

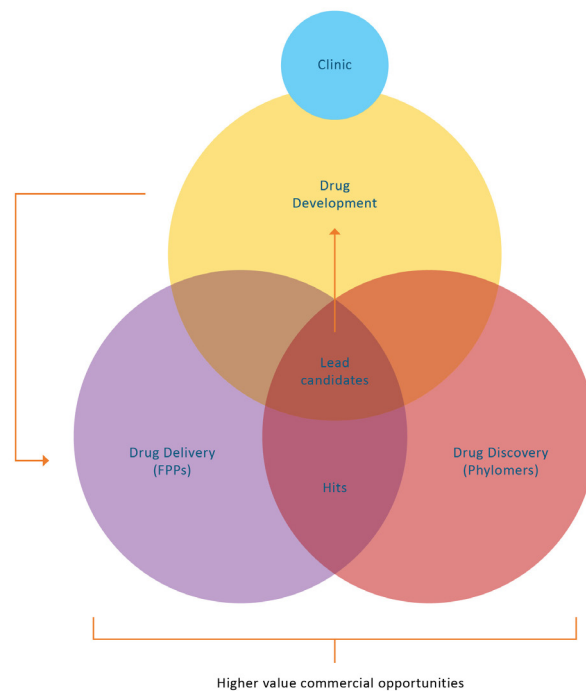
## Operational Update

July 27, 2016

Dear Shareholders,

In recent months, our team has made good progress and achieved several important technical landmarks towards de-risking our internal oncology program. These steps have now laid firm groundwork on the path towards formal pre-clinical development of our iMYC Phylomer leads against the cancer-driving Myc transcription factor and validation of our functional penetrating Phylomer (FPP) intracellular delivery technology.

Opening up the intracellular landscape creates the prospect of new, more effective cancer treatments with fewer side effects. This holds the key to unlocking commercial interest in PHYC's technology.



**Figure 1. Validating Phylogica's Drug Discovery Engine: Combining the power of the FPP intracellular delivery platform with Phylomers against key disease targets such as MYC.**

### 1. Progress on the iMYC cancer program

We are progressing well in the development of our proof of concept (POC) data pack which will allow Phylogica to better explore new and potentially lucrative commercial relationships, based on validation of our approach to targeting MYC gene driven cancers.

Most of the key feasibility criteria for the proof of concept data pack have been achieved. Some elements have been outlined in recent external presentations, and are discussed in more detail below and summarised in Table 1:

## ○ iMYC Phylomer cargo candidate selection

- A number of candidate cargoes have been shortlisted by our in-house in-vitro screening process and show comparable or better MYC-dependent cancer cell-killing activity to the Omomyc control in selected cell lines tested.
- These and other potential candidates are being further validated through an independent screening assay in coming weeks into a narrower shortlist, with Omomyc continuing to be used as a positive control for benchmarking purposes

## ○ Proof of concept data pack development

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)	progressing	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**

## ○ Potency:

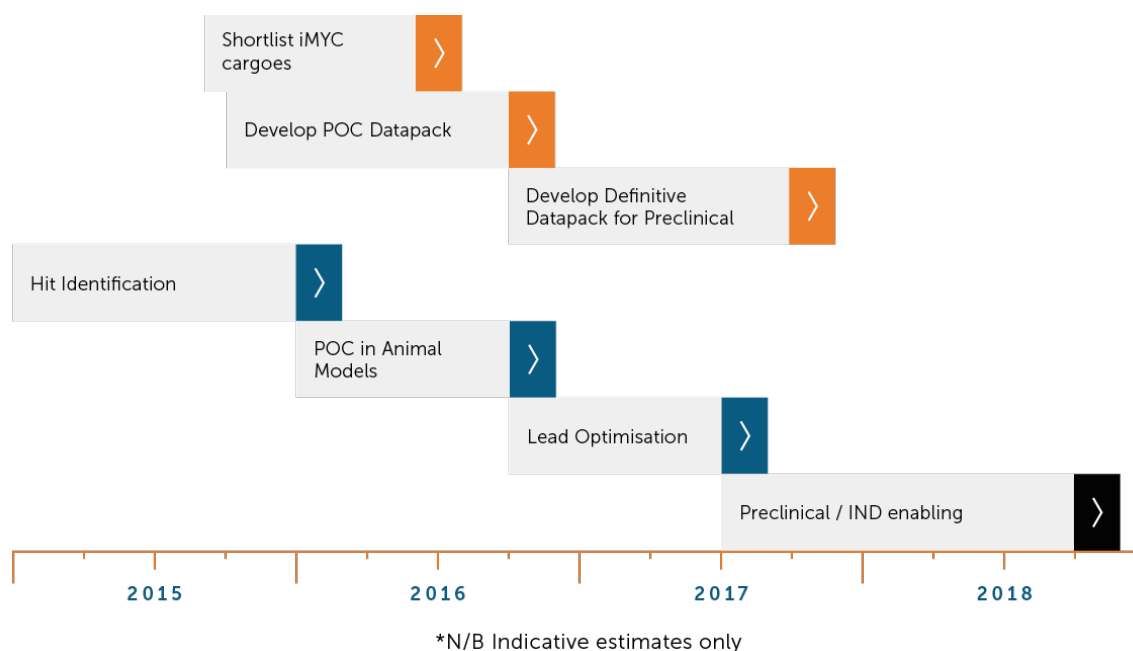
- PHYC's recent results have shown that unoptimised/unmodified iMYCs bind to their intracellular Myc target with low to mid-nanomolar affinities (i.e better than micromolar). One unoptimised iMYC candidate bound almost twice as strongly as Omomyc, the current industry gold standard experimental MYC inhibitor.

- Low to mid-nanomolar target affinities are approaching the affinity range required for an effective drug candidate, if other drug-like properties are favourable also (see below). These initial affinity levels provide a strong starting point for achieving the overall in-vitro potency level targeted for the POC pack. Optimisation is expected to lead to further improvement in potency, primarily through the use of third-party validated affinity maturation processes. This will occur once final candidates are selected.
- **Selectivity and Toxicity:**
  - One benefit of targeting transcription factors such as Myc is that it is possible to directly monitor their biological function in switching on and off known Myc target genes.
  - Recent results show that FPP-Omomyc affects known genes of the MYC pathway while not affecting sample gene sets corresponding to two other pathways (NOTCH and WNT).
  - This result is consistent with the observed continued viability of cells not over-expressing MYC when exposed to the FPP-Omomyc construct, and bodes well for further use of this process for learning more regarding selectivity and toxicity of FPP-iMYC constructs.
- **Stability**
  - Compared to Omomyc, Phylogica's iMYCs showed greater stability (reduced degradation) when incubated in 100% animal serum for up to 24 hours, which is an acceptable level of stability for proof of concept purposes.
- **Pharmacokinetics**
  - The team has been testing how much of the unmodified iMYC candidates can be detected in the blood of mice after injection. Work is being carried out to more accurately calculate these levels over time. Given the small size of the iMYC compounds, it is likely that further modification may be required to extend serum half-life. Assessment of various approaches to achieve this are underway.
  - In addition, in-vitro experiments are being undertaken to estimate the adequate serum half-life required for the FPP-Omomyc/FPP-iMYC to gain adequate cellular uptake in vivo.
  - A further benefit of directly targeting the transcription factor (Myc protein) product of the MYC gene, rather than using a nucleotide therapeutic (eg RNAi) approach, is that it should allow more straightforward access to a broad range of tissues, rather than being largely restricted to the liver. The additional potency offered by our FPP could also improve efficacy in target tissues.
- **Animal models:**
  - The Eμ-MYC lymphoma model, used in various research centres, has now been established in our laboratory - it provides one of the best-characterised models of MYC-driven cancer with a very rapid readout for testing in which to test our FPP-iMYC hits.
  - Further refinement to the variables of the model (such as injection timing and cancer cell load) are being made in order to give more robust readouts in preparation for routine screening. This intravenous lymphoma model will build on what we have learned from the intratumoral breast cancer animal model outlined in previous announcements.

## ○ Scalable production:

- Due to their size, FPP-iMYC fusions are likely to be produced at scale by recombinant synthesis in bacterial fermentation. The ease by which such compounds can be produced in soluble form following expression in the microorganism E.coli, and straightforwardly purified by standard methods can be an indicator of the feasibility of recombinant production by fermentation at larger scales.
- Several iMYCs - along with Omomyc – have successfully undergone such a fermentation scale production, purification and concentration process, generating sufficient yields in soluble form for larger-scale animal studies.
- While further challenges can arise at industrial scaling, recombinant production at high purities and yields at the fermentor scale augurs well for the feasibility of advanced development of such candidates.

Following the POC data pack, the development of the definitive data pack (which includes lead optimisation) required in order to commence formal pre-clinical development, will commence by Q4 and will continue into 2017 (Figure 2). A group of international drug discovery and preclinical development experts has also recently been engaged to review PHYC's scientific and strategic plans, in order to refine Phylogica's oncology program.



**Figure 2: Targeting MYC - Development Program timelines**

## 2. Progress on FPP Platform development

In addition to the internal oncology development program, Phylogica's low-cost external partnership strategy is continuing to help independently validate diverse applications of the FPP-based intracellular delivery platform with a range of cargoes.

- We recently reported data from such a collaboration with Murdoch University, showing that FPPs can effectively deliver oligonucleotide therapy in an animal model. This may be due to improving access to tissues of the remaining therapy that has not been sequestered in the liver.
- This growing validation of our delivery capability is expected to lead to additional licensing opportunities around the use of the FPP platform as a cell penetrating peptide of choice to deliver cargoes of interest to pharma partners.

## 3. Progress on other external collaborations and discussions

In the last quarter, we've signed two new non-disclosure agreements (NDA) with international pharmaceutical companies to discuss various elements of Phylogica's technology portfolio. We've also commenced one new material transfer agreement (MTA) and renewed an existing MTA.

These are in addition to continuing a number of active discussions/NDAs and MTAs commenced in previous periods. Although these discussions and collaborations are at an early stage and 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.

Updates on previously announced collaborations include:

### ○ STAT 5 and YB1 inhibitors oncology program

- We have continued work on our STAT5 and YB1 inhibitors in oncology, which are at an earlier stage of development than our MYC program.
- We have intensified these efforts by collaborating with other specialist researchers, including at the Dana Farber institute in the US, who have well-established and proven in-house in-vitro and animal models for the blood cancers of interest.

### ○ Phoremest alliance

- Phenotypic screening carried out as part of our joint venture with drug target discovery company PhoreMost based in Cambridge UK, has now shown that Phylogica's Phylomer ("PROTEINI") libraries routinely work highly effectively across multiple cancer pathways, yielding high quantity and quality hits in the phenotypic screening process.
- This success is in part due to the wide structural (i.e. shape) diversity of the Phylomer libraries, whereas other approaches using conventional random peptide or small molecule libraries typically yield much lower hit rates due to their biases towards particular preferred target structures. This limits the utility of such libraries in phenotypic screens, given the number of compounds that can be screened for a particular biological phenotype is relatively constrained.

- Chris Torrance, Phoremest CEO:

*"We saw remarkably high hit rates for Phylomers able to reverse cancer 'phenotypes' in different types of cancers. We are highly encouraged by these findings and will be expanding efforts to use these Phylomers as leads to develop small-molecule drugs. In tandem, we will be working with Phylogica to develop Phylomer-based drugs against these novel intracellular targets."*

- Genentech collaboration

- Our collaboration on antimicrobials is progressing, with Genentech continuing to evaluate the leads it has received before determining, by the end of this year, whether to licence or extend its option over the peptides.

The coming months will be a pivotal period in Phylogica's development, as we complete our proof of concept and definitive data packs; and prepare to enter a formal preclinical oncology drug development program. The company is increasingly better-positioned to transform its scientific advances into commercial success, with our promising cancer program, our intracellular delivery technology, and a differentiated discovery platform. We look forward to updating you further on our progress.

Stephanie Unwin  
Chair  
Phylogica Limited

For further information, please contact:

Ms Stephanie Unwin  
Tel: +61 8 9286 1219  
Email: [stephanieu@phylogica.com](mailto:stephanieu@phylogica.com)

### Forward looking statements

Any forward looking statements in this ASX announcement have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside Phylogica's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this ASX announcement include known and unknown risks. Because actual results could differ materially to assumptions made and Phylogica's current intentions, plans, expectations and beliefs about the future, you are urged to view all forward looking statements contained in this ASX announcement with caution. Phylogica undertakes no obligation to publicly update any forward-looking statement whether as a result of new information, future events or otherwise. This ASX announcement should not be relied on as a recommendation or forecast by Phylogica. Nothing in this ASX announcement should be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.