 10-19 = "moderate" and 0-9 = "severe". In PBT2's Phase IIa trial the patient's MMSE average was 23. Mildly-affected patients are where most investment in Alzheimer's drugs is expected to be directed in the future as diagnosis capabilities improve.

²⁹ Consider, for example, Medivation's experience with Dimebon at six months - Dimebon's overall ADAS-cog lift at this point was 4 points, but for mild patients it was only 2.4 points whereas for moderate patients it was 5.8 points.

³⁰ 36 weeks was the period in which PBT1 was placebo-controlled. The 84 week extension study to which we referred above as generating a hypothetical 10 point difference was using historical rates of decline for the placebo group.

³¹ Praxis is the process of getting an idea and initiating and completing a new motor task.

³² Not sexual orientation, but rather a patient's 'situational awareness' - such as their name and home city or what time of day it is.

Regulators like the test where PBT2 performed well

observers of Alzheimer’s agree that a drug that boosts or maintains Executive Function has significant value as a therapy and is more likely than other drugs to keep a patient out of hospital. In addition NTB is understood to be more reliable in assessing mild Alzheimer’s³³ and ADAS-cog less so.

- **Regulatory agencies are open-minded about what test is appropriate.** The FDA and other regulators have indicated to drug developers that they’re comfortable with measures of clinical efficacy other than ADAS-Cog. In particular Europe’s drug regulator, the EMEA, indicated in 2007 that it regarded NTB as a validated measure³⁴.

PBT2 scored well on ‘Executive Function’. The good news from the Phase IIa trial was that treated patients who received 250 mg of PBT2 per day for 12 weeks performed well on Executive Function, as measured by NTB, in two out of the four test batteries as well as overall:

- In the **Category Fluency Test**, patients have to say as many words as possible from a category in 60 seconds³⁵. Here PBT2 registered a gain of 2.4 words over baseline, as against a 0.3 word decline for placebo (p = 0.041).
- In the **Trail-Making Test, Part B**, patients are given a sheet of paper covered with circles marked with both numbers (1 – 13) and letters (A – L). The patients are then required to draw lines to connect the circles in an ascending pattern, alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). In this test PBT2-treated patients gained an average 42 seconds in terms of time taken over 12 weeks whereas the placebo group’s speed dropped by 6 seconds (p= 0.009).
- In the **Executive Function z-score**, where the results of the various NTB tests were aggregated, PBT was able to establish, in an analysis first presented in July 2009 (a year after the *Lancet Neurology* paper)³⁶, that there had been an error in the initial calculation of the overall Executive Function. Whereas previously it had been thought that PBT2 hadn’t generated a statistically significant Executive Function z-score at the 250 mg dose, in fact it had, with a p-value of 0.042.

We think these three pieces of data indicated that PBT2 had strength in terms of Executive Function. We say this cognisant of the fact that PBT2 did not turn in a statistically significant outperformance against placebo in all NTB tests. However we think this can be explained by some tests being ‘easier’ than others. For example, PBT2 didn’t outperform placebo in Trail-Making Test Part A with statistical significance. However in this test the circles are only marked with numbers rather than letters and numbers, making it notionally easier for untreated patients to keep up with the treated patients than would be the case with Trail-Making Test Part B.

Why ADAS-Cog didn’t lift so strongly in this trial – and why we think it ultimately will. In the Phase IIb trial PBT2 did improve average ADAS-Cog levels by around 1 point whereas placebo saw a 1 point worsening. So the numbers

³³ Elan and Wyeth with bapineuzumab have used NTB as a key measurement tool in trials of that drug.

³⁴ See the EMEA’s, *Guideline on medicinal products for the treatment of Alzheimer’s disease and other dementias*, July 2007. We note with interest this comment from Nature Biotechnology in August 2008: “Not only is the attrition rate for Alzheimer’s disease therapeutics notoriously high, but also any company hoping to bring a drug to market faces a further layer of uncertainty: how open will the FDA be to new ways of proving efficacy for drug candidates? In March, Russell Katz, director of the agency’s neurology products division told a meeting of the coalition to Accelerate Cure/Treatments for Alzheimer’s Disease that Alzheimer’s disease Assessment Scale cognitive subscale (ADAS-cog), long the standard in Alzheimer’s disease measures, might not be required to prove a therapy works. He said the same about the Clinician’s Interview-Based Impression of Change plus caregiver interview, another common gauge. Some had worried that the FDA might look less fondly on such tests as the Neuropsychological Test Battery (NTB), but Katz’s remarks seemed to indicate the bar may be lowered, or criteria at least potentially relaxed.”

³⁵ For example, if the category is ‘farm animals’, acceptable words would include “sheep”, cow” and “goat”.

³⁶ At the 2009 International Conference on Alzheimer’s Disease in Vienna. The paper, presented by Dr. Craig Ritchie, was entitled “PBT2 for Alzheimer’s Disease: An Update on Clinical Development”.

were moving in the right direction. However the relatively small 2.2-point difference meant that PBT2's improvement wasn't statistically significant ($p=0.17$). We think there were two reasons for this:

- 1 **there weren't enough patients in the treated group** (ie n was only 27) – higher numbers were likely result in a lower p-value;
- 2 **they were only measured for 12 weeks**. The data from PBT1 indicated only a relatively narrow 2-3 point range separated treated and untreated groups at the 12 week mark whereas the gap had widened to more like 5 points by week 24 and, in the severe patients, to 7 points by 36 weeks;
- 3 **they were mild patients**. As we noted above, ADAS-cog tends to be less reliable in mild patients as against moderate patients.

In short, more patients, a wider range of patients (ie both mild and moderate) and a longer measurement period would likely give the data that was missing in this trial. Getting a favourable ADAS-Cog number would give significant comfort to potential licensees that the drug works. It's also worth noting that at a six-month measurement point IVIG, now in a Phase III trial for the treatment of Alzheimer's being sponsored by Baxter, only had a 2.6 point ADAS-cog lift whereas by nine months the gap had widened to 5.4 points³⁷.

PBT2's Phase IIb trial has been properly structured

PBT intends to proceed with a A\$20m Phase IIb clinical trial of PBT2 in order to generate the extra validating data that it didn't get in Phase IIa. We estimate the work would take around two years to produce results and therefore not generate data until around late 2011, however the upside is likely to be a significant increase in the drug's attractiveness to clinicians:

- **The trial will be properly 'powered'**. PBT estimates that its \$20m will test around 600 patients rather than the 78 that were involved in the Phase IIa³⁸, allowing sufficient patient numbers to establish statistical significance across all test batteries;
- **The trial will have sufficient time factor**. In this trial patients will be tested for six months, which we think given the PBT1 data would allow sufficient time for the drug to start contributing substantial gains over placebo;
- **The trial is expected to have a wider variety of subjects**, with both mild and moderate patients likely to be represented.

In our view success in this trial would make licensing of the drug to Big Pharma on favourable terms to PBT a fairly straightforward exercise, and we have valued PBT on the assumption that a favourable 2011 result generates a licensing deal.

Data continues to build on PBT2's effectiveness

While the Phase IIb trial has yet to begin, PBT continues to gather data on the effectiveness of PBT2 as a drug:

- **PBT2 has multiple mechanisms of action**. Until recently PBT had assumed that PBT2's main mechanism of action was protecting neurons from destruction or damage. Research presented in March 2009, from work done in animal models, demonstrated a second mechanism of action – that of

PBT2's Phase IIb trial will gather the data that was missing in Phase IIa

³⁷ See <http://nyp.org/news/hospital/ivig-alzheimers-trial.html>.

³⁸ We understand that the Phase IIa trial cost around A\$5m for 80 patients whereas the forthcoming trial, while costing four times as much, processes 7.5 times the number of patients. The lower cost is, in part, because this time around the trial investigators won't be perform expensive spinal taps on these patients to prove their amyloid levels are going down, this having been established in the Phase IIa trial. Also, PBT envisages that Phase III trials of the drug would be a better venue to revisit the mechanism of action.

preventing loss of synaptic function between neurons, so that they can communicate with each other. This is important because neuronal connections are the primary method in which memory is stored.

- **PBT is potentially a 'smart drug'.** In July 2009 PBT announced the results of a study demonstrating that PBT2 could restore brain function in normal mice that are cognitively impaired simply because of ordinary aging. What this indicated was the drug has potential therapeutic benefit in very early stage Alzheimer's where patients have fewer amyloid plaques. It also suggested a use beyond the Alzheimer's market as a 'nootropic', meaning that it enhances mental function rather than merely treating cognitive deficits.

With PBT continuing to fund small laboratory studies of PBT2 we expect more of this kind of data between now and 2011 to strengthen the case that ultimately leads to a licensing of PBT2.

A second use for PBT2 in Huntington's disease

This drug is our drug. Lovers of folk music will know about Huntington's disease, an inherited neurodegenerative disorder characterized by intellectual decline and involuntary limb movement, since it first came to public attention in the late 1960s when it claimed Woody Guthrie as one of its more prominent victims. PBT has demonstrated efficacy of its AD compound PBT2 in animal models of Huntington's and is planning a possible Phase II trial with PBT2. In valuing PBT2 we've included no additional upside from Huntington's - we assume the drug can become a blockbuster on Alzheimer's alone - however we see three reasons why Huntington's is important for PBT:

- As the Phase I studies are completed for PBT2, the drug is actually 'Phase II ready' for Huntington's;
- The markets for Huntington's and Alzheimer's are complimentary, so there is no potential for market cannibalisation;
- The second indication provides extra value in a licensing agreement and 'back up value' should PBT2 fail in Alzheimer's.

A faster path to market. Only around 30,000 people in the US have Huntington's, but at present there are limited treatment options³⁹. Consequently the advantage of clinical success for PBT2 candidate is likely to be a 'fast track' to market.

There is potential for a second indication for PBT2 in Huntington's

³⁹ Only the Biovail / Lundbeck drug Xenazine is approved in the US with a Huntington's indication. It gained FDA approval in August 2008. The Danish drug developer Neurosearch is in Phase III with a drug called pridopidine.

PBT's solid pipeline

As well as PBT2 for Alzheimer's, PBT is working on a number of earlier stage programmes that could potentially prove valuable over time.

Different compound libraries

We noted earlier that PBT scientists had designed PBT2 based on the chemical properties of PBT1. Specifically, what they created was a library of around 200 MPACs that could broadly be described as derivatives of cloquinol, since they were built on that drug's chemical 'scaffold'. However they also created several other compound libraries:

- the PBT3, PBT4 and PBT5 class libraries, which also have MPAC-type activity but use different scaffolding to the PBT2 class.
- the 'Amyloid Targeting Metallocomplex' class, which work via a different mechanism of action, in that they can block the metal binding site of amyloid beta, potentially preventing it from forming into plaques⁴⁰.

The libraries improve PBT's 'optionality'. We see the commercial value of these compound libraries as allowing PBT more 'shots on goal' in terms of potential new products. For example, the Amyloid Targeting Metallocomplex library is currently being screened for a potential Alzheimer's drug but this could significantly yield a low-cost Alzheimer's diagnostic, which would be valuable given that at present there is no convenient way to image the brain for Alzheimer's⁴¹. As at mid-2009 several potential drugs have emerged from PBT3 class for Parkinson's and brain cancer.

Early stage drug candidates

A potential Parkinson's drug. PBT announced in May 2008 that it had identified an MPAC apparently effective against Parkinson's disease. In Parkinson's a serious drop in the level of dopamine in the brain leads gradually to tremors, speech impediments, movement difficulties, and in many cases dementia. PBT's compound was able to protect the cells of the *substantia nigra* in the MPTP mouse model of Parkinson's, as well as increase motor function in treated animals. By mid 2009, PBT has identified several Parkinson's drug candidates with election of one as its development lead expected shortly. Should this compound advance, the potential market is large. The US alone is believed to have more than a million Parkinson's patients, with the total health care cost somewhere between US\$5bn and US\$6bn. What makes Parkinson's particularly lucrative target for drug developers is the relatively long time a patient will be on medication – in many instances longer than ten years.

A potential brain cancer drug. PBT has identified at least one MPAC compound from its library that appears to work well against brain cancer while leaving normal brain cells untouched. The value for PBT here is that its MPACs are all orally available and can cross the blood-brain barrier, areas where other potential brain cancer drugs often fall down. The market for drugs that can treat brain cancer is lucrative because of the lack of effective treatments. Only around 19,000 American adults are diagnosed annually with primary brain tumours⁴², but

PBT may have something interesting in brain cancer

⁴⁰ See Proc Natl Acad Sci U S A. 2008 May 13;105(19):6813-8. Epub 2008 May 7.

⁴¹ Makers of imaging equipment such as Siemens are currently working on this.

⁴² Source: National Cancer Institute.

Schering-Plough's Temodar drug, which only prolonged life by 2.5 months over radiation therapy in clinical trials, still enjoyed US\$1.0bn in sales in calendar 2008.

A potential Alzheimer's vaccine

PBT's Alzheimer's vaccine work is worth watching

For several years now PBT scientists have worked on a potential Alzheimer's therapeutic vaccine comprising a monoclonal antibody, where the target of the antibody vaccine is a specific toxic form of amyloid beta that cannot be broken down in the brain and generates neurotoxic hydrogen peroxide. If the immune system can be persuaded to recognize and deal with the toxic amyloid beta species, the result could be a treatment that deals with amyloid plaques and oligomers in the brain without attacking healthy tissue. We think this technology approach has some merit in that Elan and J&J are also developing an anti-Alzheimer's monoclonal antibody that targets all forms of amyloid in the brain and in blood vessels, but that vaccine may not be specific enough in terms of its target and potential safety. We regard PBT's work in the area as worth watching.

Value in the pipeline

We see PBT's growing pipeline as helping manage the clinical risk associated with PBT2, particularly since the relevant intellectual property can be licensed out at little further cost to PBT. Consequently we've chosen to include some pipeline value in our valuation of PBT as a whole.

Strong leadership

The management

We have a high regard for the leadership team at PBT, which approaches the building of the company first from a commercial, then from a scientific perspective.

- **Executive Chairman Geoffrey Kempler** has already built a successful business in Australia, having been for some years the Australian distributor of the Aveda range of cosmetic products. Kempler founded PBT in 1997 and has overseen the development of the company since its inception. Under Kempler PBT has pushed up the value chain, from the relatively low value PBT1 to the higher-value PBT2 and then to the building of a potentially valuable pipeline.
- **Chief Operating Officer Dianne Angus**, who has been with the company since 2002, initially joined as VP of Intellectual Property and Licensing and has since overseen most aspects of the company's growth from a business development and research perspective. We feel that Ms Angus has provided valuable scientific input to structuring the company's clinical effort for commercial success.

The scientific talent

An impressive aspect of PBT is the scientists that have been associated with the company since its beginnings in the late 1990s. One of the highest honours an Alzheimer's researcher can aspire to is the Potamkin Prize for Research in Pick's, Alzheimer's and Related Diseases⁴³. The scientific advisory board PBT has assembled has three Potamkin winners out of the 46 who have been so-honoured since 1988. Professor Colin Masters won in 1990, Professor Rudy Tanzi won in 1996 and Professor Ashley Bush took out the prize in 2003.

Colin Masters, for many years Professor of Pathology at the University of Melbourne, led a group that in the mid-1980s was one of the first to unravel the amino acid sequence of the amyloid protein. **Ashley Bush**, now heading up the Oxidation Biology Laboratory at the Mental Health Research Institute of Victoria, studied under Colin Masters at Melbourne.

In the 1990s Bush, together with his longtime colleague **Rudy Tanzi**, a Professor of Neurology at Harvard, pioneered the metal/protein interaction thesis that lies at the heart of PBT's approach. Tanzi is noted for his work on the genetics of Alzheimer's, having been one of the discoverers of the location of the Huntington's gene in 1983 as well as the location of APP, the amyloid precursor protein gene, in 1987⁴⁴. What started Bush and Tanzi looking at metal/protein interactions was work Tanzi did with Wilson's disease, a genetic disorder in which copper accumulates in tissues. Tanzi found that when he was extracting APP he was also extracting the Wilson's gene, suggesting that APP has a metal-binding site. Bush, then working in Tanzi's lab, developed the implications of this and the result, indirectly, was the MPAC approach and Prana Biotechnology.

PBT's scientific advisory board is world-class in terms of its contribution to Alzheimer's research

⁴³ Pick's is a little-known neurodegenerative disease which causes changes in personality and behaviour long before memory is affected.

⁴⁴ For more on this see Tanzi's 2000 book *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease* (with Ann. B Parson - New York: Basic Books), which mentions the origins of PBT towards the end.

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 PBT.

We see a number of risks related to PBT

PBT is not without risk

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

- 1 **Clinical risk** – There is the risk that PBT2 could join the abovementioned Phenserine, Alzhemed and Flurizan as a failed Alzheimer's compound should PBT2 not outperform placebo with statistical significance.
- 2 **Trial structuring risk** – There is the risk that the Phase IIb trial of PBT2 could be incorrectly structured to generate the kinds of data that Big Pharma is looking for. For example, ADAS-cog and NTB are considered appropriate Alzheimer's metrics in 2009 but may go out of fashion by 2012. Or alternatively six months may be too short a measurement period whereas nine or twelve months may be more appropriate.
- 3 **Sentiment risk** – Biotech-oriented investors tend to prefer drug development stocks where the lead candidate is in Phase III rather than Phase II. Consequently PBT may have difficulty attracting favourable sentiment in the near term even though PBT2's performance to date has been strong.
- 4 **Timing risk** – There is the risk that PBT could take much longer to organise PBT2's Phase IIb trial sites and then recruit and treat patients than the roughly two years we have postulated in this note.
- 5 **Partnering risk** – There is the risk that Big Pharma's interest in Alzheimer's may lessen due to the difficulties associated with developing significant new drugs. Consequently PBT may find that its potential partners are striking too hard a bargain for PBT shareholders to enjoy a strong return.
- 6 **IP risk** – There is the risk that PBT could find itself locked in dispute over patent infringement should its MPAC approach be found to lean too heavily on unrelated or unlicensed predecessor science.
- 7 **Burn rate** - At present PBT has around \$10m cash and has burned around \$600,000 per month since its March 2000 IPO, having raised around \$79m in equity capital in ten individual rounds since that time. It will likely have to make further capital raisings to fund this burn rate as well as the Phase IIb trial of PBT2, and these may be conducted at times when Australian biotech is out of favour.

Appendix I – A PBT glossary

ADAS-cog – Short for Alzheimer’s Disease Assessment Scale - Cognitive Subscale. A measure of cognition in Alzheimer’s Disease patients. An ADAS-Cog test is a battery of individual tests of such abilities as word recall and recall of test instructions etc.

Alzheimer’s disease (also called presenile dementia) - A brain disorder that affects parts of the brain that control thought, memory, and language. Alzheimer’s is understood to afflict between 1 and 2% of the population of the Western world.

Amyloid – A starch-like protein that is found deposited in plaques in the brain tissue of people who have died from Alzheimer’s.

Amyloid beta – An amyloid protein that results when Amyloid Precursor Protein is cut by a secretase enzyme. Amyloid beta can form into plaque in brain tissue and contribute to loss of brain function. A Beta 40, an amyloid beta protein which is 40 amino acids in length, is the more common, however a slightly longer protein called A Beta 42, which as the name suggests is 42 amino acids long, tends to aggregate into plaques more easily.

Amyloid hypothesis – The hypothesis that beta amyloid protein is the primary cause of Alzheimer’s disease.

Amyloid plaques – The clumps of amyloid in the brain that indicate that a person died of Alzheimer’s disease.

Amyloid targeting metallocomplexes – PBT-designed drugs that can block amyloid beta’s metal bind site.

Antibodies – Immune system proteins that can bind to an antigens and help to neutralise the potentially harmful effects of the cells carrying the antigens. Antibodies are commonly used in drug therapy for this reason. A monoclonal antibody is an antibody specific to a single target. Bapineuzumab is an anti-amyloid monoclonal antibody.

APOE4 – A gene that codes for a version of Apolipoprotein E, a cholesterol transport protein. The E4 version of the APOE gene contains a polymorphism associated with a majority of late-onset Alzheimer’s disease cases. The gene for APOE was discovered in 1992 on chromosome 19. Elan is targeting APOE4 positive patients with its bapineuzumab drug.

APP – Short for Amyloid beta Precursor Protein, a protein found in the outer layer of brain cells which, when snipped by the secretases, results in amyloid beta. The gene for APP was located on chromosome 21 around 1987.

Aricept – A cholinesterase inhibitor drug from Pfizer (generic name donepezil) that treats Alzheimer’s by boosting the amount of acetylcholine in the brain.

Bapineuzumab – An Alzheimer’s antibody drug currently being developed by Elan and Wyeth.

Baseline – The beginning point of a clinical trial study.

Big Pharma – A collective term referring to the world’s largest pharmaceutical companies such as Eli Lilly, J&J, Merck, Novartis and Pfizer.

Blockbuster – A drug that sells more than US\$1bn worth of product within a calendar year. The Alzheimer’s drugs Aricept and Namenda are blockbusters.

Blood-brain barrier – A wall of cells which line the blood vessels in the brain so tightly that only selected substances are permitted to pass through.

Cerebrospinal Fluid (CSF) – A fluid that surrounds the central nervous system. Physicians can check on the levels of amyloid beta in the brain by using a lumbar puncture to assay for the fluid.

Clioquinol – An old anti-amoebic drug with which PBT conducted their proof of concept studies for the MPAC approach. The drug was banned from the Japanese market in 1970 because up to 10,000 Japanese patients developed peripheral nerve damage and sometimes blindness partly as a result of taking it.

Cognition - A term which covers multiple aspects of mental function such as a memory and language. In Alzheimer's cognition is often measured by ADAS-Cog.

Dementia – The group of brain disorders that seriously affects the patient's ability to carry out daily activities.

Dimebon – A competitor drug to PBT2 from the San Francisco-based Medivation. Dimebon is an old Russian anti-histamine that performed particularly well in a Phase II trial as an Alzheimer's drug.

Dopamine – A neurotransmitter sometimes called the 'happiness chemical' because it plays a role in signaling reward in the brain. It also plays a role in body movement. A hallmark of Parkinson's disease is a drop in dopamine levels.

Enzyme - A protein that helps speed up in biochemical reactions in the body. Examples are secretase and cholinesterase.

Executive Function – A general term to describe the brain's ability to organise itself to get things done. PBT2 did well in boosting Executive Function in the treated patients in its Phase IIa trial.

Free radicals – Molecules with unpaired electrons that therefore have to combine with complementary molecules before they become stable. If a free radical bonds with a positive charge molecule, its charge is neutralised. Oxygen in the free radical form can damage cells in the body in a process called oxidative stress.

Huntington's disease – An inherited, degenerative brain disease characterized by intellectual decline and involuntary limb movement. Its most famous victim was the American folk singer Woody Guthrie (1912-1967). The disease is caused by an errant protein called huntingtin.

Hydrogen peroxide – A chemical (H₂O₂) that is often used in textiles and hair as a bleaching agent. The interaction of redox-active copper ions and amyloid beta results in the production of hydrogen peroxide.

In Vitro – Latin for 'in glass', meaning 'in the test tube'.

In Vivo – Latin for 'in life', an instance where a pharmaceutical idea is tried out in a living body, generally in animals such as mice.

IVIG – Short for Intravenous Immunoglobulin, IVIG is antibody-rich blood plasma. Baxter is trialling IVIG as a potential Alzheimer's treatment.

Mechanism of action – The way in which a drug affects a disease's underlying pathology so as to bring about an improvement in the patient.

Metal Protein Attenuating Compound (MPAC) – A compound that can weaken the interaction between metals and proteins. Clioquinol is an MPAC. The 'MPAC approach' is a method of treating Alzheimer's pathology using MPACs.

Microtubules – 'Train-track'-like structures within a cell, which route nutrients and molecules around the cell. Tau protein forms the 'railway ties' that hold the microtubule tracks in place.

MPAC – See Metal Protein Attenuating Compound.

MPTP - A by-product of 'synthetic heroin', or MPPP, which causes Parkinsonian symptoms in users. This drug, when administered to rats, can be used to create an animal model of the disease.

Neurons – Nerve cells or brain cells.

Neurotransmitters - Chemicals that neurons use to communicate with each other.

NTB - Short for Neuropsychological Test Battery, a set of tests used to evaluate the mental state of Alzheimer's patients that is considered particularly useful in measuring Executive Function. PBT tested PBT2 using NTB.

Oligomer - A protein molecule that consists of repeating molecular subunits. Amyloid oligomers are considered a toxic element in Alzheimer's disease.

Open label - A clinical trial in which both investigators and patients know that the patients are getting the drug being tested.

Orally available - Drugs that can be reduced to pill form, such as PBT2, with obvious advantages in terms of delivery to patients.

Oxidative stress - Cell damage that results from oxygen-linked free radicals.

Parkinson's disease - A neurodegenerative disease associated with a drop in dopamine levels. Parkinson's is characterized by tremors, speech impediments, movement difficulties, and often dementia.

PBT1 - PBT's code name for clioquinol.

PBT2 - A 'rationally designed' MPAC for the treatment of Alzheimer's and Huntington's diseases. PBT2 completed a Phase IIa clinical trial in Alzheimer's in early 2008.

PBT3, PBT4, PBT5 - New classes of MPACs developed by PBT.

Phase - A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample. Phase III tests for efficacy in a large sample.

Pivotal trial - A Phase III clinical trial to prove that the drug is effective in a large patient group.

Presenile dementia - Another term for Alzheimer's Disease.

Proof-of-concept - A 'pilot' trial of a compound on a small number of patients that is conducted so as to prove that a particular scientific idea has merit rather than to persuade a regulator to approve the compound for commercial use. PBT's trial of clioquinol was a proof-of-concept trial.

P-value - A measure of statistical significance. Generally a p-value below 0.05 is considered 'statistically significant'.

Secretase - An enzyme that cuts APP to form amyloid beta. There are three secretases, alpha-secretase, beta-secretase, and gamma-secretase. The secretases have often been targets for Alzheimer's drugs.

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

Subcutaneous - Injected via hypodermic needle rather than via infusion.

Synaptic function - Synapses are the junction between the terminal of a neuron and another neuron, over which nerve impulses pass. There is evidence that PBT2 can prevent loss of synaptic connection between neurons.

Tau protein - A protein named after the 19th letter of the Greek alphabet whose function is form the 'railway ties' that hold the microtubule 'tracks' in place. In some neurodegenerative disorders Tau is altered so that so-called 'neurofibrillary tangles' result.

Transgenic mouse model - A mouse whose genetic make-up has been altered so as to model a particular disease state.

Z score - A measure of how many standard deviations from the mean a particular value of data lies.

Appendix II – PBT’s capital structure

Figure 9 – PBT’s current capital structure

Shares (ASX Code PBT)	232,945,639	Price (c)	23.0	
Unlisted options	29,089,134	Undiluted cap (\$m)	53.6	
Total diluted shares	262,034,773	F.D. cap (\$m)	62.6	
Unlisted options	Number	Exercise price (AUD)	Expiry date	Cash (\$m)
	4,352,893	\$0.45	30-Nov-09	1,941,390
	2,677,500	\$0.00	30-Jun-10	0
	2,000,000	\$0.50	30-Jun-10	1,000,000
	5,395,112	\$0.37	31-Oct-10	1,996,191
	1,281,815	\$0.00	31-Oct-10	0
	2,400,000	\$0.30	31-Oct-10	720,000
	5,395,112	\$0.43	30-Nov-10	2,319,898
	341,865	\$0.00	31-Dec-11	0
	3,800,000	\$0.57	17-Dec-12	2,174,411
	10,000,000	\$0.30	11-Sep-13	3,000,000
	1,444,837	\$0.00	7-Aug-14	0
<i>Average</i>	39,089,134	\$0.336	15-Oct-11	13,151,890

SOURCE: PBT. NOTE THE DEC '12 LINE OF OPTIONS HAS A US\$0.50 EXERCISE. THE SEP '13 OPTIONS RELATE TO THE RECENT \$6M CAPITAL RAISING AND HAVE YET TO BE ISSUED

Figure 10 – PBT’s capital raising history

Previous raisings	Capital raised (\$m)	Price	Shares issued	% of current shares on issue	Note
Mar-00	8.0	\$0.50	16,000,000	6.9%	IPO
Feb-01	5.0	\$0.75	6,666,666	2.9%	
Sep-03	5.0	\$0.70	7,102,853	3.0%	
Jun-04	28.8	\$0.72	40,000,000	17.2%	
Dec-04	4.8	\$0.50	9,506,666	4.1%	Option exercise
Nov-06	4.7	\$0.30	15,616,246	6.7%	
Dec-06	1.8	\$0.30	6,148,222	2.6%	
Oct-07	8.0	\$0.27	29,778,699	12.8%	
May-08	7.3	\$0.40	18,125,000	7.8%	
Sep-09	6.0	\$0.20	30,000,000	12.9%	
Total	79.34	\$0.51	156,277,686	67.1%	

SOURCE: PBT

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

Stuart Roberts
Analyst Authorisation

Jonathan Snape
Authorisation

Research Team

Sanjay Magotra
Head of Research
Senior Industrial Analyst
Infrastructure/Utilities
T 612 8224 2880
E smagotra@sceq.com.au

Daniel Blair
Industrial Analyst
Telco and Media
T 612 8224 2886
E dblair@sceq.com.au

Peter Chapman
Senior Resources Analyst
Oil/Gas/Gold
T 612 8224 2847
E pchapman@sceq.com.au

Fleur Grose
Resources Analyst
Iron Ore/Coal/Diversifieds
T 612 8224 2845
E fgrose@sceq.com.au

Johan Hedstrom
Senior Resources Analyst
Energy
T 612 8224 2859
E jhedstrom@sceq.com.au

TS Lim
Financials Analyst
Banks/Regionals
T 612 8224 2810
E tslim@sceq.com.au

Sarah McCloy
Executive Assistant
Research Team
T 612 8224 2885
E smccloy@sceq.com.au

Alexandra McPhee
Senior Industrial Analyst
Consumer/Rural/Retail
T 612 8224 2894
E amcphee@sceq.com.au

Hamish Perks
Industrial Analyst
Emerging Growth
T 612 8224 2804
E hperks@sceq.com.au

Andrew Peros
Industrials Analyst
Building Materials/Steels
T 612 8224 2838
E aperos@sceq.com.au

Stuart Roberts
Industrial Analyst
Healthcare/Biotech
T 612 8224 2871
E sroberts@sceq.com.au

Jonathan Snape
Senior Industrial Analyst
Emerging Growth
T 613 9235 1601
E jsnape@sceq.com.au

Mathan Somasundaram
Quantitative Analyst
Head of Quant & Data Services
T 612 8224 2825
E mathan@sceq.com.au

Lafitani Sotiriou
Analyst
Financials/Industrials
T 612 8224 2813
E lsotiriou@sceq.com.au

Janice Tai
Quantitative and System Analyst
T 612 8224 2833
E jtai@sceq.com.au

Joel Weiss
Quantitative Analyst
T 612 8224 2895
E jweiss@sceq.com.au

This document is intended solely for the information of the particular person to whom it was provided by Southern Cross Equities Limited and should not be relied upon by any other person. Although we believe that the advice and information which this document contains is accurate and reliable, Southern Cross Equities Limited has not independently verified information contained in this document which is derived from publicly available sources, directors and proposed directors and management. Southern Cross Equities assumes no responsibility for updating any advice, views, opinions, or recommendations contained in this document or for correcting any error or omission which may become apparent after the document has been issued. Southern Cross Equities Limited does not give any warranty as to the accuracy, reliability or completeness of advice or information which is contained in this document. Except insofar as liability under any statute cannot be excluded, Southern Cross Equities Limited and its directors, employees and consultants do not accept any liability (whether arising in contract, in tort or negligence or otherwise) for any error or omission in this document or for any resulting loss or damage (whether direct, indirect, consequential or otherwise) suffered by the recipient of this document or any other person.

This document has not been written for the specific needs of any particular person and it is not possible to take into account each investor's individual circumstances and that investors should make their adviser aware of their particular needs before acting on any information or recommendation. Southern Cross Equities Limited, its employees, consultants and its associates within the meaning of Chapter 7 of the Corporations Law may receive commissions, underwriting and management fees, calculated at normal client rates, from transactions involving securities referred to in this document and may hold interests in the securities referred to in this document from time to time.

Southern Cross Equities Ltd and its associates hold a beneficial interest in 10,000 PBT shares and 3.5 million 3-year PBT options exercisable at 30 cents as at the date of this report. This position is subject to change without notice.