PHYLOGICA

BREAKTHROUGH PEPTIDE THERAPEUTICS

**November 2014**

*In this edition:*


- *Research agreement with Genentech*
- *Phylogica Launches Oncology Program*
- *Three grants for novel research*
- *Technology Focus: The Endosomal Escape Trap*


## Phylogica in research deal with US biotech pioneer

Phylogica was delighted to announce its latest research collaboration with Genentech, the US-based biotechnology company regarded as one of the most influential leaders in the development of new cancer treatments.

A subsidiary of the Roche Group, Genentech pioneered the use of recombinant DNA technology in the 1970s to produce the synthetic human insulin that became the world's first ever genetically engineered therapeutic agent.

Today, the company is still regarded as one of the world's biotech success stories, developing and manufacturing an array of bestselling drugs for diseases ranging from breast, lung and colorectal cancer to stroke, asthma, arthritis and cystic fibrosis.

The new Genentech agreement represents Phylogica's fifth partnership with a leading pharmaceutical company – an unprecedented number for an Australian biotech company within a period of less than five years.

Genentech's collaboration with Phylogica will focus on novel applications of our Endosomal Escape Trap – a proprietary screening system designed to identify peptides with the capacity to penetrate cells and deliver their biologically active cargoes via the cells' endosomes.

The Genentech agreement validates the industry's growing interest in our endosomal escape technology, which is described in greater detail in this newsletter. Phylogica is confident the agreement may lead to an expanded partnership with Roche as we continue to explore the novel potential of our peptides to deliver therapeutic drug cargoes to cells infected with cancer and other deadly diseases.


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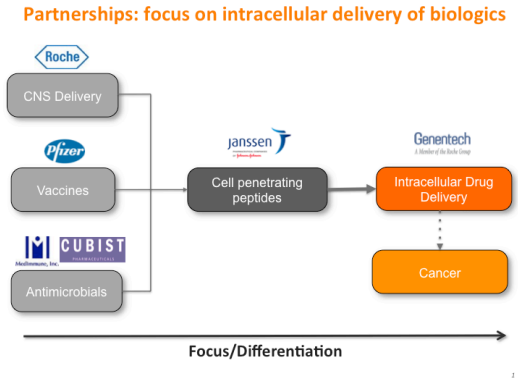
## Phylogica launches oncology programme - offers new prospects for cancer drug discovery




Phylogica is delighted to officially announce the launch of its proprietary programme to develop Phylomer drugs to treat breast cancer. The goal is to combine our validated intracellular drug delivery solution with Phylogica's unique drug discovery engine, to develop Phylomer-based drugs against high-value cancer targets. While the initiative will initially focus on breast cancer, the targets chosen are also relevant to other common malignancies, including colon, lung, brain and pancreatic cancers.

Phylogica's Oncology Program will investigate the ability of its Phylomer peptides to inhibit the activity of transcription factors – a class of target considered the master regulators of many genes involved in cancer. While transcription factors are among the most validated targets in cancer, they have generally proven intractable to small molecule drugs.

However, mounting evidence suggests that larger biologics drugs – including Phylomers – can be more effective at inhibiting transcription factors. More compelling still, Phylomer technology has already proven particularly well-suited to addressing transcription factor targets such as AP-1, where we have shown we can protect against the effects of burns and inflammation.

Further drivers underlying our rationale for selecting a breast cancer focus include the fact we can rapidly progress the programme towards key scientific and commercial inflexion points and that we can map-out a development path towards regulatory approval. Importantly, the company has been preparing the ground-work for the oncology programme for some time and has already made significant progress towards achieving some of the earlier technical milestones as indicated in the figure below. We look forward to providing regular updates over the coming weeks and months aimed at providing more details about the nature of our oncology programme and the exciting progress we've been making.

## Phylogica's Proprietary Oncology Programme

| Program | Indication | Discovery | Functional Validation | Preclinical |
|---|---|---|---|---|
| Stat 5/3 | Breast Cancer | | | |
| Myc | Breast Cancer | | | |
| YB1 | Breast Cancer | | | |

## New grant funds to spur research collaborations

Phylogica has recently been awarded three grants worth over $650,000 to fund specific drug delivery and drug discovery projects. They include:

**ARC Linkage Grant to Develop Drugs Targeting a Novel Cancer Target**

In collaboration with the University of Queensland, Phylogica was awarded a prestigious ARC linkage grant of $546,420 to develop drugs against a novel cancer target. This project will focus on another transcription factor called SOX18, which acts as a master regulator switch, controlling the spread of cancer throughout the body.

**Two Research in Business Grants**

Phylogica has been awarded two grants totalling $110,000 from the Research in Business scheme – an initiative of Enterprise Connect and the Australian Federal Government. The grants will be used to fund novel applications of the Endosomal Escape Trap, including: discovery of cell-penetrating antimicrobial peptides; discovery of cell-penetrating peptides that can modulate a class of intracellular proteins called G-coupled protein receptors (GCPRs); and new approaches to modulating GCPRs via their intracellular components.

## TECHNOLOGY FOCUS

## The Endosomal Escape Trap: Entering a new chapter in peptide drug delivery

To help explain our Phylomer technology to shareholders, we are introducing a new Technology Focus section in this newsletter. To kick things off, we would like to tell you more about our Endosomal Escape Trap (EET), which forms the core of Phylogica's proprietary drug delivery technology.

### What is the EET?

**The Endosomal Escape Trap is a technology that facilitates the discovery of a new generation of cell-penetrating peptides that more efficiently deliver therapeutic cargoes into cells.** Developed by Phylogica over three years, the EET provides a highly sensitive 'tagging system' for identifying extremely rare peptides that can cross cell membranes and enter inside the cell.

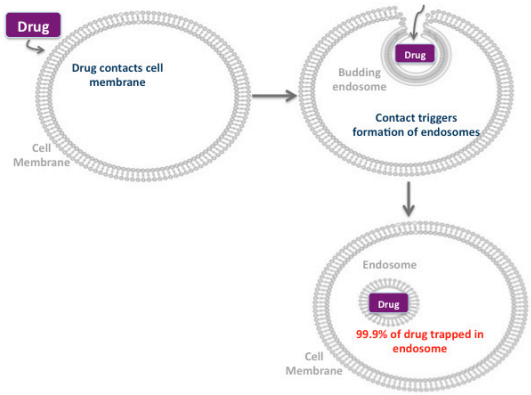
### What problem is the EET addressing?

One of the greatest challenges facing the pharmaceutical industry today is how to deliver large biologics drugs such as proteins and peptides safely and effectively inside cells. Biologics represent the fastest growing class of pharmaceuticals, including antibodies, enzymes and peptides which is expected to be a market worth $200 billion globally by 2027. Cells have evolved powerful defenses to protect themselves from the outside world, including the cell membrane – which forms a relatively impermeable barrier around the cell – and a process called endocytosis.

### What is endocytosis and why does it matter?

When a drug comes into contact with the cell surface, it is quickly surrounded by a segment of the cell membrane that buds off to form a small droplet or vesicle called an endosome. This process known as 'endocytosis' enables the cell to sense and control its interaction with the outside world while maintaining a barrier that protects its intracellular environment. The process is so efficient that 99% of material brought to the cell by this method remains trapped within the endosome and separate from the intracellular machinery until it can be processed for degradation or delivered to its address inside the cell. Developing strategies to allow drugs to efficiently 'escape' from the endosome is a major technical challenge for the industry that would substantially improve the efficiency of biologics drug delivery. Addressing this challenge represents a major commercial opportunity, given that biologics is the fastest growing class of pharmaceuticals and that more than 80% of potential new targets are found inside cells.

**The Problem:** Drugs are trapped in endosomes




### How does the EET work?

The four key elements to the technology are:

1. Phylomer libraries containing tens of billions of different peptides are displayed on the surface of bacteriophage (phage), which are small viruses that naturally infect bacteria. Phage can be considered biological nanoparticles decorated with Phylomer peptides. All Phylomer peptides are linked to a unique tag, referred to as the Avitag, which can be labelled by an enzyme called biotin ligase or BirA.
2. The Phylomer libraries are then screened against human

cells expressing the BirA enzyme. When the phage-displayed libraries come into contact with the cell surface, they are internalised into the cell endosomes by endocytosis.

3. In those rare cases where Phylomer peptides facilitate phage escape from the endosome into the truly intracellular compartment of the cell, these phage particles are tagged by the BirA enzyme that recognises the Avitag sequence displayed along with the Phylomer peptides on the surface of the virus. This tagging is critical as it allows us to discriminate between untagged phage trapped in endosomes and those that have made it to the cytoplasm where many drug targets are found inside cells.

4. The final step is to break the cells open to release the cellular contents including any internalised phage. Phage labelled with a biotin molecule are captured, amplified and then analysed to determine the nature of the peptide that facilitated the escape from the endosome.

**What makes the EET technology successful?**

The EET is highly sensitive. We can screen libraries containing tens to hundreds of billions of peptides and rescue less than 1,000 phage which have made delivered their biologics cargoes inside the cells. This sensitivity enables us to discover rare cell penetrating peptides from our world-leading libraries of diverse peptide compounds.

**What has the EET technology achieved so far?**

Using the EET, we have already identified more than 100 unique cell penetrating candidates. When a panel of approximately 80 hits were assessed in downstream functional assays designed to quantify the efficiency of cell penetration, we observed a functional hit rate of about 13% – considered high by drug discovery standards.

To further validate the EET technology, Phylogica has developed a suite of assays to measure the amount of drug Phylomer peptides can deliver inside cells. The outcome of this work has established two very important findings.

- First: Cell penetrating Phylomers can improve the delivery of smart drugs (ie large biologics cargoes) by up to 160-fold.
- Second: Cell penetrating Phylomers are at least 37 fold more efficient at delivering such biologics cargoes inside cells than the TAT peptide – previously considered the gold standard for cell penetrating peptides that has tested in multiple clinical trails (see figure 3 below).

These exciting results, along with other supporting data validate Phylogica's powerful claim that it has identified the world's 'Best in Class' cell penetrating peptides for delivery biologics cargoes inside cells. Current efforts are focussed on further demonstration of the value of this approach, by showing our peptides can deliver validated cancer drugs inside cells at therapeutically relevant concentrations. Early-stage experiments have generated some very exciting data that we look forward to disclosing in subsequent investor updates. Stay tuned!

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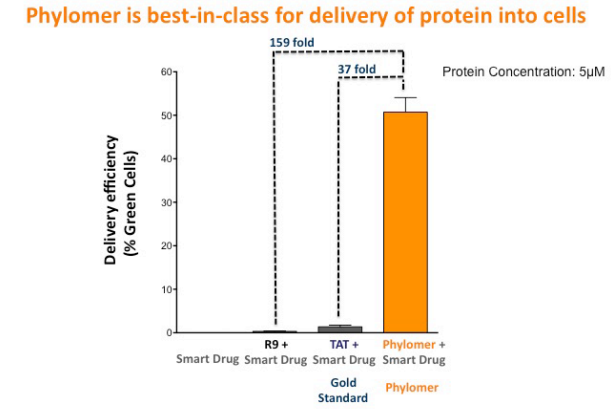


Figure 3.

*Comparison of the efficiency of delivery of a protein cargo to the cytoplasm (inside the cell) using Phylogica's newly developed 'Split GFP' Functional Assay. The Phyomer was 37 fold and 159 fold better at delivering the protein cargo into cells than two of the best characterised cell penetrating peptides (CPPs), known as 'TAT' and 'R9', respectively. TAT is considered the Gold Standard CPP as it has had extensive clinical validation.*

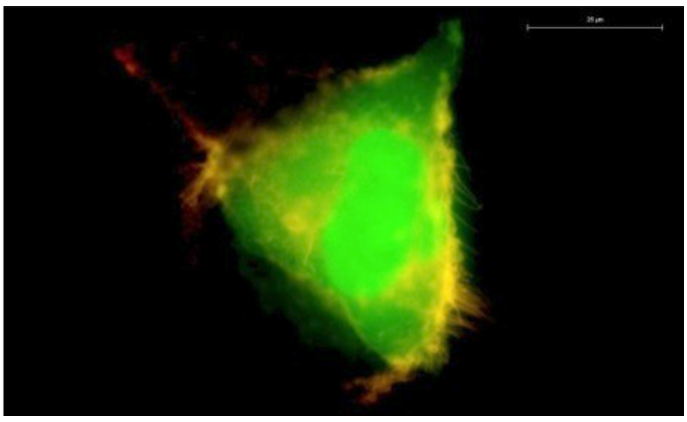

*Figure 4. Fluorescent assays allow visualization of only those protein cargoes efficiently delivered into cells via endosomes and released to the cytoplasm/nucleus.*

PHYLOGICA (ASX: PYC)
Contact Dr Richard Hopkins, CEO
Email richardh@phylogica.com
Telephone +61 (0) 405 656 868
Address PO Box 8207
Subiaco East, Western Australia 6008

**Please register for electronic communication by emailing your name to farzanak@phylogica.com with REGISTER in the subject line.**