PHYLOGICA

# Operational Update

September 30, 2016

Dear Shareholders,

**Following our previous operational update, we are pleased to report further progress has been made over the past 3 months in 3 key areas:**

**i) intracellular delivery technology – further validation of our FPP intracellular delivery technology platform.**

**ii) oncology program – progression of our program aimed at the high-value intracellular cancer target Myc, using our proprietary iMYC cargoes.**

**iii) commercialisation - external discussions and collaborations have continued as commercial interest builds in PYC's technology as these milestones progress.**

**In addition, a review by a panel of international drug discovery and preclinical development experts was completed in August with the outputs being used to refine Phylogica's approach to the hit to lead phase that will take us through to the start of formal preclinical development efforts next year. Business development and commercialisation advisors with extensive experience in the pharmaceutical industry have been engaged to assist in maximising the potential of Phylogica's assets.**

## 1. Progress on FPP Platform Development

Internally, advances have been made in more accurately quantifying FPP (functional penetrating Phylomer) delivery and refining our understanding of the delivery mechanism:

- We have established that FPP-mediated delivery is very rapid, beginning to occur within a few minutes and the majority of delivery occurring within one hour.
- We have also been able to quantify the approximate concentration of the protein which we have delivered into the cell and shown this to be greatly superior to that achievable with the conventional cell penetrating peptide TAT.
- This progress is in addition to the encouraging FPP data outlined below in section 2, that we are generating from our i-MYC oncology program.

Externally, interest is increasing with further discussions and collaborations underway regarding assessment of the FPP delivery platform for use with proprietary cargoes of potential partners in various disease areas.

## 2. Progress on the i-MYC cancer program

Our proof of concept (POC) data pack continues to advance, and work is commencing on some aspects of our definitive data pack required in order to undertake formal preclinical development in the second half of 2017. Table 1 summarises the elements of the program, with relevant updates detailed below:

- iMYC Phylomer cargo candidate selection
  - By assessing against a number of criteria including drug-like properties and FPP compatibility, a narrower shortlist of 9 proprietary iMYC candidates has now been produced and ranked against the 'gold standard' positive control Omomyc. From these, the most suitable leads will be chosen for optimisation.
- Data pack development
  - Toxicity:
    - Further experiments have shown no evidence of FPP-mediated toxicity when FPP without cargo was compared to FPP-Omomyc or other FPP constructs.

      These include results from intravenous (IV) animal model experiments (discussed further below), where no toxicity signals were observed from a control construct containing FPP without cargo.
  - Pharmacokinetics (PK)
    - We have been able to achieve modest improvements in PK, following assessment of certain half-life extension technologies.
    - Other established approaches are also being evaluated to further enhance the PK and biodistribution profiles of our molecules. Such optimisation can have a major effect on the overall potency of compounds *in vivo* as they allow for increased drug exposure levels over time.
  - Animal models:
    - We have recently obtained early indications that certain FPP-Omomyc constructs, when delivered systemically by IV injection, are active in two independent animal models of cancer. The two models of disease used were our in-house Eμ-MYC lymphoma model and an externally conducted breast cancer model. This IV data builds upon intratumoral data outlined in previous announcements.
    - For example, we have repeatedly found that IV administration of an FPP–Omomyc construct, caused a statistically significant reduction in the growth of Eμ-MYC tumour cells in the bone marrow of mice injected with tagged lymphoma cells, compared to injection of the control of Omomyc alone (i.e.without linkage to a cell penetrating FPP).
    - These data suggest that our functional penetrating peptides (FPPs) are active, even when administered via the IV route. This result is particularly encouraging given that these FPP sequences have not yet been optimised and are rapidly cleared from the circulation. (indicating that our lead optimisation phase could significantly enhance the efficacy of our ultimate lead).
    - Having established that the FPPs are functional, they will be tested in coming months in conjunction with our lead iMycs, in order to determine which are the best candidates for lead optimisation and half-life extension approaches.
    - Although the animal data may require further repeats with an optimized candidate to progress pharma discussions on the i-MYC program, these results have given us additional confidence in

the potential of the i-MYC program, in addition to providing more evidence in support of the FPP platform and its ability to carry cargoes into the cell.

| PROPERTIES | POC FEASIBILITY SIGNAL (2H 2016) | STATUS OF POC | OPTIMAL LEAD CANDIDATE (2H 2017) |
|---|---|---|---|
| **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 | progressing | 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 | progressing | >4 hrs serum half life in mice/ rats |
| **Efficacy in Animal Models** | Confirmed activity in animal models 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

Since the end of June, we've signed an additional 2 new non-disclosure agreements with international pharmaceutical companies to discuss elements of Phylogica's technology portfolio.

These discussions and collaborations are at an early stage, and are in addition to those announced previously. Although these early discussions may not necessarily result in licensing or other types of deals, advancement to these stages signals a growing level of interest in Phylogica's progress.

In coming months, we expect to have further information on some of our ongoing collaborations, including with Phoremost, the Dana Farber Institute in the US (researching our Phylomer inhibitors aimed at the STAT5 and YB1 oncology targets) and our Genentech collaboration on antimicrobials.

**We are pleased with Phylogica's progress since our previous update and look forward to updating you on future progress from our intracellular delivery technology; promising cancer program; and differentiated discovery platform.**

**Stephanie Unwin**

**Chair**

**Phylogica Limited**

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**Forward looking statements**

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