Operational Update

April 4, 2017

Dear Shareholders,

We are pleased to inform you that Phylogica has continued to make strong progress in its three key focus areas over the first quarter of 2017:

- **i) intracellular delivery technology – our FPP optimisation program has now clearly demonstrated that reducing the length of particular FPPs does not reduce their activity. This knowledge provides more scope to improve the potency of the FPP-payload conjugate.**
- **ii) internal oncology program – proof of concept feasibility on our iMyc program is now complete. We continue to progress our shortlisted iMyc leads through the optimisation process to further strengthen our comprehensive data pack.**
- **iii) commercialisation – there has been encouraging progress covering both commercial and academic collaborations.**

Our refreshed website has also now gone live and can be seen at www.phylogica.com

1. Progress on FPP platform development

Our work this quarter has further supported our FPP (Functional Penetrating Phylomer) intracellular delivery platform both with the combination of our FPPs with our iMyc payload, as well as the combination of our FPPs with the payloads of external partners.

Our team have been working hard in screening additional new FPPs for their capacity to enter cells and escape the endosome, as well as in determining which regions of the FPP are required for activity. This latter information is valuable in directing optimisation screens to further improve the activity of our FPPs.

In order to optimise the FPPs themselves we have been validating both genetic and synthetic assays to enable rapid testing of mutated FPP derivatives for improved uptake. We have also continued to test a range of our FPPs with different cargoes, both internal and those of our partners.

Derivatives of our current primary FPP hits have been characterised and have shown that in some cases the FPP length can be reduced without loss of activity. This result opens the way for more rapid optimisation through synthetic chemistry and genetic approaches, enabling a tailored approach for further improving the ability of the FPP to cross the cell membrane and escape the endosome with a drug payload, and thus improving the potency of the FPP-payload conjugate.

In addition, we are validating a sensitive assay (i.e. a test) for FPP activities which allow even better quantitation of their activity in the nanomolar range, which is highly relevant for therapeutic application.

2. Progress on the i-MYC cancer program

Our proof of concept (POC) feasibility data pack is now complete, with preliminary data on pharmacokinetics (PK) giving us confidence to continue optimising our shortlisted candidates and developing our comprehensive data pack to support formal pre-clinical studies.

After further consultation with international pharma experts in oncology drug development, we have adjusted our plan to include additional approaches and activities. These experts have recommended enhancements to our drug development plan to further strengthen our comprehensive data pack for transition to formal preclinical development.

To incorporate these enhancements (and contingent on whether back-up approaches are required) we expect to be in a position for the iMyc program to enter formal preclinical development by late 2017 or early 2018.

Table 1 below summarises the elements of the program, with relevant updates as follows:

- Lead optimisation progress

  As mentioned last quarter, 5 candidates with high quality features were selected for optimisation, with early stages of the optimisation process commenced. This process has continued in this quarter with further work being undertaken in multiple areas including:

  - Potency:
    - Affinity maturation and other approaches have continued in order to achieve further increases in potency.
  - Pharmacokinetics (PK):
    - Our initial PK and biodistribution studies in the past with unoptimised FPP-iMyc and FPP-Omomyc constructs showed evidence of rapid clearance from the plasma, predominantly via the liver and kidney.
    - The Phylogica team have been testing a variety of PK extension technologies to evaluate which technology is optimal for improvement of half life and retention in the blood (our goal for blood cancers), and for reduction of the rate of rapid hepatic and renal clearance.
    - Encouragingly, in our initial *in vivo* PK studies, comparing un-modified FPP-Omomyc to the same protein conjugated to the half-life extender PAS, we saw an increase in plasma elimination half-life of about 300% for the PAS-conjugate, compared to the un-modified FPP-Omomyc protein. Further, the biodistribution results showed a retention of the FPP-Omomyc PAS-fusion protein in plasma. At 60 minutes only 8% of detected un-modified protein was measured in plasma and 84% was distributed between liver and kidneys, whereas 51% of the detected FPP-Omomyc PAS-fusion protein was still found in plasma, at the same time-point, with only 44% distributed between liver and kidneys.
    - With this improvement in half-life and biodistribution, we have validated an acceptable solution to the challenge of rapid hepatic, renal and plasma clearance. Further experiments need to be performed to confirm these preliminary findings from the initial biodistribution and PK studies with 6-8 animals per cohort, respectively. Other additional/backup solutions continue to be evaluated.
    - Phylogica will continue to improve these approaches in order to apply to the optimised candidates that will emerge from our iMyc program.

- Selectivity:
  - In drug resistant breast cancer cells, we have now identified a signature of Myc target genes which we propose to use to monitor the dose-responsive pharmacodynamic effects of our inhibitors over time in animal models.
  - We have completed more biophysical assays on our most active Myc hits, showing that they bind to both human and mouse Myc target proteins.
  - Some of the hits selectively bind to N-Myc and some bind to c-Myc, while others have a universal binding specificity for both Myc target proteins, illustrating increased versatility. For example, the ability to bind N-Myc selectively, provides the opportunity to more specifically target an even wider variety of tumours including neuroblastoma.

PROPERTIES	POC FEASIBILITY SIGNAL	STATUS OF POC	OPTIMAL LEAD CANDIDATE
In-vitro Potency	Demonstration of low micromolar potencies	✓	Demonstration of nanomolar potencies
Selectivity	Evidence for modulation of downstream targets and initial binding kinetics	✓	Confirmed inhibition of MYC and downstream targets, detailed binding kinetics, solved target/ligand structure
Toxicity	Evidence of maintenance of viability for FPP vs FPP-cargo at micromolar concentrations in-vitro	✓	Preclinical tox pack in-vivo. (rodents, non GMP)
Serum Stability	>40% stability after 12 hrs in static serum	✓	>80% stability after 12 hrs in static serum
PK Profile	Evidence of delivery to target tissue and acceptable level of renal clearance	✓	>4 hrs serum half life in mice/ rats
Efficacy in Animal Models	Confirmed activity in animal model of disease (following IV injection)	✓	Confirmed activity in disease-relevant animal models (following IV injection)
Scalable production/ formulation	Recombinant expression at adequate yields and good solubility for animal studies	✓	Recombinant expression at adequate yields and good solubility for scaling-up to further animal and then human studies

Table 1: POC Data Pack Milestones

3. Progress on other external collaborations and discussions

In January, Phylogica presented at the Bioscience Showcase in San Francisco (which was held alongside the JP Morgan Healthcare Conference) and also undertook a number of individual meetings with potential partners and collaborators. In addition to the discussions and non-disclosure agreements (NDAs) established in previous quarters, this has exposed more potential partners to Phylogica's technology.

- Genentech – Antimicrobial collaboration moves into next stage
  - Following the exclusivity extension with US$2m milestone payment received from Genentech, which we announced last quarter, we have begun work with Genentech on the next stages of the research program to discover novel antibiotics utilizing Phylogica's Phylomer® drug discovery platform, including our proprietary cell penetrating peptide discovery technology.
- Brunel University London – new iMyc in-vitro data in additional tumour type
  - Early *in vitro* data has shown a very strong reduction in viability of predominately N-myc overexpressing neuroblastoma cells with administration of iMyc constructs (virally expressed). This data is promising as it further validates the potential iMyc across a broad number of tumour types, and supports the new data we have generated on selectivity, outlined in Section 2 above.
- Murdoch University – oligonucleotide delivery collaboration progressing
  - Last quarter, we reported that preliminary IV animal experiments showed evidence of efficacy and low-toxicity in the delivery of exon-skipping oligonucleotides in models of both Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA) to muscles in a range of locations (including cardiac, diaphragm and tibia). Further animal experiments and analysis are underway to reinforce the evidence of lower toxicity of FPPs versus other CPPs.
- Dana Farber – STAT5 and YB1 programs advancing with further in-vitro data
  - Our collaboration with Dana Farber using our proprietary Phylomer oncology payloads continues - with viral expression of constructs being used to generate *in vitro* evidence for specific effects of some of our iSTATs on STAT5 but not the related STAT3 control. The magnitude of the effect is significant with prolactin induction (which induces STAT5) but not IL16 (which induces STAT3). Inhibitory effects of the iSTATs are seen on MOL14 (AML) cells. With iYB1, significant effects on viability and MYC expression in MOL14 (AML) cells and HCT116 colon cancer cells has been seen.
- Phoremost – strong phenotypic screen hits obtained using Phylomers on key cancer pathways
  - Recent Phoremost screens have included screens against the undruggable KRAS and YAP cancer pathways. For these screens, several strong hits have been obtained in primary screens of 5-million Phylomer (PROTEINi) sequences. A reasonable subset of these have been confirmed in secondary assays and are now moving through a proprietary process to identify their cellular targets; as are hits from other previous screens.

With our iMyc program proceeding well, along with our Stat5 and YB1 programs, and FPP intracellular delivery platform, we have made a strong start to 2017. We are looking forward to sharing further updates with you as the year progresses.

Stephanie Unwin

Chair

Phylogica Limited

For further information, please contact:

Ms Stephanie Unwin
Tel: +61 8 9286 1219
Email: stephanieu@phylogica.com

Forward looking statements

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