NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

Phylogica (ASX: PYC)

Evaluation Report – Monday 1 May 2017

In Good Company

Phylogica is a Perth-based biotechnology company focused on peptide drug development. Peptides are potentially very valuable as the basis for future world-leading drugs, and Phylogica has a powerful discovery engine with its Phylomer platform. Most importantly, having discovered how peptide drugs can be delivered intra-cellularly, the company is able to address hitherto 'undruggable' targets. This should in turn open the way for a pipeline of potential blockbuster drugs. The company has already signed collaboration agreements with AstraZeneca, Roche, Pfizer and J&J. In due course, each of these can yield substantial milestone payments (one such already received). In addition to the outsourced projects, the company also has its own three, highly-prospective, in-house programmes focused on cancer targets. This report has been commissioned by Phylogica to provide a third-party valuation of the company. We value Phylogica at 5.2 cents per share base case and 14.2 cents per share optimistic case. We regard 10 cents per share as a reasonable mid-range valuation for Phylogica.

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

About NDF Research

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

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

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

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

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

In this report

Executive summary – Valuation 10 cents per share

We value Phylogica at 5.2 cents per share base case and 14.2 cents per share optimistic case. Phylogica is an Australian biotechnology company based in Perth focused on peptide drug development. The company's stock is publicly traded on the Australian Securities Exchange (ASX: PYC). This report has been commissioned by Phylogica to provide a third-party valuation of the company. We value Phylogica at 5.2 cents per share base case and 14.2 cents per share optimistic case. **We regard 10 cents per share as a reasonable mid-range valuation for Phylogica.**

Who is Phylogica? Phylogica was built on a suite of 'Phylomer' libraries that allow new, versatile peptides to be identified. In recent years, the company has executed collaboration agreements over Phylomers with a number of major pharma companies including Roche, Pfizer, AstraZeneca and J&J. More recently the company has commenced building its own suite of in-house programmes, all of which are pre-clinical. A key feature of Phylogica's technology is its ability to create cell-penetrating peptides, allowing peptides to be used for the first time to interact with drug targets that existing within cells. Phylogica's lead candidate goes after a valuable intra-cellular drug target called Myc, which plays a role in many cancers.

Our valuation approach for Phylogica. We valued the company using a probability-weighted DCF approach. We took the major in-house pipeline programmes – Myc, Stat5 and Yb1 – as well as the major pharma collaborations that have been announced to date – with Genentech, Pfizer, Janssen/ J&J, and Medimmune/ AstraZeneca – and assumed commercial payoffs from prospective licensing deals of these programmes. We then calculated a DCF of this programme and weighted it by the historic probability of success of early-stage clinical programmes. We cross-check this against comparable listed companies to determine if the valuation is realistic.

Reasons for the suggested current undervaluation of Phylogica. At 4.5 cents per share Phylogica is currently trading way under the valuation range we have suggested for the company. We believe there are three main reasons for this undervaluation:

1) The market on which Phylogica stock trades, the ASX, has historically tended to undervalue Life Science companies compared to Nasdaq and Euronext.
2) The company has been public on ASX since March 2005 without having taken a compound into the clinic. It therefore would be regarded by many knowledgeable observers as being too 'early stage'.
3) The company has historically lacked institutional investors with a sophisticated knowledge of the Life Sciences sector, which we believe could help re-rate the company.

Why Phylogica has the potential to re-rate to our target price. We see four factors as helping re-rate the stock towards our target price

- New institutional investors coming into the company;
- Progress with some of the existing collaborations;
- Potential partnering deals related to the core Myc, Stat5 and Yb1 programmes;

- A new CEO with strong Big Pharma connections.

NDF Research's expertise and experience. NDF Research is the trading name for Stuart Roberts, who is an equity analyst by background with around 13 years' experience covering ASX-listed companies in the Healthcare, Biotechnology and Medical Devices field (2002-2015) as well as 16 months' operational experience within two ASX-listed biotech companies (2015-2016). Stuart Roberts is RG146 compliant for the purposes of providing general advice related to securities.

Introducing Phylogica (ASX: PYC)

What are peptides and why do they make great drug candidates? Peptides are simply strings of amino acids, which are the building blocks of proteins. Peptides, which medicinal chemists classify as 'large molecules', have long been regarded as great drug candidates due to their potential for better targeting of proteins that are disease causing than small molecules[1]. In recent years, many new peptide drugs have gained approval in a variety of indications (see Figure 1). However, one of the historic problems with peptide drug discovery has been the identification of candidates with the right drug-like properties from among the trillions of potential amino acid combinations. An early approach involved screening a drug target against synthetic peptides randomly created from combinatorial libraries[2]. The problem with this was that most successful peptide drugs are not just strings of amino acids. They often have, in addition, distinct 'secondary' and 'tertiary' structures[3] because of the various ways in which the protein sub-structures within the peptide naturally fold when the peptide is adopting a particular shape. That particular shape is what helps the peptide fit the target surface. Get the structures wrong and the peptide might have some binding ability against the target in question, but won't bind to the target tightly enough or won't get to the target in the first place because it will be unstable.

What are Phylogica's Phylomers and why do they make better peptide drugs than those from other peptide drug discovery platforms? Phylomers are peptides derived from natural protein fragments encoded by biodiverse ancient bacterial genomes. In the 1990s the Australian geneticist Professor Paul Watt, working successively at Harvard and Oxford and then at the Telethon Institute for Child Health Research (now Telethon Kids Institute) in his native Perth, had the insight that nature had already selected a broad suite of distinct and stable protein structures capable of binding to biological molecules, and that these proteins could be found in the genomes of evolutionary diverse microbes often to be found in extreme environments. Sequence enough of the relevant genomes, and a drug discovery team could have a library containing virtually all the classes of natural scaffold in the protein world, of which there may be ~4,000[4]. The resulting peptides, which Watt called Phylomers, could be screened against targets of interest inside living cells using two-hybrid-based high-throughput screening processes[5]. The Watt laboratory started building their Phylomer platform around 1997 and Phylogica was founded in 2001 to commercialise it. We describe the platform in more detail in Appendix I of this note. Over the

[1] Chem Biol Drug Des. 2013 Jan;81(1):136-47.
[2] Such as, for example, phage display - see Curr Opin Biotechnol. 1996 Dec;7(6):616-21.
[3] A protein's primary structure is its sequence of amino acids. Its secondary structure is the presence of 'alpha-helices' or 'beta-sheets', the two most common protein folding patterns in nature. Its tertiary structure is the overall three-dimensional folding of the molecule.
[4] PLoS One. 2012;7(6):e38913. Epub 2012 Jun 13.
[5] Nat Biotechnol. 2006 Feb;24(2):177-83.

years Phylomers have been used to create numerous drug candidates with target affinities generally in the low to mid-nanomolar range before any optimisation. That represents a superior quality and quantity of hits than can be achieved using conventional peptide libraries of random amino acid composition.

Why is Phylogica particularly interested in cell-penetrating peptides? Most potential drug targets are within cells, where they can theoretically be reached by small molecules that can get through the cell membrane, but not by large molecules that are too big to get through. Small molecules, however, are often unsuitable for drugging these intra-cellular targets because the target proteins are basically too flat. Large molecules such as peptides wouldn't have a problem with this flatness if they could actually get to the target. Phylogica believes that it has solved the problem of intra-cellular delivery of peptides, opening up vast potential for drug discovery efforts by its potential partners.

Why is Phylogica going after cancer targets such as Myc? Many proteins that play a key role in cancer formation, survival and progression have been known about for decades but have been too difficult to drug with conventional pharmacology. Myc is one such target, and Phylogica is also going after Stat5 and Yb1. Phylogica believes that early success with these internal programmes will not only validate its cell-penetrating peptide platform but also create potential blockbuster drugs.

Figure 1: A selection of FDA-approved peptide drugs

Brand	Generic	Website	Approval	Company	Indication
Forteo	teriparatide	www.forteo.com	Nov-02	Eli Lilly	Osteoporosis
Fuzeon	enfuvirtide	www.fuzeon.com	Mar-03	Roche	HIV infection
Symlin	pramlintide	www.symlin.com	Mar-05	AstraZeneca	Type 2 Diabetes
Byetta	exenatide	www.byetta.com	Apr-05	Eli Lilly	Type 2 Diabetes
Somatuline	lanreotide	www.somatulinedepot.com	Aug-07	Ipsen	Acromegaly
Nplate	romiplostim	www.nplate.com	Aug-08	Amgen	Immune thrombocytopenia
Firmagon	degarelix	www.firmagon.com	Dec-08	Ferring	Prostate cancer
Victoza	liraglutide	www.victoza.com	Jan-10	Novo Nordisk	Type 2 Diabetes
Egrifta	tesamorelin	www.egrifta.com	Nov-10	Theratechnologies	HIV-related abdominal fat
Firazyr	icatibant	www.firazyr.com	Aug-11	Shire	Hereditary angioedema
Kyprolis	carfilzomib	www.kyprolis.com	Jul-12	Amgen	Multiple myeloma
Linzess	linaclotide	www.linzess.com	Aug-12	Allergan / Ironwood	Irritable Bowel Syndrome
Signifor	pasireotide	www.signifor.com	Dec-12	Novartis	Cushing's disease
Gattex	teduglutide	www.gattex.com	Dec-12	Shire	Short Bowel Syndrome

Why Phylogica can justify NDF's valuation

1. **Peptides can make great drugs and the peptide market is growing rapidly**. The potential of peptides for exquisite targeting of disease-causing protein-protein interactions, combined with the ease with which they can be manufactured today, means that any peptide drug discovery platform which can address challenges associated with this class, could potentially be very valuable.

2. **Phylogica has a powerful peptide drug discovery engine.** Its Phylomer platform of over 400 billion peptides, from thousands of structural families, is not only large enough to guarantee multiple hits against just about any target with high affinity, but also allows selection of cell-penetrating peptides to access targets inside cells.
3. **Phylogica's cell-penetrating peptides seem to work *in vitro* and *in-vivo***. With Phylogica having solved the puzzle of how to detect peptides that can efficiently access intracellular targets in the cytoplasm or nucleus through its Endosomal Escape Trap and Split-GFP Complementation Assay, it is on track to be a leader in this rapidly emerging field.
4. **Phylogica is going after hitherto 'undruggable' targets**. The company's in-house drug discovery programmes, led by a programme targeting the oncogene c-Myc, have the potential to yield highly valuable drugs given that these intra-cellular targets have yet to be properly drugged by small molecules, which can only theoretically access a small proportion of potential targets.
5. **The c-Myc programme could be world-leading**. c-Myc's role as a 'master regulator' of both cellular growth and metabolism makes it an attractive drug target, but, so far, no group or company has been able to properly drug this target. Phylogica has *in vivo* evidence that it can properly deliver new Myc-targeted drugs, and *in vitro* evidence that its own proprietary cell-penetrating peptides can be effective c-Myc and N-Myc antagonists.
6. **The Phylomer platform is highly versatile,** as illustrated by evidence that cell-penetrating peptides can deliver a range of peptides, proteins and even antisense oligonucleotides, and that it can greatly improve the efficiency of intracellular delivery of these conjugated drugs.
7. **Phylogica can gain composition-of-matter intellectual property protection over its Phylomers**. While the latest methods of creating Phylomer libraries give Phylogica patent protection over to about 2027, those libraries can continue to yield patentable amino acid sequences for new drugs more-or-less indefinitely.
8. **Phylogica has worked on a number of collaborations with large pharma since 2009**. Its involvement with high profile companies such as Medimmune/AstraZeneca, Genentech/Roche, Pfizer and J&J suggests that the Phylomer technology is of great interest to the global pharma industry.
9. **The Genentech/Roche collaboration appears particularly promising**. This collaboration, focused on antimicrobials for drug-resistance bacteria, saw Phylogica paid a US$2m milestone payment in December 2016. The collaboration has great potential given the incentives now available to developers of new generation antimicrobials under America's GAIN Act of 2012.
10. **Phylogica is highly differentiated and competitive with other companies working on cell-penetrating peptides,** with Phylogica's advantage being its specific focus on cell-penetrating peptides, its technology base that can ensure that peptides can reach their intra-cellular target, and that size of the Phylomer libraries, ensuring a high hit rate on any target of interest.
11. **Several listed comparables in the peptide space have attracted large market capitalisations,** most notably Ra Pharmaceuticals, Protagonist Therapeutics and Peptidream.

Phylogica can discover cell-penetrating peptides

Cell-penetrating peptides are now Phylogica's main focus. Around 2010 Phylogica began to concentrate its drug discovery and development efforts specifically on peptides that could penetrate inside cells and bind to intracellular targets. Its reason for doing so was four-fold:

- Probably more than 80% of potential drug targets were intracellular[6], where traditionally they hadn't been reachable with large molecules such as monoclonal antibodies, due to the difficulty of getting those kinds of drugs through the cell membrane[7];
- Many of the proteins that would make good drug targets – those that engage in intracellular interactions with other proteins – lacked the deep hydrophobic involutions that could be drugged with small molecules – only large molecules could reliably do this job[8];
- Conventional cell-penetrating peptides (CPPs), while having been known about since the late 1980s[9], had yet to achieve widespread application despite their apparent advantages[10], since the hydrophilic nature of peptides generally made cell membranes impermeable to them. Consequently, very few cell-penetrating peptides had advanced into clinical trials in a therapeutic indication[11];
- At around 400 billion large individual peptides, with an average size of about 30 amino acids[12], Phylogica believed its Phylomer libraries were now structurally diverse enough to be able to yield the rare peptide candidate that would prove cell-penetrating.

Big Pharma is interested in cell-penetrating peptides. Seven years ago Phylogica's potential for entering this space had already attracted the attention of a large pharmaceutical company, with Roche announcing in December 2009 that it was evaluating the cell-penetrating ability of Phylomers[13]. Since 2010, with the help of Roche and other pharma collaborators, including repeat deals from within the Roche group, Phylogica has built up a large body of knowledge showing that Phylomers can yield competitive cell-penetrating peptides. We argue that in 2017 any drug discovery platform that enables the discovery of cell-penetrating peptides stands to create significant shareholder value, and that Phylogica has the potential to pioneer this field.

Delivery of Phylomers with TAT, 2010. When Phylogica began its pivot towards the cell-penetrating peptide space, it first used a well-characterised non-proprietary peptide called TAT to get Phylomer peptides into cells. TAT is a protein from HIV[14], whose protein transduction domain has been known since the late 1980s to be cell-

[6] Nat Rev Drug Discov. 2006 Dec;5(12):993-6.
[7] Intracellular delivery of monoclonal antibodies is known about (see, for example, Immunol Lett. 2002 Oct 21;84(1):63-7) but we think it's fair to say that this field is in its early days. An early commercial pioneer is Sorrento Therapeutics (San Diego, Ca., Nasdaq: SRNE, www.sorrentotherapeutics.com) which is working on such antibodies with City of Hope in Los Angeles. The ASX-listed Patrys (Melbourne, Australia, ASX: PAB, www.patrys.com) has as its lead candidate an antibody called Deoxymab 3E10, which can penetrate all the way through to the cell nucleus. It does so by binding to extracellular DNA which gets to the nucleus through a nucleoside transporter. Once in the nucleus 3E10 interferes with DNA repair processes, making it a potentially excellent anti-cancer antibody.
[8] Methods Enzymol. 2012;503:3-33.
[9] FEBS Lett. 2013 Jun 19;587(12):1693-702. Epub 2013 May 10.
[10] ie only 3 kDa for a Phylomer versus 150 kDa for a monoclonal antibody.
[11] A notable exception is AM-111, for the treatment of acute sensorineural hearing loss. This drug, from Auris Medical (Zug, Switzerland, Nasdaq: EARS, www.aurismedical.com) is a cell-penetrating peptide designed to inhibit JNK. AM-111 is now in Phase 3. For Phase 2 data see Otol Neurotol. 2014 Sep;35(8):1317-26.
[12] Ranging from 10 to about 100 amino acids.
[13] See the Phylogica market release dated 18 December 2009 and headlined '*Phylogica enters agreement with Roche to evaluate its proprietary technology on disease targets within cells*'.
[14] Its main role is to increase the level of transcription of the HIV double-stranded DNA – see J Gen Virol. 2010 Jan;91(Pt 1):1-12. Epub 2009 Oct 7.

penetrating[15]. In several *in vitro* and *in vivo* experiments[16] Phylogica showed that TAT-Phylomers could drug potentially valuable intra-cellular targets such as AP-1 (a previous target of earlier Phylomer work – see below), MAL[17] and Sonic Hedgehog[18], but Phylogica abandoned conventional cell-penetrating peptides due to their well characterised inefficiency, which limited their potency and potential clinical application.

First Generation Cell-Penetrating Phylomers, 2011. The next logical step for Phylogica was to discover if it had its own cell-penetrating peptides in its Phylomer libraries. The company searched for these by attaching the peptides to phage virus particles and then running them through various cell-types. If the phage showed up within the cells, that was evidence that the Phylomer peptide had gotten through. By using positive and negative selection Phylogica could discover many peptides that would only penetrate specific cell types. This approach is particularly useful in in diseases such as cancer where the aim is to find peptides that will only kill tumour cells. It was the Roche collaboration which initially fuelled the effort to discover cell-penetrating peptides in the Phylomer libraries. By October 2010 the collaboration had yielded some hits[19], and by May 2011, Phylogica was using the technology to identify peptides that had potential to cross the blood-brain barrier[20]. As Phylogica ran its screens it found they were yielding completely new types of cell-penetrating peptides with multiple methods of getting into cells. Perhaps not surprisingly, many of them came from membrane-associated proteins and from bacterial virulence factors already known to be involved in cell invasion. Phylogica had filed for patent protection over its method of screening for cell-penetrating peptides, as well as composition-of-matter over the peptides themselves[21].

Second Generation Cell-Penetrating Phylomers, 2013. In January 2012 Phyologica announced a collaboration with J&J's Janssen Biotech unit focused on the discovery of new Phylomer cell-penetrating peptides[22]. Janssen was looking for peptides that could deliver one of its proprietary compounds intracellularly. The Janssen collaboration, which was extended in January 2013[23], was to be instrumental in helping Phylogica perfect its cell-penetrating peptide technology, by allowing the company to develop a solution to the problem of 'endosomal entrapment', which is a key bottleneck of intracellular delivery of biologics. Phylogica's scientists were finding that their peptides were making it through the cell membrane[24], but not binding to their intended intracellular target in sufficiently high concentrations. The endocytosis process which allows some external macromolecules to pass through the cell membrane, and involves such molecules being wrapped in a piece of the cell membrane (known as the 'endosome') for the journey into the cell, was working fine. However, the peptide, more often than

[15] The structure of TAT is GRKKRRQRRRPPQ – see Cell. 1988 Dec 23;55(6):1189-93.
[16] See Slide 15 of the Phylogica presentation dated 25 May 2011 and headlined '*Beyond TAT: Exploring natural protein-derived Phylomer peptides for cell penetration'*.
[17] A 'TLR adaptor' mediating downstream activation of Toll-Like Receptors. MAL is regarded as an interesting target for future anti-inflammatory drugs – see Am J Pathol. 2007 Feb; 170(2): 518–525.
[18] A protein in a signalling pathway implicated in the development of some cancers – see Cancers (Basel). 2016 Feb; 8(2): 22.
[19] See the Phylogica market release dated 21 October 2010 and headlined '*Phylogica and Roche complete first stage of partnership*'.
[20] See the Phylogica market release dated 23 May 2011 and headlined '*Phylogica and Roche extend collaboration to evaluate potential for Phylomer delivery to brain*'. The experiment that demonstrated that cell-penetrating peptides could be discovered specific to particular cell types arose from this interest in the blood-brain barrier. Phylogica showed that it could identify cell-penetrating Phylomers that only penetrated 'Bend.3', a mouse brain endothelial cell line, and not two other endothelial cell lines, Huvec and SVEc4-10 (See Slide 25 of the Phylogica presentation dated 25 May 2011 and entitled '*Beyond TAT: Exploring natural protein-derived Phylomer peptides for cell penetration*'). Bend.3 is often used to model the blood-brain barrier (see Biol Pharm Bull. 2013;36(3):492-5).
[21] See *Method of determining, identifying or isolating cell- penetrating peptides,* WO/2012/159164, priority date 23 May 2011, Invented by Paul Watt, Richard Hopkins and Katrin Hoffmann.
[22] See the Phylogica market release dated 3 January 2012 and headlined *'Phylogica licenses technology to Janssen Biotech'*.
[23] See the Phylogica market release dated 31 January 2013 and headlined *'Phylogica achieves milestone in pharma collaboration'*.
[24] Helped by the fact that the Phylomer was conjugated to a receptor-binding domain. This approach was chosen so as to maximise the chances of delivery.

not, remained stuck inside the endosome, which is not unexpected since cells use this endosomal entrapment as a kind of quarantine to keep foreign material away from the rest of the cell's contents. Phylogica fixed that well-described issue with the development of an 'Endosomal Escape Trap' to detect the very rare peptides that could make it out of quarantine. It also developed a validating 'Split-GFP Complementation Assay' to accurately quantify the level of endosomal escape[25]. Phylogica indicated to the market that it had achieved this breakthrough in July 2013[26] shortly after it filed for patent protection over both tools[27]:

- The 'Endosomal Escape Trap' was simply the fusion of the cell-penetrating Phylomer displayed on the surface of a bacterial virus to another peptide called an AviTag[28]. The AviTag would only be detected should the cell-penetrating peptide make it out of the endosome, delivering the entire virus cargo with it. Phylogica believes that peptide endosomal escape is a 'one in a billion event', so it requires a library of Phylogica's size to be able to garner significant numbers of candidates.
- The Split-GFP Complementation Assay represented a way of lighting up the cell-penetrating peptide when it had made it out of the endosome. GFP is simply Green Fluorescent Protein, a glow-in-the-dark molecule from jellyfish that is commonly used to report the presence of proteins of interest[29]. 'Split GFP' is a method of monitoring protein interactions where GFP 11, a 15-amino-acid GFP fragment, is fused to the test protein while GFP 1-10 is used as a detector fragment. When GFP 1-10 connects to GFP 11, the result is fluorescent GFP[30]. In Phylogica's version of the Split-GFP Complementation Assay, GFP 11 was connected to the cell-penetrating peptide and lit up when it bound to intracellular GFP 1-10. Phylogica published the details of this assay in December 2015[31].

Phylogica has now identified potent cell-penetrating peptides. Phylogica is calling its cell-penetrating peptides, as identified via the Endosomal Escape Trap and the Split-GFP Complementation Assay, 'Functional Penetrating Phylomers' (FPPs), since they have the potentially to properly act as drugs on intracellular drug targets, either to deliver Phylomer cargoes or as carriers for other drugs. The company's data suggests these peptides represent a significant step forward for the field.

- From around 2015 Phylogica was routinely reporting levels of delivery up to 37 times higher than that achievable with TAT[32] and 159 times higher than with another well-known cell-penetrating peptide called R9[33], particularly at low concentrations where conventional cell-penetrating peptides struggle to efficiently deliver cargoes.

[25] For background on the technology see Richard Hopkin's presentation entitled *'The Endosome Escape Trap: A tool to discover more efficient cell penetrating peptides'* at phylogica.com.
[26] See the Phylogica market release dated 1 July 2013 and headlined *'Phylogica expands collaboration with Janssen for peptide-drug conjugates'*.
[27] See *Method of monitoring cellular trafficking of peptides*, WO/2014/205518, priority date 26 June 2013. Invented by Richard Hopkins, Katrin Hoffmann, Tatjana Heinrich, Paula Cunningham, Paul Watt and Nadia Milech.
[28] AviTag is based on the standard streptavidin-biotin complex often used in biotechnology to achieve protein capture. The interaction between streptavidin and biotin is one of the strongest non-covalent interactions in nature. Typically, biotin will be tagged to the substance being captured, and streptavidin used to detect where the tags are. An AviTag is a15 amino acid peptide which has been enzymatically biotinylated with *E. coli* biotin ligase (BirA) – see Methods Mol Biol. 2015; 1266: 171–184.
[29] GFP is a research tool so powerful that it won the 2008 Nobel Prize in Chemistry for the Americans Martin Chalfie and Roger Tsien and the Japanese Osamu Shimomura.
[30] Nat Methods. 2006 Oct;3(10):845-54.
[31] Sci Rep. 2015; 5: 18329.
[32] See the company's 9 April 2015 presentation, slide 11.
[33] Which, as the name implies, is simply of a string of nine arginines (single letter code R) – see Proc Natl Acad Sci U S A. 2000 Nov 21;97(24):13003-8.

- When the company took a well-known pro-apoptotic peptide cargo[34] and delivered it with an FPP called PYJo2 into MDA468, a triple-negative breast cancer cell line, the result was significantly better delivery than was the case with TAT[35]. This provided good proof of concept that FPPs would work in a cancer setting.
- In mid-2016 Phylogica was able to show, in a collaboration with the Perth-based creators of Sarepta Therapeutics' Eteplirsen drug[36], that Phylomers could be used to improve the delivery of antisense oligonucleotides into cells *in vitro* and *in vivo*[37].

Phylogica is now working on a pipeline of cell-penetrating peptides to treat cancer. The lead candidate is an oncogene called c-Myc which drug developers have been interested in targeting for over 30 years.

Targeting Myc – the lead programme

c-Myc is an important intracellular cancer target. Phylogica indicated its interest in going after c-Myc with a cell-penetrating peptide in October 2013[38]. *MYC* is an oncogene, that is, a cancer-causing gene, located on chromosome 8 that has been of interest to drug developers since its discovery in the early 1980s[39]. The attraction is the role played by *MYC*'s protein product, c-Myc, as a 'master regulator'[40] of both cellular growth and metabolism[41]. c-Myc as an oncoprotein is overexpressed in most human cancers and contributes to the cause of at least 40% of them[42], including solid tumours like prostate[43], breast[44], liver[45], pancreatic[46] and lung[47] cancers, and blood cancers such as Acute Myeloid Leukaemia[48]. Indeed, such cancers appears to be addicted to c-Myc, so that forcing them to go 'cold turkey' is fatal (to the tumour)[49]. Another form of Myc called N-Myc (also called Myc-N) is overexpressed in the devastating childhood cancer neuroblastoma.

Why c-Myc has yet to be properly drugged. The trouble with c-Myc as a drug target is twofold. Firstly, c-Myc is involved in many cellular processes in healthy cells, meaning that any drug must be specifically targeted to cancer

[34] Called $(KLAKLAK)_2$, this peptide targets the mitochondria of cancer cells – see Cancer Res. 2005 Aug 1;65(15):6891-900.
[35] See the company's 7 June 2016 for the Bio meeting presentation entitled '*Expanding new target space inside cell with biologics using Phylomer peptides*', slide 14.
[36] Sarepta Therapeutics (Cambridge, Ma., Nasdaq: SRPT, www.sarepta.com) gained FDA approval in September 2016 for Eteplirsen, an 'exon-skipping' drug for the treatment of Duchenne's Muscular Dystrophy. This drug had originally been created by Professors Steve Wilton and Sue Fletcher at the University of Western Australia. They now work at Murdoch University. Exon skipping involves masking faulty exons with antisense oligonucleotides so that the rest of the relevant protein can assemble. Sarepta has been able to show that cell-penetrating peptides can improve the delivery of its RNA-like phosphorodiamidate morpholino oligomers into muscle cells (see Biochem Soc Trans. 2007 Aug;35(Pt 4):826-8).
[37] See the company's market release dated 15 June 2016 and headlined '*Cell-penetrating Phylomers improve delivery of oligonucleotide drugs inside cells*'.
[38] See the 25 October 2013 Phylogica presentation for the Annual General Meeting, slide 32.
[39] J Virol. 1982 Jun;42(3):773-9. The original gene had been identified in the late 1970s by a pioneer of oncogene research, the American Michael Bishop, in the late 1970s. Bishop won the Nobel Prize for Physiology or Medicine in 1989 with his fellow American Harold Varmus for their oncogene work.
[40] Via various partner proteins, most notably 'MAD' and 'MAX' (see Mol Cell Biol. 1999 Jan; 19(1): 1–11).
[41] This 'master regulator' role is one reason why c-Myc is useful in regenerative medicine when reprogramming somatic cells into induced pluripotent stem cells - see Cell. 2006 Aug 25;126(4):663-76. Epub 2006 Aug 10.
[42] Clin Cancer Res. 2009 Nov 1;15(21):6479-83. Epub 2009 Oct 27.
[43] Genes Cancer. 2010 Jun; 1(6): 617–628.
[44] Genes Cancer. 2010 Jun; 1(6): 629–640.
[45] World J Hepatol. 2010 Jan 27; 2(1): 16–20.
[46] Mod Pathol. 2002 Apr;15(4):462-9.
[47] Cancer Res. 2000 Jan 1;60(1):143-9.
[48] Cancer Chemother Pharmacol. 2015 Jul;76(1):35-46. Epub 2015 May 9.
[49] Genes Cancer. 2010 Jun;1(6):597-604.

cells as well as to the actual intracellular oncoprotein. Secondly, the c-Myc protein is small and lacking in good binding sites for conventional drugs[50], making it difficult to reach even with small molecules.

Omomyc shows the way towards drugging c-Myc. In the early 2000s Dr Laura Soucek, working at Sapienza University in Rome, developed a c-Myc inhibitor called Omomyc. This drug is simply a 90 amino-acid mutant version of a domain of c-Myc[51] that, by binding to the protein, prevents its usual cancer-causing downstream action with other proteins, including its binding to an activation partner called 'Max'[52]. Subsequent work by Soucek et. al., in the laboratory of Professor Gerard Evan[53], identified that the Omomyc protein had some cell-penetrating capability, and, *in vivo*, did not seem to cause any lasting damage to healthy tissue or engender drug resistance[54]. The Omomyc drug is now being developed by a Spanish drug development company called Peptomyc[55]. However, Phylogica's data has shown that the intrinsic cell penetration ability of Omomyc is limited, only allowing *in vitro* activities in the mid-to-high micromolar potency range. Phylogica has shown *in vitro* and *in vivo*, that there are much more efficient means of intracellular delivery of Omomyc:

- In March 2015 Phylogica announced that Oncomyc, when delivered with a cell-penetrating FPP, had killed drug-resistant breast cancer cells *in vivo*, and that this formulation was synergistic with a large and a small molecule drug[56] - the monoclonal antibody drug Erbitux and the small molecule docetaxel[57]. This was the abovementioned PYJ02 FPP, one again being delivered into MDA468 triple negative breast cancer cells. Phylogica's data indicated that the PYJ02/Omomyc combination was effective at nanomolar concentrations[58].
- In November 2015 Phylogica announced that it had followed up the earlier work with a better-powered animal study. This work showed that the FPP-Oncomyc product *in vivo* would bring about a statistically significant reduction in tumour size following direct injection[59]. The model used was the T11 syngeneic mouse model for the particularly aggressive 'claudin low' breast cancer subtype which has a mammary cancer-stem-cell-like phenotype[60]. The Phylogica FPP peptide was now given the code name '1746'.
- In December 2015 Phylogica showed that the combination of FPP(1746)-Omomyc plus an unnamed 'pro-death' peptide – which we now know to be BIM[61] - could increase cell-killing by around six-fold, resulting potencies firmly within the nanomolar range[62]. This work was undertaken in collaboration with Dr Doug Fairlie at La Trobe University in Melbourne.

[50] Nat Rev Cancer. 2014 Apr;14(4):248-62. Epub 2014 Mar 13.
[51] The full c-Myc protein is 439 amino acids in size.
[52] Ordinarily the Myc basic helix-loop-helix zipper domain dimerises with Max and then binding to the DNA E-box. When Omomyc dimerises with Myc it can't bind the E-box – see Cancer Res. 2002 Jun 15;62(12):3507-10.
[53] Professor of Biochemistry at the University of Cambridge.
[54] This work was presented at AACR in April 2016 - see Cancer Res 2016;76(14 Suppl):Abstract nr 2923.
[55] Barcelona, Spain, privately held, www.peptomyc.com.
[56] See the company's market release of 30 March 2015 *headlined 'Phylogica peptide fusion kills aggressive breast cancer cells'.*
[57] Erbitux (generic name cetuximab, see www.erbitux.com) is only FDA approved for head and neck cancer and metastatic colorectal cancer but, in combination with docetaxel, has shown some activity in triple-negative breast cancer – See Int J Cancer. 2016 May 1;138(9):2274-80. Epub 2015 Dec 28.
[58] See the company's 7 June 2016 for the Bio meeting entitled *'Expanding new target space inside cell with biologics using Phylomer peptides'*, slide 17.
[59] See the company's market release of 5 November 2015 *headlined 'Phylogica's intracellular targeting drug achieves significant reduction in tumours in animal model of cancer'.*
[60] Cancer stem cells are cells that can give rise to a tumour. Cancer stem cells traditionally have been difficult to kill with conventional chemotherapy and radiotherapy.
[61] BIM is a pro-apoptotic member of the Bcl-2 family – see EMBO J. 1998 Jan 15;17(2):384-95. For data see Phylogica's 11 January 2017 presentation entitled *'Using novel cell-penetrating Phylomer peptides to access intracellular targets with biologics', slide 57.*
[62] See the company's market release of 9 December 2015 *headlined 'Combination therapy escalates potency of Phylogica peptides against Myc-driven cancer'.*

- During 2016 the company showed, in the Eμ-myc model commonly used to study B cell lymphomas[63], that FPP-Omomyc would reduce the proliferation of lymphoma cells in spleen and bone marrow after intravenous delivery[64].
- Gene expression work has shown that FPP-Omomyc is highly specific to the Myc pathway and doesn't appear to have 'off-target' effects on other pathways such as WNT and Notch[65].

Phylogica believes it has a significantly more powerful Myc inhibitor than Omomyc in the works. By mid-2016 the company had various Phylomers which, when linked to FPPs, seemed to work better than Omomyc *in vitro*. Phylogica called these candidates 'iMyc' peptides and the company is now working towards functional validation of them before taking its preferred candidate into pre-clinical[66] in either late 2017 or early 2018. Currently Phylogica has drugs of its own that would work at high nanomolar to low micromolar concentrations, but is improving the potency of these primary hits by routine affinity maturation approaches. Phylogica's main challenge with this programme is improving the half-life of the candidates which (like most peptides and small proteins) are rapidly cleared from circulation. The company is evaluating a range of technologies, including a recombinant half-life extension technology called PASylation[67] where Phylogica has experienced good results[68]. Phylogica anticipates that the candidate selected will be initially studied in blood cancers such Acute Myeloid Leukemia, one of the lymphomas, or Multiple Myeloma, but it would also have potential application in solid tumours such as breast and lung cancer.

Phylogica will be one of the few companies with a Myc inhibitor in the clinic. There are currently no specifically-developed direct c-Myc inhibitors in the clinic. Dicerna[69], an RNA interference company, had been in early clinical trials with an inhibitor of Myc-encoding messenger RNA (mRNA) until September 2016 when the company discontinued its programme, mainly because its candidate wasn't knocking down enough Myc[70]. Aptose Biosciences[71] has an anti-Myc small molecule called APTO-253 expected to start Phase 1b in 2017. It was originally developed as an inducer of KLF4, a tumour suppressor gene, and its indirect anti-c-Myc mechanism was identified later. Importantly, APTO-253 is not a direct Myc inhibitor since it works upstream to affect expression of the *MYC* gene. The fact that so few companies are going after such a potentially valuable target suggests significant upside should Phylogica yield a candidate with sufficient Myc-antagonism. A direct Myc inhibitor might be expected to have fewer side effects than an indirect inhibitor acting upstream of the target which could affect the transcription of multiple genes in addition to *MYC*. The BET-Bromodomain inhibitors are such a new class of drugs which inhibit *MYC* expression alongside hundreds of other genes, resulting in unintended side effects such as reactivation of

[63] This model, in which mice are transgenic for a c-Myc gene, has been around since the 1980s – see J Exp Med. 1988 Feb 1;167(2):353-71.
[64] See the company's 25 November 2016 Annual General Meeting presentation, slide 19.
[65] See the company's 11 January 2017 presentation entitled '*Using novel cell penetrating Phylomer peptides to access intracellular targets with biologics*', slides 35-38.
[66] See the company's 7 June 2016 for the Bio meeting entitled '*Expanding new target space inside cell with biologics using Phylomer peptides*', slide 27-29.
[67] This technology, developed by a German company called XL-protein GmbH (Friesing, Germany, privately held, www.xl-protein.com), involves a long sequence of the small amino acids proline, alanine, and serine. This 'PAS' sequence, by adopting a random coil structure in aqueous solution, generates the kind of hydrodynamic volume that allows for extensions of protein half-lives. PASylation is better than PEGylation (ie the combining of a drug with polyethylene glycol to increase its half-life) because the latter technology provides the extended half-life of PEG, but, being a single recombinant protein, does not require multiple conjugation/purification steps. Phylogica announced that it was working with XL-protein on PASylation of Phylomers in January 2011, but at that time it was not in the context of cell-penetrating Phylomers.
[68] See the company's Operational Update market release of 4 April 2017
[69] Watertown, Ma., Nasdaq: DRNA, www.dicerna.com. Dicerna is being built on 'DsiRNA', that is, 'Dicer substrate short-interfering RNA' molecules designed to be processed by an enzyme called Dicer. DsiRNA molecules are understood to be effective as gene silencers because Dicer is the initiation point for RNA interference molecules in the human cell.
[70] See the Dicerna press release dated 26 September 2016 and headlined '*Dicerna prioritizes resources to advance GalXC product candidates*'.
[71] San Diego, Ca., Nasdaq: APTO, www.aptose.com.

latent HIV virus[72]. More selective upstream inhibitors may, however, be valuable if they effect both Myc indirectly and another selected oncoprotein target directly. Examples of such targets include STAT5 and Yb1, which Phylogica is also seeking to target with cell-penetrating peptides.

Phylogica's cell-penetrating peptides can hit multiple members of the Myc family. Phylogica has indicated[73] that some of its hits bind to c-Myc and some to N-Myc. This is significant because a Phylomer specifically targeted to N-Myc could be indicated for neuroblastoma, a cancer of the nerve cells and the most common solid tumour, other than brain tumours, in paediatric patients. N-Myc has been known about as a significant prognostic factor for neuroblastoma since the 1990s[74] and is considered the most obvious drug target for the condition could it possibly be drugged[75]. Neuroblastoma is a rare cancer, with perhaps only 700 cases a year in America[76] but a Phylomer indicated for the condition would likely experience a rapid path to market including, potentially, Breakthrough Therapy Designation[77] from the FDA.

Targeting Stat5 and Yb1

Stat5 and Yb1 are also important oncogenes. Phylogica first indicated that it was interested in Stat5 and Yb1 as intracellular cancer targets of interest in November 2014[78]. Like c-Myc, these two targets have been around for a long while, and have a high level of relevance across a range of cancer types, but they have yet to be properly drugged in a direct manner since, like many transcription factors, they are challenging targets for small molecules. Phylogica is collaborating on both Stat5 and Yb1 with researchers at Dana-Farber Cancer Institute in Boston.

- **Stat5** is part of the JAK/STAT pathway of cell signalling molecules that take signals from the cell surface down to the cell nucleus for transcription of various genes into proteins. Stat5 is particularly interesting among the STAT protein family not only because aberrant (ie persistently activated) Stat5 shows up in a wide variety of cancers – including the leukemias, and breast and prostate cancer - but also because it plays a critical role in the function and development of Regulatory T cells[79]. This means that Stat5 may help suppress an anti-tumour immune response[80]. As with Myc, Stat5 is hard to drug with small molecules because it is a transcription factor which lacks hydrophobic binding pockets[81].
- **Yb1** is a 'cold shock protein', whose regular function is to promote intracellular stress adaptation responses[82]. Its role as a transcription factor may contribute to its tendency to show up in various cancers including breast and prostate cancer as well as osteosarcoma[83]. Importantly, it seems to play a role in

[72] A bromodomain is simply a protein that recognizes acetylated lysine residues. Bromodomains from a protein family called BET (Bromodomain and Extra-Terminal) have been found to be regulatory factors for c-Myc. See Cell. 2011 Sep 16;146(6):904-17. Epub 2011 Sep 1.
[73] See the company's Operational Update market release of 4 April 2017.
[74] J Clin Oncol. 1997 Mar;15(3):1171-82.
[75] Cold Spring Harb Perspect Med. 2013 Oct; 3(10): a014415.
[76] Source: www.cancer.org.
[77] Breakthrough Therapy Designation generally means a fast route to approval for new drugs where preliminary clinical evidence indicates a substantial improvement on clinically significant endpoints over available therapies for serious or life-threatening conditions. The Breakthrough Therapy Designation system was put in place by the FDA in 2012.
[78] See the 27 November 2014 Phylogica presentation for the Annual General Meeting, slide 17.
[79] J Interferon Cytokine Res. 2016 Apr;36(4):226-37. Epub 2015 Dec 30.
[80] Immune Netw. 2009 Dec; 9(6): 209–235.
[81] Pharmaceuticals (Basel). 2013 Aug; 6(8): 960–987.
[82] Responding to stresses such as hyperthermia (as the name suggests) but also radiation, drug treatment, and viral infection.
[83] Br J Cancer. 2013 Mar 5; 108(4): 836–847.

multi-drug resistance in a variety of cancers[84]. Yb1 is particularly attractive as a cancer target as it is expressed at low levels in normal cells (compared to cancer cells), minimising the chance of side effects[85]. Interestingly, in 2013 a group in Germany identified a feed-forward loop between Yb1 and *MYC* in multiple myeloma in which *MYC* induces Yb1 expression, while Yb1 itself enhances the translation of *MYC* mRNA into protein, to amplify the *MYC* effect[86]. In 2010, a group in Canada developed a cell-penetrating peptide that acted as a molecular decoy to Yb1 in terms of preventing the protein from being phosphorylated from other upstream elements of the PI3K/AKT pathway[87]. In addition, siRNA targeting of Yb1 is known to significantly inhibit growth of multiple cancer cell types, including colorectal, breast and non-small-cell lung[88].

Phylogica's major pharma partners

As well as its own programmes, Phylogica has worked with five main pharma collaborators over the last seven years:

Roche, December 2009. This collaboration focused on cell-penetrating peptides. Financial terms were not disclosed at the time, however we later learned that Roche paid a US$435,000 option fee and agreed to a 'pre-negotiated 8 figure option exercise deal'. As we noted above, this collaboration was instrumental in helping Phylogica learn how to tackle the cell-penetrating peptide problem. We understand the collaboration, while not formally terminated, was effectively stalled after 2011, apparently due to structural changes. However, Roche's Genentech unit started working with Phylogica in another collaboration in 2014 and Genentech continues to work with Phylogica today (see below).

Medimmune/AstraZeneca, August 2010. This deal is focused on antimicrobial peptides. Initially the work was focused on finding new drugs to attack *Pseudomonas aeruginosa*, a common cause of hospital-acquired pneumonia. Medimmune paid US$0.75m upfront and committed to another US$0.75m in research funding for the first twelve months, while Phylogica can receive up to US$98m in milestones. Phylogica was able to show, early on in the collaboration, that its peptides could kill multi-drug resistant bacteria.

Pfizer, December 2010. This license is focused on peptide-based vaccines. Pfizer paid US$0.5m upfront and Phylogica can receive up to US$134m in milestones. In December 2011 Phylogica announced that the first stage of the collaboration was complete after various candidate peptides had been discovered, and an undisclosed milestone had been paid. A second milestone was reached in April 2012.

Janssen/J&J, January 2012. This collaboration, which, like the earlier Roche collaboration, was focused on cell-penetrating peptides, was initially timed for 18 months of research funding. The first 12 months of the collaboration saw Phylogica conjugate a Janssen drug target to various Phylomers. The last six months saw these

[84] Biochemistry (Mosc). 2006 Feb;71(2):146-54.
[85] Biochem J. 2013 Jan 1;449(1):11-23.
[86] Leukemia 27 (2), 441-450. 2012 Jul 09.
[87] PLoS One. 2010 Sep 10;5(9). pii: e12661.
[88] J Natl Cancer Inst. 2012 Jan 18;104(2):133-46. Epub 2011 Dec 28.

Phylomers screened against targets of interest, leading to an expansion of the collaboration in July 2013. It was the Janssen collaboration that helped Phylogica develop the Endosomal Escape Trap and the Split-GFP Complementation Assay, with approximately A$2.5m in funding support.

Genentech/Roche, August 2014. This collaboration was initially announced by Phylogica as focusing on 'novel approaches to drug discovery'. It transitioned into a formal licensing deal focused on antimicrobials for drug-resistant bacteria in December 2014. Genentech paid US$0.5m upfront and Phylogica could receive up to US$142m in downstream milestone payments. Genentech extended the exclusivity period of the collaboration in December 2016 and paid Phylogica the first US$2m milestone payment. This collaboration is potentially very promising given the incentives now available to developers of new generation antimicrobials under America's GAIN Act of 2012[89].

Phylogica's Brisbane and Cambridge connections

Phylogica is working on a Phylomer-based biosensor at the Institute for Molecular Bioscience in Brisbane. Phylogica announced in July 2013 that it was collaborating with the University of Queensland's Institute for Molecular Bioscience (IMB) on a potential Phylomer-based biosensor device. Biosensors are simply assays that can detect biological molecules and then digitise the signal for further analysis. While biosensors have been around since the 1960s, they started to become commonplace in the early 1990s with the rise of the DNA microarray which allowed thousands of genes to be tracked simultaneously. More recently the protein microarrays have been growing in popularity but there are problems with accuracy in that the capture molecules used for detection (such as antibodies) tend to have structural bias in terms of what they detect. The IMB team collaborating with Phylogica believe that they can overcome this is issue by exploiting the higher quality (affinity) and quantity (hit rate) of Phylomer libraries. Given the massive size of the biochip market – perhaps US$4bn now and growing 20% pa[90] - the commercial upside for Phylogica could be considerable.

Phylogica has developed phenotypic screening expertise with Phoremost in Cambridge. Phylogica announced in March 2011 that it was helping several researchers from the University of Cambridge, led by the Professor Ashok Venkitaraman, form a spin-out drug discovery company[91]. That company, now known as Phoremost[92], has built live-cell assay systems that can identify cryptic intracellular drug targets in phenotypic screens and show how these targets might effectively be drugged. Phenotypic screening is simply the use of cells of a particular disease phenotype to source drugs that can modify that phenotype. Phoremost uses Phylomer libraries (they call them 'Protein-i' libraries) to find hitherto 'undruggable' targets and drug them. The KRAS oncogene is a good example of a target which Phoremost knows how to hit[93]. The Phylomer libraries were formally licensed to Phoremost in

[89] Short for Generating Antibiotic Incentives Now, the GAIN Act provides, among other incentives, an additional five years of market exclusivity – with or without a patent – for agents the FDA names as Qualified Infectious Disease Products. These products can also receive Priority Review and Fast Track Designation.
[90] See *The Rise of Biochips* by Nishitha Chandra, Medical Expo Magazine, 9 June 2015.
[91] For some background to this relationship, see Phylogica's market release dated 4 September 2008 and headlined *'Phylogica partners with leading UK researchers to develop new cancer drugs'*, as well as the market release of 4 March 2009 headlined *'Leading cancer research group validates Phylogica's peptide library advantages'*.
[92] Babraham, Cambridge, UK, privately held, www.phoremost.com.
[93] Sci Rep. 2016 Jul 14;6:29741.

April 2015 in return for a 7.5% equity stake in the company and commercialisation rights. There is potential for further Phylomers to be added to Phylogica's pipeline from Phoremost's drug discovery efforts. Importantly, the deal with Phoremost is non-exclusive, leaving the way open for Phylogica to offer its own phenotypic screening services to the pharma industry in the future.

Phylogica's competition

We see several, mostly privately-held, companies with the potential to rival Phylogica as a source of novel peptide structures or cell-penetrating peptides for use as therapeutics:

- **Aileron Therapeutics**[94]. This company has pioneered the concept of 'stapled peptides' – peptides that are chemically stabilised so that they fold into a therapeutically useful 'alpha helical' shape. Aileron's lead candidate, ALRN-6924, targets the tumour suppressor protein p53[95]. Phylogica would argue that stapled peptides may be cell-penetrating, but it's not clear whether stapling is sufficient to solve the problem of endosomal entrapment.
- **Arrowhead Pharmaceuticals**[96] was a player in anti-cancer peptide-drug conjugates for a while following its 2012 acquisition of Alvos Therapeutics, a company which used phage display to identify its peptide candidates. Since around 2014, however, Arrowhead has been focused on RNA interference. In late 2016 Arrowhead abandoned all its programmes that had involved a cell-penetrating peptide called EX1[97] as a delivery vehicle, because that peptide appeared to be toxic in non-human primates[98].
- **Avelas Biosciences**[99]. This company is working on activatable cell-penetrating peptides that activate in the presence of enzymes secreted at the tumour site. Avelas, is, however, more of a diagnostics company that a therapeutics company – the lead application is GFP-based imaging for cancer surgery.
- **Bicycle Therapeutics**[100]. This company's platform enables the discovery of bicyclic peptides (that is, peptides in which the amino acids form two connected rings) to hit hitherto undruggable targets. At the moment, its focus is 'bicycle-drug-conjugates' to hit cancer targets. Phylogica argues that Bicycle's conjugates don't really compete with cell-penetrating Phylomers, since the aim with drug-conjugate-type products in cancer is generally to use cell-surface receptors and the endosome to get to the cell's 'waste disposal compartment', the lysosome[101].

[94] Cambridge, Ma., privately held, www.aileronrx.com.
[95] Proc Natl Acad Sci U S A. 2013 Sep 3;110(36):E3445-54. Epub 2013 Aug 14.
[96] Pasadena, Ca., Nasdaq: ARWR, www.arrowheadpharma.com.
[97] EX1 is an amphipathic peptide from a component of bee venom called melittin, which has long been known for its ability to break out of the endosome – see Bioconjug Chem. 2003 Jan-Feb;14(1):51-7.
[98] See the Arrowhead press release dated 29 November 2016 and headlined '*Arrowhead Pharmaceuticals focuses resources on subcutaneous and extra-hepatic RNAi therapeutics*'.
[99] La Jolla, Ca, privately held, www.avelasbio.com.
[100] Babraham, Cambridge, UK, privately held, www.bicycletherapeutics.com.
[101] Where the cancer-killing drug in the conjugate can properly blow up the whole cell simply by spilling its arsenal of degradative enzymes.

- **PEP-Therapy**[102]. This company designs cell-penetrating peptides with improved proteolytic resistance[103]. Phylogica would argue that the drug concentrations required, being in double-digit micromolar levels, are too great[104].
- **Permeon Biologics**. This company, part of the stable of the VC house Flagship Pioneering[105], is working on a class of cell-penetrating protein called 'Intraphilins' whose ability to get through the cell wall is based in their having an unusually high net positive charge[106]. The problem with these peptides is endosomal entrapment[107].
- **Sutro Biopharma**[108]. This company, while it is primarily focused today on antibodies and antibody-drug-conjugates, has developed considerable expertise in new peptide manufacturing methods that involve focused libraries of non-natural amino acids. This technology attracted the interest of Pfizer in a collaboration announced in early 2011.
- **Xigen**[109]. This company's ICPT technology allows intracellular delivery of peptides through cell-penetrating carrier motifs. XG-102 for various ophthalmic indications is in Phase 3[110]. Phylogica believes that the Xigen drugs can only work in high concentrations, hence the need for topical delivery.

We see Phylogica's competitive advantage versus these companies as being threefold

1) The company's specific focus on cell-penetrating peptides which specifically address the key challenge with conventional cell-penetrating peptides such as TAT, Penetratin and R9, namely, endosomal entrapment.
2) The company's proprietary technology that ensures that peptides can reach their intra-cellular target.
3) The size of the Phylomer libraries, ensuring a high hit rate on any target of interest.

Valuation – A probability-weighted approach

The chances of a new drug candidate just starting out in the clinic are about one in five. Drug development is risky, and many drug candidates fail either at pre-clinical, in the various clinical stages of development (Phase 1, 2 and 3), or at the regulatory stage when agencies have to make the decision to approve or not approve a drug. For clinical stage drug candidates, there are databases available[111] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One recent estimate is shown in Figure 2:

[102] Paris, France, privately held, www.pep-therapy.com.
[103] Ther Deliv. 2015 Feb;6(2):139-47.
[104] See Mol Pharmacol. 2006 Apr;69(4):1115-24. Epub 2005 Dec 30 and PLoS One. 2013 Apr 23;8(4):e60816Print 2013.
[105] Cambridge, Ma., privately held. See flagshippioneering.com/companies/permeon-biologics-inc.
[106] Chem Biol. 2011 Jul 29;18(7):833-8.
[107] See *Aiming the big molecule arsenal* by Andy Extance, Chemistry World, 13 December 2016.
[108] South San Francisco, Ca, privately held, www.sutrobio.com.
[109] Epalinges, Switzerland, privately held, www.xigenpharma.com.
[110] Pharmacol Res Perspect. 2014 Feb; 2(1): e00020.
[111] Most notably from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).

Figure 2: Historical probabilities of success in drug developments[112]

	SMALL MOLECULES	LARGE MOLECULES
Phase 1	63%	84%
Phase 2	38%	53%
Phase 3	61%	74%
Filing for approval	91%	96%
Phase 1 to approval	13%	32%

Looking at Figure 2, we see most drug candidates make it through Phase 1 (the safety stage of development) – 63% in the case of small molecules and 84% in the case of large molecules. For those that survive Phase 1 and enter Phase 2, only 38% of small molecules and 53% of large molecules are successful. And so on. Some drugs are successful in the clinical stage but then rejected by regulators - 8% (ie 100% minus 91%) for which approval is sought in the case of small molecules, and 4% in the case of large molecules. Multiplying the probabilities in each case suggests that the probability that a drug entering Phase 1 will ultimately gained regulatory approval is around 13% for small molecules and 32% for large molecules.

We argue that the reason large molecules have a historically higher success rate than small molecules are threefold

1) Historically the biotechnology industry from the 1980s worked on 'low-hanging fruit' proteins that were easier to develop;
2) Large molecules (eg monoclonal antibodies) have tended to be better targeted and therefore safer and more effective.
3) Large molecules have often been used in Orphan indications where the hurdles to gain approval are lower.

Peptide therapeutics are classified as large molecules. In our valuation work we have assumed that Phylogica will get drug candidates into the clinic (ie will not experience 'pre-clinical failure') and that those drugs will have the kind of chances of success as those represented in Figure 2. However, for conservatism's sake we have taken a rough midpoint between the small molecule and the large molecule probabilities of ~21%.

Valuation – Discounted cash flows

We develop Discounted Cash Flow (DCF) models for each major programme in Phylogica. As a broad approach, we took the various programmes and collaborations Phylogica is working on, and assumed commercial payoffs from prospective licensing deals of these programmes. Which is to say, we assumed that Phylogica did not seek to become a fully-integrated pharmaceutical company but partnered out its various programmes. We calculated

[112] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

DCFs of these programmes and weighted them by the historic probability of success of early-stage clinical programmes, as per the section above.

Cost of capital. A key question in developing a DCF model is the cost of capital. At NDF Research we use the following approach:

- **Risk-Free Rate**. We use the Australian Ten Year Bond Rate, which is currently 2.6%;

  Market Risk Premia. We use three basic MRPs for Life Science companies - 7.5% for 'medium risk' companies[113], 9.5% for 'high risk' companies and 11.5% for 'speculative' companies. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'. We regard Phylogica as Speculative.

  Ungeared beta. We use an ungeared beta of 1.1.

This approach suggests a discount rate for Phylogica of 15.3% at the present time.

Elements of the commercial payoff for each programme – pre-launch. We estimated, for each Phylogica programme, a base case and an optimistic case for the following elements:

- Level of expenditure required prior to a licensing deal;
- Timing of a prospective licensing deal;
- Level of upfronts in the deal (in US$);
- Level of milestones in the deal (in US$) – we assume that the probability of receiving those milestones declined evenly over time. We weighted the dollar value of milestones towards completion of Phase 2 and 3 as well as including some sales milestones.

For the current collaborations, there were in several cases milestone figures disclosed, but we had to estimate royalty rates.

Commercial life of future products. We assume that a product enjoys 15 years of commercial exclusivity, after which sales erode due to generic competition. While patent protection for a drug is notionally 20 years, patent term extension in the US only covers that part of clinical programme after the filing of an IND. This reduces the exclusivity window by a few years. For large companies marketing blockbuster drugs the window is around 15-16 years[114].

Elements of the commercial payoff for each programme, post-launch. We estimated, for each product that ultimately could be launched from the programmes, a base case and an optimistic case for the following elements:

- Date of product launch in the US;

[113] We assume that 'low risk' in the Life Sciences industry in Australia and New Zealand does not yet exist for most companies given the formative nature of the industry today.
[114] Consider the Roche/Genentech cancer drug Herceptin. It gained FDA approval in September 1998 and enjoyed peak sales in 2014, for a 16-year window. Going further back in time, Amgen gained FDA approval for Epogen in June 1989. Its peak sales year was 2004, another 16-year window.

- Date of product launch for the Rest of the World (RoW);
- Level of royalties, as a percentage of net sales;
- The level of sales (in US$) to be achieved in the US at year five post launch;
- The level of sales (in US$) to be achieved in the RoW at year five post launch;
- The growth rate of sales in both the US and the RoW between years 6 and 14;
- The percentage of the US and RoW markets still held by the product when it goes generic;
- The terminal growth rate of the product franchise.

Currency: We converted the US dollar cash flow streams into Australian dollars at the forecast exchange rates listed in Figure 3:

Figure 3: Our AUDUSD exchange rate forecasts

Half	AUDUSD
30/06/2017	0.757
31/12/2017	0.747
30/06/2018	0.737
31/12/2018	0.728
30/06/2019	0.718
31/12/2019	0.709
30/06/2020	0.700
Later periods	0.700

Tax: We used the Australian corporate tax rate of 30%.

'Platform discount'. Many partnership arrangements that allow pharma companies to access a platform are for evaluation purposes and not focused on particular products. The probability that a partnership will become dormant is higher for these kinds of deals. Consequently, we assume that only one in five of Phylogica's 'platform deals' will translate into products in the clinic, and therefore value only 20% of the notional upside of such deals in our overall valuation of Phylogica.

Valuation – Project parameters

Figure 4: Myc project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2020	2019
License upfront (USDm)	50	100
License milestones (USDm)	250	500
Royalty rate	10.0%	15.0%
Earliest approval	2025	2024
Peak sales (USDm)	1,100	1,800

Figure 5: Stat5 project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2021	2020
License upfront (USDm)	25	50
License milestones (USDm)	100	200
Royalty rate	7.0%	11.0%
Earliest approval	2027	2026
Peak sales (USDm)	700	1,200

Figure 6: Yb1 project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	10	5
License date	2022	2021
License upfront (USDm)	25	50
License milestones (USDm)	100	200
Royalty rate	7.0%	11.0%
Earliest approval	2029	2028
Peak sales (USDm)	700	1,200

Figure 7: Medimmune project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	0	0
License date	2011	2011
License upfront (USDm)	0	0
License milestones (USDm)	98	98
Royalty rate	4.0%	7.0%
Earliest approval	2028	2027
Peak sales (USDm)	700	1,200

Figure 8: Pfizer project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	0	0
License date	2011	2011
License upfront (USDm)	0	0
License milestones (USDm)	134	134
Royalty rate	4.0%	7.0%
Earliest approval	2028	2027
Peak sales (USDm)	400	600

Figure 9: J&J project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	0	0
License date	2012	2012
License upfront (USDm)	0	0
License milestones (USDm)	130	130
Royalty rate	4.0%	7.0%
Earliest approval	2028	2027
Peak sales (USDm)	400	600

Figure 10: Genentech project parameters

	Base case	Optimistic case
PYC investment required (AUDm)	0	0
License date	2015	2015
License upfront (USDm)	0	0
License milestones (USDm)	140	140
Royalty rate	4.0%	7.0%
Earliest approval	2028	2027
Peak sales (USDm)	700	1,200

Valuation – The next funding round

Phylogica is funded until well into 2018. Phylogica held A$7.08m in cash as at March 2017. At the burn rate prevalent in calendar 2016 (~A$520,000 per month) this would fund the company well into mid-2018. Phylogica's last four annual R&D tax rebates from the Australian government have ranged in size from A$1.8m to A$2.3m[115].

We recommend two years funding. Obviously, for pre-revenue companies, best practice dictates the longest-possible funding window. We believe a 2.5-year window, calculated without regard to the potential for tax rebates,

[115] A$1.8m in the September 2013 quarter, A$2.0m in the March 2015 quarter, A$2.1m in the December 2015 quarter and A$2.3m in the March 2017 quarter.

works well for Phylogica, which suggests that the next raising ought to seek A$15m. This funding could see Phylogica significantly re-rate by moving a Myc inhibitor product into or close to the clinic.

Valuing the next raising. We assumed for the purposes of this valuation that Phylogica would raise A$15m at 3 cents per share.

Valuation – Putting it all together

We completed our valuation of Phylogica by adding.

1) The individual programme DCFs;
2) The notional value of the tax losses (ie the A$45m in retained losses multiplied by the 30% Australian corporate tax rate);
3) The current cash on hand (A$7.08m as at March 2017);
4) The notional value of A$6m p.a. in corporate overhead, discounted in perpetuity at the discount rate calculated above, and adjusted for tax.
5) The $0.8m that can be received from option exercises by November 2019;
6) A$15m in cash to be raised to fund the next stage of development.

Valuating range 5.2 cents / 14.2 cents. As per Figure 11, we value Phylogica at 5.2 cents per share base case and 14.2 cents per share optimistic case. We regard 10 cents per share as a reasonable mid-range value of the company.

Valuing the future optionality of the platform. Drug discovery platforms, once they demonstrate apparent sustainability though a number of successful pharma partnerships, tend to generate a share price premium for future products beyond those that are in clinical or pre-clinical development. Typical examples include:

- Alnylam Pharmaceuticals[116] (US$4.7bn market capitalisation[117]) and Ionis Pharmaceuticals[118] (US$6.0bn), for antisense-based drugs;
- Genmab[119] (US$12.2bn) and MorphoSys[120] (US$1.8bn), for monoclonal antibodies;
- Nektar Therapeutics[121] (US$2.9bn), for pegylated drugs;
- Seattle Genetics[122] (US$9.7bn), for antibody-drug conjugates;

[116] Cambridge, Ma., Nasdaq: ALNY, www.alnylam.com.
[117] Market capitalisations 28 April 2017 close on Nasdaq and elsewhere.
[118] Carlsbad, Ca., Nasdaq: IONS, www.ionispharma.com.
[119] Copenhagen, Denmark, Nasdaq OMX Copenhagen: GEN, www.genmab.com.
[120] Planegg, Germany, Xetra: MOR, www.morphosys.com.
[121] San Francisco, Ca., Nasdaq: NKTR, www.nektar.com.
[122] Bothell, Wa., Nasdaq: SGEN, www.seattlegenetics.com.

- Kite Pharma[123], for immuno-oncology involving the engineering of T cells (US$4.5bn).

We have included no future platform optionality for Phylogica in our valuation, because we believe the company is not commercially advanced enough to warrant this. Having said that, we believe that the execution of licensing deals with substantial upfronts could allow analysts to reasonably add such optionality.

Figure 11: Our valuation of Phylogica

	Base case	Optimistic case
Myc (A$m)	69.0	206.7
STAT5 (A$m)	19.4	64.9
YB1 (A$m)	15.1	52.1
Medimmune (A$m)	4.3	6.6
Pfizer (A$m)	5.4	7.2
J&J (A$m)	5.3	7.0
Genentech (A$m)	5.9	8.5
Total programme value	124.4	352.9
Value of tax losses	13.0	13.0
Corporate overhead	-27.5	-27.5
Cash now (A$m)	7.1	7.1
Cash to be raised (A$m)	15.0	15.0
Option exercises (A$m)	0.6	0.6
Total value (A$m)	132.6	361.1
Total diluted shares (million)	2,542.7	2,542.7
Value per share	$0.052	$0.142
Valuation midpoint	$0.097	
Share price now (A$ per share)	$0.045	
Upside to midpoint	115.6%	

[123] Santa Monica, Ca., Nasdaq: KITE, www.kitepharma.com. CAR-T is widely considered one of the Next Big Things in cancer immunotherapy. It is a form of 'adoptive' T cell therapy in which a patient's own T cells are engineered to increase their cancer-fighting properties, and then returned to the patient. CAR-T involves engineering of T cells carrying chimeric antigen receptors (CARs), these receptors being a combination of antibodies and T cell signalling molecules.

Comparable companies to Phylogica

We think the following publicly-traded companies are comparable to Phylogica and provide a good cross-check valuation[124]:

Figure 12: Comparable companies to Phylogica

Company	Location	Code	Market cap (USDm)	Web
Ra Pharmaceuticals	Cambridge, Ma.	Nasdaq: RARX	559	www.rapharma.com
Adaptimmune Therapeutics	Abingdon, UK	Nasdaq: ADAP	489	www.adaptimmune.com
Zealand Pharma	Glostrup, Denmark	Nasdaq OMX Copenh	467	www.zealandpharma.com
Minerva Neurosciences	Cambridge, Ma.	Nasdaq: NERV	275	www.minervaneurosciences.com
Compugen	Tel Aviv, Israel	Nasdaq: CGEN	208	www.cgen.com
vTv Therapeutics	High Point, NC	Nasdaq: VTVT	179	www.vtvtherapeutics.com
Protagonist Therapeutics	Milpitas, Ca.	Nasdaq: PTGX	162	www.protagonist-inc.com
Phylogica	Perth, Australia	ASX: PYC	67	www.phylogica.com.au

- **Adaptimmune Therapeutics**. This company, a pioneer of the immuno-oncology approach called 'adoptive T cell therapy', has been built on technology for engineering increased affinity T-cell receptors, achieved via *in vitro* molecular evolution using phage display. The company's lead product is an engineered TCR to the cancer antigen NY-ESO-1, for which it is in Phase 2/3 studies in synovial sarcoma and in multiple myeloma. A major partnering deal with GSK in June 2014 could see that company could pay US$350m over the period to 2021 for enhanced TCR-engineered autologous T cells targeting NY-ESO-1 and other targets.
- **Compugen**. This genomics-based drug discovery company identifies candidates, including peptides using elaborate *in silico* discovery processes[125]. Its main area of focus is immuno-oncology and autoimmune diseases. Compugen developed a discovery platform to predict cell penetrating peptides for drug delivery in 2010.
- **Minerva Neurosciences**. This CNS drug developer has clinical candidates in schizophrenia, major depressive disorder and insomnia. MIN-301, the company's investigational neuregulin-1 compound, is in pre-clinical development for the treatment of Parkinson's Disease. The company has a platform allowing it to search through libraries of neuregulin peptides looking for hits in various CNS conditions.
- **Protagonist Therapeutics**. This company's platform, originally developed at the University of Queensland, allows the development of oral peptide therapeutics, beginning with the selection of peptide scaffolds as starting points against specific targets. The company's lead compound is PTG-100, an α4β7 antagonist for the treatment of inflammatory bowel disease. This candidate is in Phase 1.

[124] Market capitalisations 28 April 2017 close on Nasdaq and elsewhere.
[125] Biopolymers. 2010;94(6):701-10.

- **Ra Pharmaceuticals**. This company's platform enables the discovery of synthetic macrocyclic peptides. The lead RA101495 peptide, which targets Complement C5, has completed Phase 1. Other compounds are pre-clinical. A 2013 collaboration with Merck & Co. is worth US$200m in upfronts and research funding.
- **vTv Therapeutics**. This company's TTP Translational Technology is an automated drug discovery process that moves genomic and proteomic data into small molecule therapeutics. The platform works well in terms of discovering drugs that block protein-protein interactions. vTv's lead Azeliragon compound seems to slow cognitive decline of mild Alzheimer's. It is now in Phase 3.
- **Zealand Pharma**. This company, focused on peptide drugs, developed Adlyxin, a GLP-1 agonist for the treatment of Type-2 diabetes FDA-approved in 2016 and marketed by Sanofi. Zealand's pipeline includes a number of peptides in Phase 2 including Glepaglutide, a GLP-2 analogue for the treatment of short bowel syndrome (SBS).

While providing a good example of what the market can achieve if it favours a peptide story, we chose not to include the Japanese company **Peptidream**[126] in our list of comparables. Peptidream has been built on the 'Flexizyme', which is an artificial ribozyme[127] that can charge virtually any amino acid onto any transfer RNA *in vitro*[128]. What this allows is the synthesis of peptides containing multiple distinct non-standard amino acids, allowing in turn peptide libraries of almost limitless chemical diversity to be created. On top of this, Peptidream can easily make cyclic peptides from its library. Big Pharma clearly likes the combination of these two capabilities[129], as evidenced by collaborations with many leading pharma companies such as Genentech, Lilly and Bristol-Myers Squibb. The reason we have chosen to exclude Peptidream is that its current market capitalisation of US$3.4bn on the Tokyo Stock Exchange[130] makes it something of an outlier given that the earliest clinical programme, a BMS programme in the immuno-oncology space, has yet to make it into Phase 2.

Minimum valuation – level of previous investment

The replacement value of Phylogica is ~A$50-60m. We tracked previous investment into the company and estimate that around A$50-60m (US$38-45m) has been put into the Phylomer platform beginning in the late 1990s:

- Phylogica estimated in 2005 that A$4m in grants and infrastructure funding had supported the early efforts by Watt et. al. to develop the Phylomer platform, after which A$3m was invested in seed capital prior to the IPO[131].

[126] Tokyo, Japan, TYO: 4587, www.peptidream.com.
[127] Ribozymes are enzymes within cells that help string amino acids into proteins.
[128] Nucleic Acids Symp Ser (Oxf). 2006;(50):35-6.
[129] Methods Mol Biol. 2012;805:335-48.
[130] 28 April 2017 close.
[131] Source: Phylogica IPO prospectus dated 22 February 2005, page 9.

- Around A$47m has been invested in various equity and convertible note funding rounds from 2005 onwards, at an average 2.5 cents per share (see Figure 13).

We would regard A$50m as a reasonable 'end of the world valuation' case for Phylogica, in the event that a major market downturn serious depressed the stocks of all publicly-traded Life Science companies.

Figure 13: Previous capital raisings by Phylogica

Date	Shares (million)	% of current shares on issue	Price (AUD)	Raised (AUDm)	Type of raising
Mar-05	25	1.3%	0.200	5.0	IPO
Sep-06	13	0.6%	0.290	3.7	Placement
Jun-07	21	1.0%	0.250	5.2	Option exercise
Apr-09	52	2.6%	0.050	2.6	Placement
Dec-09	20	1.0%	0.100	2.0	Placement
Aug-10	47	2.4%	0.050	2.4	1 for 5 rights issue
Mar-11	88	4.4%	0.059	5.2	Placement
Dec-11	41	2.0%	0.053	2.1	Placement
Nov-13	401	20.1%	0.015	6.0	2 for 3 rights issue
Jul-15	1,002	50.4%	0.010	10.0	1 for 1 rights issue
Total	1,709	85.9%	0.026	44.3	
Apr-09 to Nov-12	174	8.7%	0.017	2.9	Convertible notes
Total	1,883	94.6%	0.025	47.2	

Re-rating Phylogica

Traditionally there has been an 'ASX discount' for publicly traded Life Science companies. While ASX has been a reasonably reliable capital market for pre-revenue Life Science companies since around 1999, traditionally Life Science companies traded on the ASX have traditionally had a lower market capitalisation than would be the case if the company were based in the US and traded on Nasdaq. We see three main reasons for this:

1) Australia is more of a 'mining and oil' marketplace in terms of the natural affinity of its investor base.
2) There are relatively few Life Science companies that have grown to maturity from Australia.
3) Most companies go public in Australia at a level of development way below that of their US brethren, who tend to get more access to VC money.

Closing the ASX discount for Phylogica. We see four factors as helping to close the ASX discount for Phylogica over time:

1) **Sophisticated US and European investors on the register**. Australian-born ASX-listed companies that have made the leap towards a more 'US-style' investor base such as Mesoblast (ASX: MSB) and Viralytics

(ASX: VLA) have tended to raise money from sophisticated US investors that are very familiar with the Life Sciences space.

2) **Products going into the clinic**. We believe that the arrival of a Phylomer cell-penetrating peptide in the clinic can provide significant validation for the platform given the difficult nature of the targets Phylomers can potentially drug.
3) **New leadership**. Phylogica has been without a CEO since the resignation of Dr Richard Hopkins[132] in July 2016. The appointment of a new CEO, particularly if that CEO comes with a global pharma industry background, could increase investor confidence in Phylogica.
4) **Improvement in the Nasdaq market**. The Nasdaq Biotechnology Index peaked at 4,165.9 points on 20 July 2015, after having gained 35% p.a. over the previous 6 years. By 27 June 2016 it had declined by 30%, to 2,524.4 points. While the market has more-or-less stabilised and shown signs of recovery since June 2016 – at 3,114.67 it was up 23% by the end of April 2017 – the 2015/16 sell-off will have led many sophisticated investors to be a little more selective in the companies they back.

Immuno-oncology as an illustration of the ASX-discount, and how this discount can be overcome. Currently on Nasdaq and other markets companies with a major focus on immuno-oncology have an average market capitalisation of >US$500m and a median market capitalisation of >US$200m. We see the market for the stocks of companies involved in immuno-oncology as illustrating two points:

- Imugene (ASX: IMU) as an example of the 'ASX discount'
- Viralytics (ASX: VLA) as an example of how the ASX discount can be overcome.

Imugene shows the ASX discount. Imugene, with a current market capitalisation of only US$28m[133], is developing the potential in immuno-oncology of B-cell peptide vaccines, that is, peptides that stimulate a polyclonal antibody response to the target in question. It is currently entering Phase 2 with a peptide targeting the cancer antigen Her2, with a first indication in Her2-positive gastric cancer. Imugene's current market capitalisation prices it well below comparable companies such as Scancell[134], in Phase 2 in melanoma (US$38m), or Affimed[135] (US$98m), in Phase 2 in Hodgkin's Lymphoma. We see this as a prime example of the typical ASX discount.

Viralytics shows how the ASX discount can be overcome. Viralytics, with a current market capitalisation of US$190m[136], is developing an oncolytic virus product called Cavatak for the treatment of various cancers. As well as direct action and lysis of cancer cells Cavatak has an immuno-oncologic mechanism of action in which the infection promotes tumour inflammation. Cavatak is currently in various Phase 1 and 2 studies. Viralytics was impacted by the ASX discount until early 2015. Indeed, in early August 2011, it was capitalised at a mere US$32m. Viralytics was able overcome the discount through the following factors that played out over a three-to-four-year period:

- **Highly-priced comparables with good data:** The January 2011 acquisition of Biovex by Amgen for US$1bn provided a good international comparable for oncolytic virotherapy. In March 2013 Amgen read

[132] Now CEO of the cancer drug developer Pharmaust (Perth, WA, ASX: PAA, www.pharmaust.com).
[133] 28 April 2017 close.
[134] Nottingham, UK, LSE: SCLP, www.scancell.co.uk.
[135] Heidelberg, Germany, Nasdaq: AFMD, www.affimed.com.
[136] 28 April 2017 close.

out favourable Phase 3 results from the Biovex oncolytic virotherapy and that product gained FDA approval as Imlygic (talimogene laherparepvec) for the treatment of melanoma in October 2015.

- **New CEO with pharma experience**. In January 2013 Viralytics hired Dr Malcolm McColl, a former executive of CSL (the world's 28th largest pharma company) and the Melbourne-based drug developer Starpharma, as the company's new CEO;
- **Good data**. In September 2013 Viralytics reported that Cavatak's Phase 2 CALM study in metastatic melanoma had met its Primary Endpoint, with 10 patients from a total of 54 evaluable patients experiencing immune-related Progression Free Survival at six months. This demonstrated that Viralytics' oncolytic virotherapy could be clinically effective.
- **A transformative capital raise.** The January 2014 capital raising of A$27m brought a number of sophisticated US institutions onto the register.
- **Evidence that the company was part of 'tomorrow's therapy'**. In December 2014 Viralytics commenced the Phase 1 MITCI (Melanoma Intra-Tumoural Cavatak and Ipilimumab) study combining Cavatak with the Bristol-Myers Squibb checkpoint inhibitor drug Yervoy. This showed that Viralytics had joined the 'wave of the future' as a genuine immuno-oncology player. Not surprisingly, given the popularity of immuno-oncology with Life Science investors around this time, Viralytics stock took off after the JP Morgan meeting the following month.

We believe that Phylogica can have a similar experience to Viralytics, with the appointment of a new CEO and the next capital raising critical elements in the transformation. While it will be a while before Phylogica has clinical data, it can leverage substantial *in vitro* and *in vivo* data to the same effect given the breakthrough nature of cell-penetrating peptides that can achieve endosomal escape.

Phylogica's emerging leadership team

Phylogica has some capable people associated with it. We noted above that Phylogica has been without a CEO since July 2016. It does, however, have a core group of capable people around which it can build:

- **Dr Paul Watt**, Founder and Chief Scientific Adviser, was the main inventor behind not only the original Phylomer platform and its more recent iterations, but, more importantly, the enabling technologies such as the Split-GFP Complementation Assay that have allowed Phylogica in recent years to become a world leader in cell-penetrating peptides. In our experience, the level of innovation Watt has demonstrated over many years is rare in the biotech industry.
- **The Phylogica board**, which includes Watt, has a variety of skillsets suitable to building value from a drug discovery platform. Two new board members named in April 2017 – **Dr Robert Hayes** and **Dr Rick Kendall** – bring particularly enviable resumes. Hayes was Head of Biologics at Amgen, one of the world's largest pharma companies[137], and before that was a 'Venture Leader' at Janssen. Kendall, who was

[137] The world's 11th largest pharma company (source: Pharm Exec's Top 50 Companies 2016 by William Looney, Pharm Exec, 26 July 2016), with 2015 sales of US$20.9bn.

previously Executive Director of Oncology Research at Amgen, is currently VP of Research at the aforementioned CAR-T platform company Kite Pharma. Chairman **Stephanie Unwin**, currently General Manager Commercial of Synergy, the Perth-based energy retailer, brings governance skills through her background in corporate law. **Dr Bernard Hockings,** Phylogica's largest shareholder with 31% of the company, works with pharmaceuticals daily as a practising cardiologist.

Appendix I – Background to the platform

The Phylogica technology story starts with Paul Watt, who around 1997 was working at Perth's Telethon Institute for Child Health Research. Around that time, he had some drug discovery ideas regarding the old yeast two-hybrid approach to drug discovery and started collaborating on these with Dr Erica Golemis of the Fox Chase Cancer Centre in Philadelphia[138].

Yeast two-hybrid is an elegant way of discovering new proteins that may be therapeutically useful. Consider the case of a researcher with some proteins that seem to be involved in the process of a particular disease. That researcher will want to find other proteins with which the disease proteins interact, which may therefore impact on the course of the disease. Or he will also be interested in finding disruptors of those interactions. One of the ways to solve this problem is to use a gene from baker's yeast (scientific name *Saccharomyces cerevisiae*) such as GAL4, whose function is to create an enzyme called beta-galactosidase. GAL4 comes in two parts, one called the 'activating domain' and another called the 'binding domain'. The two have to be in physical contact with each other in order to create beta-galactosidase. To one domain is bound copies of the gene which creates one of the disease proteins. To the other domain is bound the genes coding for proteins obtained from the researcher's protein libraries. Both GAL4 domains are then placed inside yeast cells. The two domains will only be able to make beta-galactosidase if they can get together, and this can only happen if the candidate drug protein on one domain interacts with the disease protein on the other. The reasons biologists favour beta-galactosidase in assay systems is that it can turn another substance called X-gal into an insoluble blue dye, making it a good 'reporter gene'. In a yeast two-hybrid experiment, so long as X-gal is in the mix, the researcher doing the work can find out if two proteins are interacting (forward two-hybrid), or an antagonist is stopping an interaction (reverse two-hybrid), simply by looking at his petri dishes of yeast cells for the blue-coloured 'colonies' of yeast cells or lack thereof. Phylogica's yeast two hybrid screening platform didn't use GAL4, being an alternative system based on the LexA DNA binding domain, but did include a beta-galactosidase reporter gene and X-gal assays, in addition to growth media selections for complementation of mutations in essential yeast genes.

Paul Watt and his colleagues had ideas for better libraries to be run through yeast two-hybrid systems. Neither forward or reverse yeast two-hybrid was invented by Paul Watt. Professor Stan Fields, an American biologist now at the University of Washington, pioneered the yeast two-hybrid approach in 1989[139], and about the same time Roger Brent at Harvard developed an alternative version of two hybrid screening[140], like the one which

[138] Erica Golemis is now the Fox Chase's Deputy Chief Scientific Officer.
[139] Nature. 1989 Jul 20;340(6230):245-6.
[140] Cell. 1993 Nov 19;75(4):791-803.

the Watt group later modified. Around 1996 Dr Marc Vidal, then at Massachusetts General Hospital and now at Dana-Farber Cancer Institute, reported the first reverse two-hybrid system[141]. What Paul Watt and his colleagues set out to find in the late 1990s was a collection of proteins that would yield a better set of 'hits' when run through a two-hybrid-based high-throughput screening processes. Watt's thinking was as follows:

1) The best way to block the disease-causing interaction of two proteins is with another small, folded protein or a peptide, because only such proteins or peptides will have the surface area and the complementary shapes required to block the interface of the interacting peptides, and folded proteins will have ideal structures to do so;
2) The best place to find such high-affinity proteins and peptides is within proteins encoded by genomes of various microorganisms to be found at extreme ends of the evolutionary tree. Not only will such proteins be stable, evolution having permitted the survival of that protein over the eons (in some cases in extreme environments), they will be much more capable of binding irreversibly to a human protein. Here Watt reasoned that whereas many natural protein interactions in the human body had evolved 'intermediate affinities' in order to be reversible or at least to allow competition with other proteins – so as to keep all the proteins in a healthy equilibrium – a slime mould, for example, would be under no pressure to evolve such affinities to human proteins. Moreover, the cryptic interfaces of human proteins, which interfered with human targets, would have been selected against, thereby limiting the diversity of hits expected from a human-genome-derived library. The most diversity between proteins is found in ancient bacterial and archaeal species, which are considerably more different from one another than are human proteins.
3) Since such high-affinity proteins and peptides were of non-human origin and bound to proteins which were distinct from their natural partners, they were be more likely to have as-yet-unpatented sequences. Since such binding was unexpected, two-hybrid-based trawling of extremophile databases provided an arguable 'inventive step' and thereby a potential defence against a claim that was subsequently fought out in a notable US Supreme Court case with relation to DNA sequences[142] - namely, that natural sequences were unpatentable in their native context.
4) At only 15 to 50 amino acids in size, the probability was minimised that such peptides, should they prove cell penetrating, would have immunogenic T-cell epitopes that could result in unintended immune reactions. By contrast, larger foreign proteins almost always contain such epitopes.

Watt el. al. started with already-sequenced bacterial genomes. Having decided that age-old single cell organisms possessed what he was looking for, Watt went out and obtained, from the public domain, the sequences of many of the two dozen or so genomes of such creatures that had been fully sequenced by the late 1990s, including *Methanococcus jannaschii*, an 'extremophile' sequenced in 1996 that lives near hydrothermal vents two and a half kilometres below sea level[143]; *Synechocystis* PCC 6803, a blue-green algae sequenced in 1997 and famed for its photosynthesis skills[144]; *Treponema pallidum*, the syphilis bacterium, which was sequenced in

[141] Proc Natl Acad Sci U S A. 1996 Sep 17;93(19):10315-20.
[142] The case was Association for Molecular Pathology v. Myriad Genetics, Inc., decided in June 2013.
[143] Science. 1996 Aug 23;273(5278):1058-73.
[144] Plant Cell Physiol. 1997 Nov;38(11):1171-6.

1998[145]; and *Aquifex aeolicus*, another 'Class of 1998' organism found in the hot volcanic streams of America's Yellowstone National Park[146].

Watt et. al. brought their genomes together and 'shotgun cloned' them to make a large collection of proteins. Shotgun cloning is simply the use of old-fashioned recombinant DNA technology, firstly to cut up the strings of DNA with 'gene scissors' called restriction enzymes (whose natural function is to sever DNA at certain sequences), and then to 'paste' the individual pieces into bacteria-residing circular pieces of DNA called plasmids. The plasmids contained the genetic blueprints of the 100 million or so proteins the team was thus able to survey from the combined genomes of bacteria from extreme environments. Once these plasmids were in hand, the team could then create various protein libraries with them using their yeast two-hybrid systems. So, for instance, Watt and his Telethon Kids Institute colleagues were interested in various proteins to be found within cells that they believed were good drug targets. They fed their proteins through a forward two hybrid system against these targets and were able to build a library of interesting 'interactor' proteins. A reverse two hybrid system yielded a 'blocker' library against the same targets, but only those proteins that wouldn't interfere with healthy protein function, as indicated by a forward two-hybrid screen, got into that library. Meanwhile the Watt laboratory also created a much larger 'phage display' library. Here, the proteins were spliced into a strain of 'bacteriophage' - a virus that afflicts bacteria - thereby making it convenient for the proteins to be screened against cell-surface targets of interest. The Watt team decided to call the contents of their libraries 'Phylomers'. The 'phylo' part, from the Greek word phulon, meaning 'racial group', refers to the fact that Watt et. al. obtained their peptides from organisms of diverse 'phylogenies', that is, evolutionary origins.

The Phylomer libraries have been gradually expanded over the years as Phylogica's scientists added new genomes to their shelves, and tried out new ways of identifying individual peptides from the genomes. By 2006 there were 260 million distinct Phylomer peptides from 25 bacterial genomes[147]. Today the libraries contain over 400 billion, from >35 bacterial genomes. Around 2006 Phylogica started working on synthetic Phylomer libraries that made use of informatics to select the right genomes first, thereby making sure that certain kinds of structures were represented in a library. This know-how resulted in two basic kinds of libraries for Phylogica – the 'high complexity' libraries' from Paul Watt's original ideas, and the 'focused' libraries made up of, say, just macrocyclic peptides[148], or peptides with certain structural features, for example comprised from segments of viral genomes[149].

The Phylomer libraries always yield a surprisingly high level of hits. The sheer size of the libraries means that when Phylogica's scientists go looking for Phylomers against a target of interest they tend to find a lot. For example, in the original Roche collaboration looking for cell-penetrating peptides that could penetrate above the blood-brain barrier, Phylogica turned up close to 1,000 hits in the screen, of which close to 50 were found, upon analysis using FACS[150], to have penetrated the cell. A further 11 hits were identified via microscopy[151]. In each case

[145] Science. 1998 Jul 17;281(5375):375-88.
[146] Nature. 1998 Mar 26;392(6674):353-8.
[147] See the company's 22 September 2006 market release headlined '*Phylogica announces major expansion of drug source*'.
[148] See the Phylogica market release dated 17 July 2015 and headlined '*Phylogica and the University of Queensland receive $670k grant to develop macrocyclic Phylomer drugs*'.
[149] See the company's November 2013 corporate presentation.
[150] Short for Fluorescence-Activated Cell Sorting, FACS sorts a heterogeneous mixture of cells into two or more containers, one cell at a time, based upon the fluorescent characteristics of each cell.
[151] See Phylogica's 24 November 2011 AGM presentation, slide 14.

these hits showed up before affinity maturation could further improve the binding of the candidates. Similarly, the collaboration with Phoremost in Cambridge has yielded extraordinary hit rates in multiple phenotypic screens targeting different biological pathways involved in cancer.

Phylogica initially focused on 'exotic' targets, particularly for challenging indications like stroke. As we note above, Phylogica has been focused since around 2010 on cell-penetrating peptides. For the previous five years, Phylogica had worked on a number of in-house projects that showed, *in vitro* and *in vivo*, that it could successfully drug complex protein-protein interactions with potentially large commercial payoffs:

- **c-Jun and AP-1**. An enzyme called JNK (short for c-Jun N-Terminal Kinase) is known to be involved in neuronal cell death during or following a stroke[152]. In 2004 and 2005 Phylogica's scientists used their libraries to identify a large number of Phylomers that could act on c-Jun and disrupt its dimerisation without disrupting other, potentially positive effects of JNK in normal cells. There is a potential drug to treat stroke or neurodegeneration in this Phylomer collection. One of c-Jun's binding partners is a transcription factor called AP-1. The latter molecule, as well as being an important neuroprotection target[153], is also involved in lung inflammation resulting from acute respiratory distress syndrome (ARDS) and septic shock. Around 2007 Phylogica developed Phylomers targeting AP-1 and did discovery and pre-clinical work in a variety of indications. The ARDS data was particularly interesting[154].

- **Anti-microbials.** Phylogica developed anti-microbial Phylomers to treat a variety of infections, including infection by the opportunistic pathogen *Acinetobacter baumannii*[155]. This was useful in demonstrating the ability of peptides to join in the fight against antimicrobial resistance.

- **CD40L.** CD40 is a so-called co-stimulatory molecule found on antigen-presenting cells in the immune system. Phylogica developed a number of peptide antagonists to CD40L, which, as its name suggests, is the ligand (ie binding partner) to CD40. These Phylomers have potential as anti-inflammatories. From around 2007 the company was talking about anti-CD40L Phylomers as potential drugs for the treatment of Rheumatoid Arthritis[156]. These days there appears to be more pharma industry interest in agonists of CD40 for use in immuno-oncology[157].

Appendix II – A Phylogica glossary

Affinity – The binding ability of a drug to its designated target.

Amino acid – The building blocks of peptides and proteins. There are around 20 naturally-occurring amino acids.

[152] Nat Med. 2003 Sep;9(9):1180-6. Epub 2003 Aug 24.
[153] See Brain Res. 2010 Nov 11;1360:8-16. Epub 2010 Sep 15.
[154] See the Phylogica market release dated 5 July 2007 and headlined *'Phylogica expands pipeline to acute lung distress'.*
[155] See the company's market release of 24 August 2007 and headlined *'Phylogica enters anti-microbial field'.*
[156] See the Phylogica market release dated 15 May 2007 and headlined *'Phylogica generates multiple drug candidates for treatment of Rheumatoid Arthritis'.*; also, see the Phylogica market release dated 10 October 2007 and headlined *'Biological validation of lead compounds in Rheumatoid Arthritis programme'.*
[157] Clin Cancer Res. 2013 Mar 1;19(5):1035-43.

Antibodies – Proteins in the blood that can attach themselves to antigens, thereby neutralising them. Monoclonal antibodies are often used as drugs but cannot get into cells by their own accord.

Antigen – The 'bad guy' substance that is detected as 'foreign' by the cell stimulates the immune system to respond to the perceived threat.

Apoptosis – 'Programmed' cell death, that is, death that is naturally-occurring. Cancer cells tend to avoid apoptosis.

Bioactive – A drug that appears to be able to treat disease by hitting disease-causing proteins.

Biologic – A next generation large molecule (eg. peptide, protein or nucleic acid) drug. Biologics represent the fastest growing class of drugs today and include antibodies and peptides.

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.

Cell-Penetrating Peptide (CPP) – Peptides able to make it through the membrane of the cell.

c-Myc – An oncoprotein encoded by the master control oncogene *MYC* (italics used to distinguish the gene from the protein) which Phylogica is seeking to drug with an FPP.

Composition-of-matter – A claim in intellectual property law over the chemical composition of a new drug.

Dalton – A unit of mass, defined as one-twelve of the mass of a carbon-12 nucleus. Molecular weight is measured in daltons. A drug less than 500 daltons in size is a small molecule. A kilodalton (kDa) is 1,000 daltons

Dimer – A chemical structure formed from two sub-units.

Druggable – A protein that can be hit with a drug with, potentially, a therapeutic effect.

Endosomal Escape Trap – Phylogica's tool for identifying cell-penetrating peptides which are not only able to enter cells, but also able to get out of the endosome in which they are bound after making it across the cell membrane.

Endosome – A membrane-bound compartment inside a cell.

FPP – Short for Functional Penetrating Peptide, a Phylomer that has been demonstrated to be deliverable through the cell wall and out of the endosome to bind to an intracellular target.

Genome – The collection of genes that makes up a species. For example, the human genome has around 20,000 genes which encode more than 100,000 proteins if related 'isoforms' are taken into account.

Hit – A compound that appears able to bind and neutralise a disease-causing protein.

iMyc – A Phylomer which can hit the c-Myc oncoprotein within a cancer cell.

Immuno-oncology – An approach to treating cancer that involves harnessing the patient's own immune system to attack the cancer.

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

kDa – See Dalton.

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

Library – A collection of peptides, proteins or other molecules such as DNA that can be used to search for potential drug candidates

Large molecule – A drug with a molecular weight of >500 daltons. Biological drugs tend to be large molecules.

Macrocyclic – A molecule that forms a constrained (eg. circular) shape. In peptides, macrocyclics tend to have exquisite potency, stability and selectivity as inhibitors or protein-protein interactions.

Messenger RNA (mRNA) – The nucleic acid 'photocopier', in that it copies each individual strand of DNA so that the DNA can be turned into proteins.

Monoclonal antibodies – Antibodies cloned from a particular cell which produces a single type of antibody that is highly specific for a particular antigen.

Myc – see c-Myc.

Nanomolar – Able to work when only one billionth of a mole of drug or less are used. A mole is 6.0221415×10^{23} molecules of the pure substance being measured.

Oligonucleotides – Short strings of nucleotides, often use in antisense. Nucleotides are the combination of sugar, phosphate and one of four 'bases' that together make up DNA and RNA – they are the genetic 'letters'. Antisense involves methods for blocking the message – the 'sense' – of the DNA behind the creation of a protein.

Omomyc – An inhibitory peptide known to be able to bind the c-Myc oncoprotein which has been highly validated in multiple genetic cancer models.

Oncogene – A gene that encodes a protein (oncoprotein) able to make cells become cancerous.

Oncoprotein – A cancer causing product of an oncogene.

Pathway – A succession of molecules within a cell that passes a signal from the cell surface down to the cell nucleus. Well-known pathways include, but are not limited to MYC, PI3K/AKT, WNT and NOTCH.

Peptide – A short compound formed by linking two or more amino acids up to about 50-100 amino acids. Proteins are longer sequences of amino acids (ie. > about 50-100 amino acids).

Phage display – A technique for protein drug discovery in which DNA coding for proteins are spliced into bacteriophages, which are tiny viruses that infect bacteria. This allows huge 'combinatorial' repertoires of proteins to be created in a 'library' of bacterial cells that can be used to screen against a target of interest.

Phenotype – An organism's expressed physical traits, as opposed to its 'genotype', which is the genes that the organism inherits. The distinction underlies the fact that each gene in an organism's gene set may or may not express itself physically.

Phenotypic screening – The use of cells of a particular disease phenotype to source drugs that can modify that phenotype.

Phylomer – A class of peptide, first identified as such by Phylogica, where the peptides are derived from natural protein fragments encoded by biodiverse ancient bacterial genomes. Phylogica owns the rights to all Phylomer libraries.

Picomolar – Able to work when only one millionth of a millionth of a mole of drug or less are used. A mole is 6.0221415×10^{23} molecules of the pure substance being measured.

Proteins – Organic compounds made of one or more chains of amino acids folded into a globular form of more than about 50 to 100 amino acids in length (smaller chains of amino acids are referred to as peptides).

Screen – To run a potential target through a library looking for potential drug candidates that hit the target.

Small molecules – Drugs that have a low molecular weight (normally under 500 daltons), making them easier to penetrate cell membranes, and potentially the blood-brain barrier, and making many of them orally available. Protein drugs are large molecules, not small molecules, and as such are normally not orally available. They are, however more target selective and less likely to be associated with toxic side effects.

Split-GFP Complementation Assay – A Phylogica-developed test to quantify the amount of cell-penetrating peptide which makes it out of the endosome.

Stat5 – Short for Signal transducers and activators of transcription 5, a protein known to be a tumour promoter.

TAT – A peptide discovered in the 1980s which, before FPPs, was the 'gold standard' in cell-penetrating peptides.

Transcription factor – Proteins involved in the process of converting DNA into RNA. DNA is the body's 'recipe book' for making proteins. RNA is the nucleic acid 'photocopier' that copies the DNA for use in protein manufacture (messenger RNA) and in delivering amino acids to the ribosome factory where protein assembly takes place (transfer RNA).

Yb1 – Short for Y box binding protein 1, an oncogene which Phyogica is seeking to target with a FPP.

Yeast two-hybrid – A method of discovering proteins involved in disease interaction, or blockers to those proteins, by fusing copies of the genes that code for those proteins to genes encoding separate domains of a transcription factor, such as yeast's *GAL4* gene or the bacterial *LEXA* gene

Appendix III – Phylogica's IP position

Peptide detection method, WO/1999/035282, priority date 9 January 1998, Invented by Paul Watt and Ursula Kees.

- This patent application covers Phylogica's original Phylomer screening platform (not Phylomer libraries). This particular method is no longer used by Phylogica.

Isolating biological modulators from biodiverse gene fragment libraries, WO/2000/068373, priority date 5 May 1999, Invented by Paul Watt and Wayne Thomas[158].

- This patent application covers methods for construction and screening of Phylogica's original Phylomer library.

Improved reverse N-Hybrid screening method, WO/2001/066787, priority date 8 March 2000, Invented by Paul Watt, Richard Hopkins, Ilya Serebriiskii and Erica Golemis[159]

- This patent application covers an improved version of the year-2-hybrid screening systems that involves more reporter genes, so as to flag potential protein-protein interactions not related to the primary protein-protein interaction being assayed for.

Methods of constructing biodiverse gene fragment libraries and biological modulators isolated therefrom, WO/2004/074479, priority date 21 February 2003, Invented by Richard Hopkins, Paul Watt and Wayne Thomas

- This patent application covers sophisticated methods used to create and screen Phylomer libraries, including *in vitro* display, phage display and yeast two hybrid systems.

Modulating screening thresholds for N-hybrid screening, WO/2004/074472, priority date 21 February 2003, Invented by Richard Hopkins, Paul Watt, Vanessa Cull, Nadia Milech and Mark Fear

- This patent application covers the use of titration of media ingredients, in reverse two-hybrid assays which would provide maximal death of positive control yeast with minimal death of negative control yeast.

An improved genetic screen for interaction interface mapping, WO/2004/106543, priority date 30 May 2003, Invented by Paul Watt, Richard Hopkins and Marie Bogoyevitch

- This patent application covers a modification of a reverse-two-hybrid screen that excludes protein of interests that are incapable of binding to certain other protein partners. This helps to identify the critical binding residues at an interface between two target proteins or between a protein drug and a target protein.

Peptide modulators of cellular phenotype and bi-nucleic acid fragment library, WO/2005/119244, 3 June 2004, Invented by Paul Watt, Richard Hopkins, Mark Fear and Nadia Milech[160]

- This patent application covers the use of cells of a particular disease phenotype to source peptides from those cells that modify the phenoytpe. This is the first of Phylogica's phenotypic screening patents.

[158] This patent was granted in the US as No. 6,994,982 in February 2006; No. 7,270,969 in September 2007; and No. 7,803,765 in September 2010. It was granted in Europe as EP2230303 in January 2013.
[159] This patent was granted in Europe as EP1268842 in June 2006.
[160] This patent was granted in Europe as EP1754052 in July 2015.

Peptide inhibitors of C-Jun dimerization and uses thereof, WO/2006/017913, priority date 20 August 2004, Invented by Paul Watt, Mark Fear and Trevor Payne[161]

- This patent application covers Phylogica's anti-c-Jun peptide.

Method of constructing and screening libraries of peptide structures, WO/2007/097923, priority 20 February 2006, Invented by Paul Watt and Roland Dunbrack[162].

- This patent application covers Phylogica's method of creating synthetic Phylomer libraries. With these methods, a peptide library can be brought together containing all or part of all the independent fold structures in nature, mainly through informatics-based methods of examining the gene sequence of microbes used to create the libraries. This application provides an important extension of Phylogica's core patent life, by including libraries which are designed *in silico* based on structural information in the Protein Data Bank[163] rather than made directly from genomes. This patent extension to synthetic libraries is analogous to the strategy being pursued by the aforementioned German antibody engineering company Morphosys with its Ylanthia platform[164].

Neuroprotective peptide inhibitors of AP-1 signaling and uses therefor, WO/2008/034161, priority 19 September 2006, Invented by Paul Watt, Nadia Milech and Mark Fear[165].

- This patent application covers Phylogica's anti-AP-1 peptides.

Compositions and uses thereof for the treatment of acute respiratory distress syndrome (ARDS) and clinical disorders associated with therewith, WO/2008/154700, priority date 20 June 2007[166], Invented by Nadia Milech, Paul Watt, Patrick Holt and Deborah Strickland.

- This patent application covers the use of AP-1 inhibitors in treating ARDS.

Antimicrobial compositions, formulations and uses thereof, WO/2009/059379, priority date 14 May 2009, Invented by Paul Watt and Wayne Thomas

- This patent application covers anti-microbial peptides to treat *Acinetobacter baumannii* infection.

Peptide inhibitors of CD40L signaling and uses therefor, WO/2010/003193, priority date 11 July 2008, , Invented by Paul Watt, Richard Hopkins and Katrin Hoffmann[167]

- This patent application covers peptide inhibitors of CD40L, useful in the treatment of inflammatory disorders.

[161] This patent was granted in Europe as EP1793841 in April 2013.
[162] This patent was granted in the US as No. 8,575,070 in November 2013 and No. 9,567,373 in February 2017. It was granted in Europe as EP1987178 in March 2015.
[163] www.wwpdb.org.
[164] Ylanthia is a synthetic library of >100 billion fully human antibodies, created using 36 fixed, naturally-occurring heavy and light chain framework combinations where those combinations are pre-selected for qualities such as expression levels and stability (see MAbs. 2013 May-Jun;5(3):445-70. Epub 2013 Apr 9).
[165] This patent was granted in the US as No. 8,063,012 in November 2011 and No. 8,946,381 in September 2015.
[166] This patent was granted in the US as No. 8,822,409 in September 2014.
[167] This patent was granted in the US as No. 8,802,634 in August 2014.

Peptide inhibitors of CD40L signaling and uses therefor, WO/2012/034188, priority date 16 September 2010, Invented by Paul Watt, Richard Hopkins and Katrin Hoffmann

- This patent application covers more peptide inhibitors of CD40L, useful in the treatment of inflammatory disorders.

Method of determining, identifying or isolating cell-penetrating peptides, WO/2012/159164, priority date 23 May 2011, Invented by Paul Watt, Richard Hopkins and Katrin Hoffmann

- This patent application covers Phylogica's Endosomal Escape Trap and describes a number of FPP sequences discovered using this screen.

Methods for the characterisation of interaction sites on target proteins, WO/2013/116903, priority date 10 February 2012, Invented by Paul Watt, Bryn Hardwick, Grahame McKenzie and Ashok Venkitaraman

- This patent application covers the use of Phylomers to probe for druggable spots on targets of interest.

Method of monitoring cellular trafficking of peptides, WO/2014/205518, priority date 26 June 2013, Invented by Richard Hopkins, Katrin Hoffmann, Tatjana Heinrich, Paula Cunningham, Paul Watt and Nadia Milech

- This patent application covers Phylogica's Split-GFP Complementation Assay and a number of FPP Phylomers identified using this technology.

Appendix IV – Phylogica's capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code PYC (million)	1,990.0	97.4%	
Unlisted options (million)	52.7	2.6%	Average exercise price 1.1 cents, average expiry date 07-Jun-2018
Fully diluted shares	2,042.7		

Current market cap:	A$89.6 million (US$66.9 million)
Current share price	$0.045
Twelve month range	$0.013 - $0.045
Average turnover per day (last three months)	1.4 million

Appendix V – Phylogica's major shareholders

Phylogica currently has three substantial shareholders:

- **Dr Bernard Hockings (30.7%),** a Perth cardiologist and a non-executive director of Phylogica;
- **David Sietsma (10%),** a Sydney-based investor;
- **Tony Barton (5%),** a Perth-based investor.

Appendix VI – Papers relevant to Phylogica

Barr et. al. (2004a), *Reverse two-hybrid screening identifies residues of JNK required for interaction with the kinase interaction motif of JNK-interacting protein-1*. J Biol Chem. 2004 Oct 8;279(41):43178-89. Epub 2004 Jul 22 (full text available for free online).

- This paper describes the discovery of the binding site for Phylogica's first-generation JNK inhibitor, potentially useful in stroke and neurodegeneration. In general, it describes the use of reverse two hybrid screening to map a peptide/protein interface.

Barr et. al. (2004b), *The critical features and the mechanism of inhibition of a kinase interaction motif-based peptide inhibitor of JNK*. J Biol Chem. 2004 Aug 27;279(35):36327-38. Epub 2004 Jun 18 (full text available for free online).

- This paper describes the mechanism of action pf Phylogica's JNK inhibitor.

Watt et. al. (2006), *Protein silencing with Phylomers: a new tool for target validation and generating lead biologicals targeting protein interactions*. Expert Opin Drug Discov. 2006 Oct;1(5):491-502.

- This paper is a review of the use of Phylogica's Phylomer technology for target identification and validation as well as for therapeutic leads.

Watt (2006), *Screening for peptide drugs from the natural repertoire of biodiverse protein folds*. Nat Biotechnol. 2006 Feb;24(2):177-83.

- This review paper describes the main advantage of Phylogica's Phylomer library – that it covers every protein fold known to occur in nature. It also contains evidence that Phylomers may not necessarily have high immunogenicity potential, despite their foreign origin.

Giles et. al. (2008), *A peptide inhibitor of c-Jun promotes wound healing in a mouse full-thickness burn model*. Wound Repair Regen. 2008 Jan-Feb;16(1):58-64.

- This paper shows that Phylogica's anti-c-Jun peptide could heal wounds through prevention of apoptosis as well as promoting proliferation of keratinocytes.

Watt (2009), *Phenotypic screening of phylomer peptide libraries derived from genome fragments to identify and validate new targets and therapeutics*. Future Med Chem. 2009 May;1(2):257-65 (full text available for free online).

- This paper shows the utility of Phylogica's Phylomer technology in generating high hit rates for bioactive peptides in phenotypic screens for target discovery and validation.

Meade et. al. (2010b), *AP-1 inhibitory peptides are neuroprotective following acute glutamate excitotoxicity in primary cortical neuronal cultures*. J Neurochem. 2010 Jan;112(1):258-70. Epub 2009 Oct 28 (full text available for free online).

- This paper shows that AP-1 inhibitory peptides identified by Phylogica and delivered intra-cellularly using TAT could prevent neuronal cell death following glutamate excitotoxicity.

Meade et. al. (2010b), *AP-1 inhibitory peptides attenuate* in vitro *cortical neuronal cell death induced by kainic acid*. Brain Res. 2010 Nov 11;1360:8-16. Epub 2010 Sep 15.

- This paper shows the efficacy of Phylogica's AP-1 inhibitory peptides but in a different model,

Gow et. al. (2011), *Lack of neuroprotection of inhibitory peptides targeting Jun/JNK after transient focal cerebral ischemia in spontaneously hypertensive rats*. J Cereb Blood Flow Metab. 2011 Dec;31(12):e1-8. Epub 2011 Oct 5 (full text available for free online).

- This paper shows from rat models that two TAT- delivered peptides (Phylogica's c-Jun and Xigen's JNK1 inhibitory peptide) are probably not effective in this particularly stringent stroke model.

Ngoei et. al. (2011), *Characterization of a novel JNK (c-Jun N-terminal kinase) inhibitory peptide*. Biochem J. 2011 Mar 15;434(3):399-413.

- This paper describes an optimised version of the JNK-inhibitor describes in Barr et. al. (2004b) that distinguishes between active and inactive JNK.

Milech and Watt (2012), *The construction of "phylomer" peptide libraries as a rich source of potent inhibitors of protein/protein interactions*. Methods Mol Biol. 2012;899:43-60.

- This paper describes detailed methods to create a Phylomer library.

Meloni et. al. (2013), *The neuroprotective efficacy of cell-penetrating peptides TAT, penetratin, Arg-9, and Pep-1 in glutamic acid, kainic acid, and in vitro ischemia injury models using primary cortical neuronal cultures*. Cell Mol Neurobiol. 2014 Mar;34(2):173-81. Epub 2013 Nov 9.

- This paper shows that some of the early cell-penetrating peptides such as TAT have intrinsic neuroprotection properties and speculates that effects observed may not always require intracellular delivery, but may at times be mediated via binding of an extracellular receptor such as NMDA[168].

Ngoei et. al. (2013), *A novel retro-inverso peptide is a preferential JNK substrate-competitive inhibitor*. Int J Biochem Cell Biol. 2013 Aug;45(8):1939-50. Epub 2013 Jun 19.

- This paper describes another Phylomer-derived JNK inhibitor called D-PYC98 which works by a distinct mechanism of action to other JNK inhibitors.

Meloni et. al. (2015), *Poly-arginine and arginine-rich peptides are neuroprotective in stroke models*. J Cereb Blood Flow Metab. 2015 Jun;35(6):993-1004. Epub 2015 Feb 11 (full text available for free online).

- This paper follows on from Meloni et. al. (2013) above to show that cell-penetrating peptides with plenty of arginine residues can be neuroprotective.

Milech et. al. (2015), *GFP-complementation assay to detect functional CPP and protein delivery into living cells*. Sci Rep. 2015 Dec 16;5:18329 (full text available for free online).

- This paper describes Phylogica's Split-GFP Complementation Assay and evidence for the poor performance of most first-generation cell penetrating peptides when true endosomal escape is measured rather than merely entry into cells.

[168] N-methyl-D-aspartate (NMDA) receptors are glutamate receptors and ion channels found in nerve cells. The Lundbeck Alzheimer's drug Ebixa (Memantine hydrochloride) is an NMDA receptor antagonist.


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Roche collaboration - Dec '09
Medimmune collaboration - Aug '10
Pfizer collaboration - Dec '10
Janssen collaboration - Jan '12
Genentech collaboration - Aug '14
Genentech milestone - Dec '16

Risks related to Phylogica

Risks specific to Phylogica. We see five major risks for Phylogica as a company:

- **Funding risk.** There is the risk that Phylogica may find it difficult to raise capital from sophisticated Life Science investors.
- **Development risk**. There is the risk that Phylogica's cell-penetrating peptides may run into unforeseen problems in terms of hitting their intra-cellular targets.
- **Clinical risk.** There is the risk that it may take a long time to get a Phylogica cell-penetrating peptide into the clinic.
- **Partnering risk**. There is the risk that Phylogica may not be able to find quality partners for its cell-penetrating peptides
- **Commercial risk.** There is the risk that Phylogica's peptides may not be needed by modern medicine for a while given the continued utility of monoclonal antibodies.

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

- Biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before making an investment in any biotechnology and medical device company mentioned on this report, including Phylogica.

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