Phylogica

Creating better drugs through revolutionary intracellular therapeutics

Phylogica datapack

November 2017, BIO-Europe

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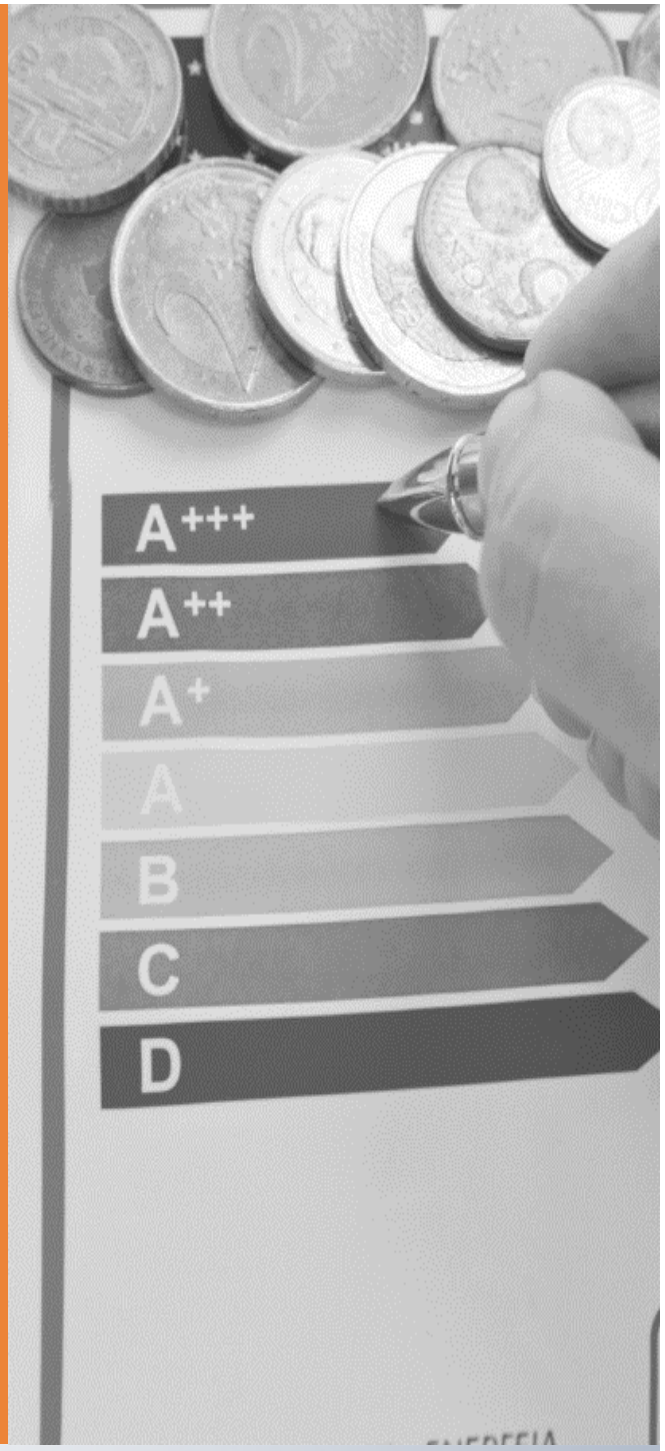


About Us

Who are we?

Biotech platform technology that enhances a highly potent class of biologic drugs

What do we do?

Expand the reach of biologic drugs to the previously undruggable intracellular environment

What makes us unique?

Our proprietary library of cell-penetrating peptides coupled with our sophisticated screening process

Experienced Management Team

In mid 2017 Phylogica revitalised its management team with senior Pharma and commercial executives:

Deep executive and commercial experience

- Executive at $3B energy utility; Head of Strategy, Chief Transformation Officer, and GM Commercial and Retail
- Over 15 years Board experience across ASX and TSX

Core Management Team

Ms Stephanie Unwin, CEO

Dr Robert Hayes, CSO

Highly seasoned pharmaceutical executive

- CEO for Janssen Centyrex
- Head of Biologics at Amgen
- Over 20 years' experience in biotech startups and pharmaceutical companies

Board of Directors

Ms Stephanie Unwin, CEO

Dr Robert Hayes, CSO

Prof. Paul Watt, NED

Dr Bernard Hockings, NED

Mr Sahm Nasseri, NED

Scientific Advisory Board

In October 2017 Phylogica established and made first appointments to its Scientific Advisory Board:

Professor Judy Lieberman

Prof Judy Lieberman is the Chair in Cellular and Molecular Medicine at Boston Children's Hospital and Professor of Pediatrics at Harvard Medical School. She has worked as a hematologist/oncologist at Tufts Medical Center and her laboratory has been in the forefront of developing RNAi-based therapeutics and using RNAi technology for genome-wide screening. Dr Lieberman also served as the Chair of the Medical Sciences section on the Council of the American Association for the Advancement of Sciences. She has received numerous awards for her research on vaccines, immunology and cancer.

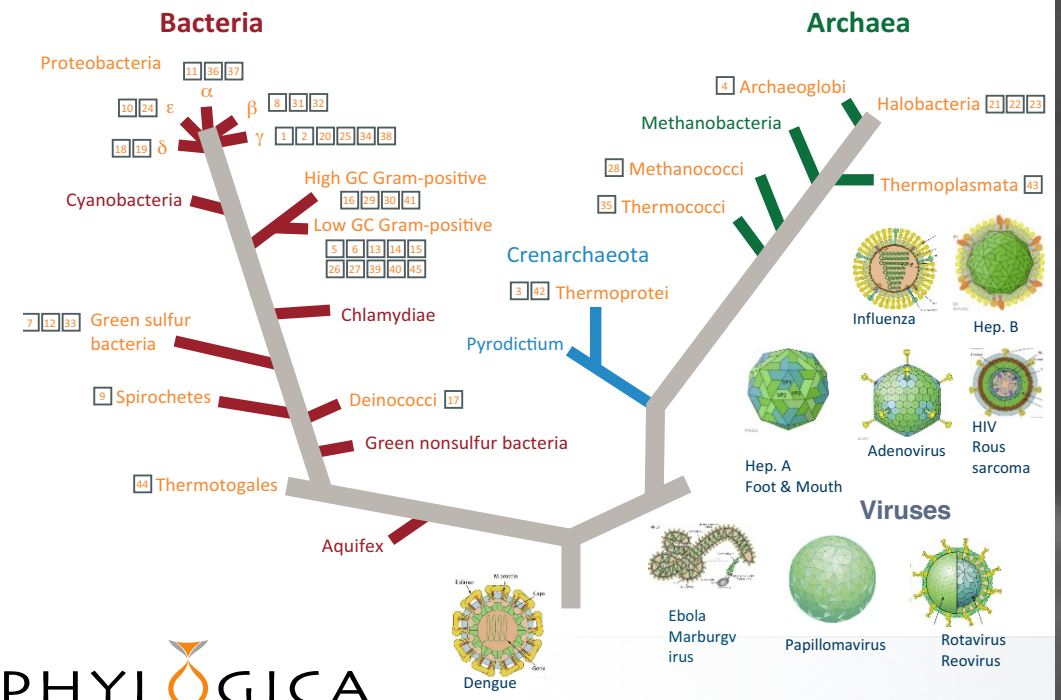
Dr Stephen Doberstein

Dr Steve Doberstein joined Nektar Therapeutics in 2010 as Senior Vice President and Chief Scientific Officer to lead all aspects of the company's drug discovery research. With over 17 years of experience in biotechnology research and development, Dr Doberstein was also responsible for directing the discovery and development of drug candidates, including antibody discovery and support of clinical development.

He was also the Vice President of Research at Five Prime Therapeutics (NASDAQ:FPRX) where he established programs resulting in multiple strategic alliances with pharmaceutical partners, built a strong proprietary pipeline and moved multiple product candidates from concept to pre-IND stages.

Our library of Phylomers®

- Phylomers are peptides derived from evolutionary diverse eubacterial and archaebacterial genomes and more recently from viral genomes (selected genes only)
- Enriched for natural secondary structures which have evolved for high affinity and biological activity
- Provide a rich source of structural motifs for screening against a wide range of targets or potential for cell penetration



1. Acinetobacter baumannii
2. Aeromonas hydrophila
3. Aeropyrum pernix
4. Archeaoglobus fulgidis
5. Bacillus cereus
6. Bacillus subtilis
7. Bacteroides thetaiotamicron
8. Bordetella pertussis
9. Borrelia burgdorferi
10. Campylobacter jejuni
11. Caulobacter crescentus
12. Chlorobium tepidum
13. Clostridium acetobutylicum
14. Clostridium difficile
15. Clostridium perfringens
16. Corynebacterium diphtheriae
17. Deinococcus radiodurans
18. Desulfovibrio vulgaris
19. Geobacter sulfurreducens
20. Haemophilus influenzae
21. Haloarcula marismortui
22. Halobacterium salinarum
23. Haloferax volcanii
24. Helicobacter pylori
25. Legionella pneumophila
26. Listeria innocua
27. Listeria monocytogenes
28. Methanococcus jannaschii
29. Mycobacterium avium
30. Mycobacterium tuberculosis
31. Neisseria gonorrhoeae
32. Neisseria menigitidis
33. Porphyromonas gingivalis
34. Pseudomonas aeruginosa
35. Pyrococcus horikoshii
36. Rhodobacter sphaeroides
37. Rhodopseudomonas palustris
38. Salmonella enterica
39. Staphylococcus aureus
40. Streptococcus pyogenes
41. Streptomyces avermitilis
42. Sulfolobus solfataricus
43. Thermoplasma volcanicum
44. Thermotoga maritima
45. Ureaplasma urealyticum (parvum)

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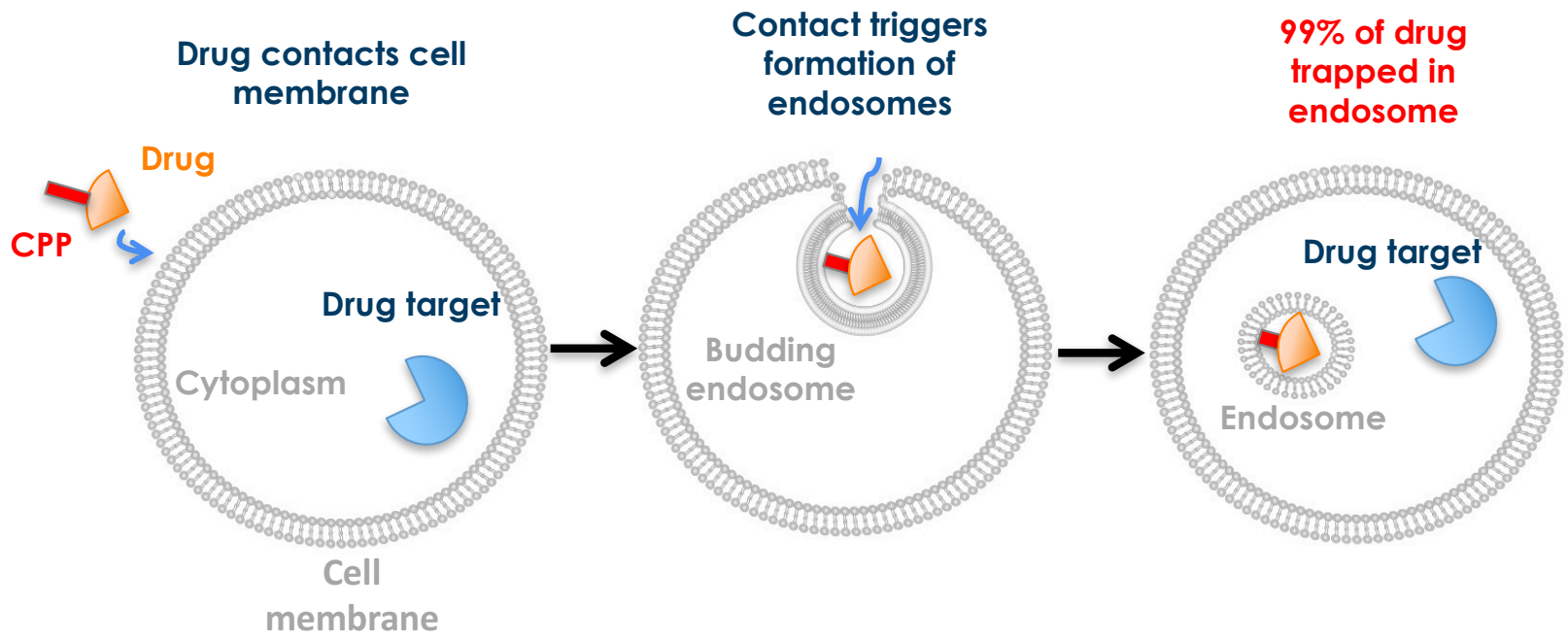
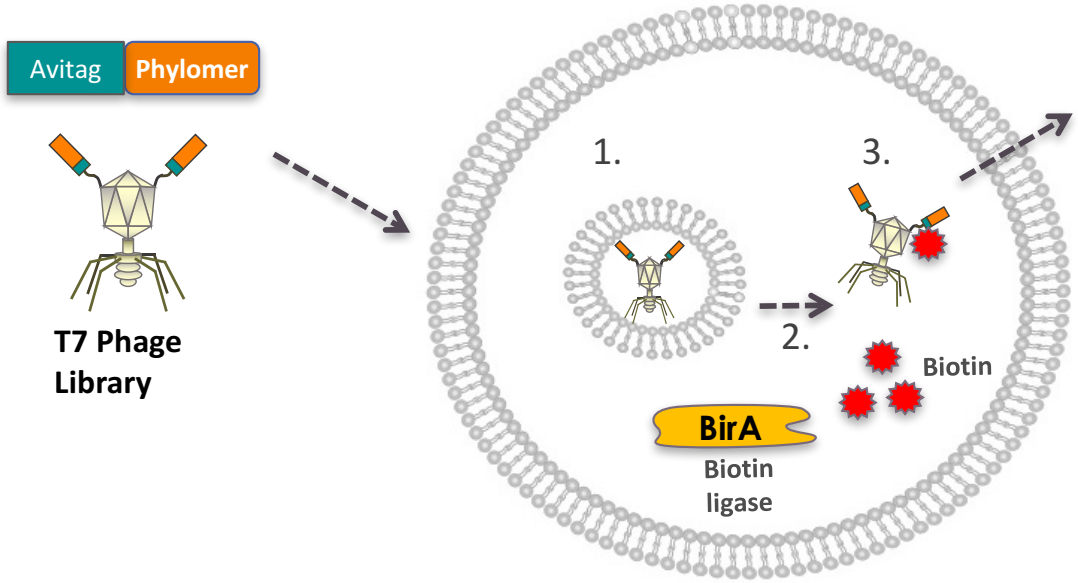
The Problem: drug cargoes are trapped in the endosomes



Conventional CPPs are often only active at concentrations of > 10 μM limiting feasible clinical application (toxicity and high costs)

Our Solution: Phylogica's endosomal escape trap



-Repeat biopanning (x2) - sequencing

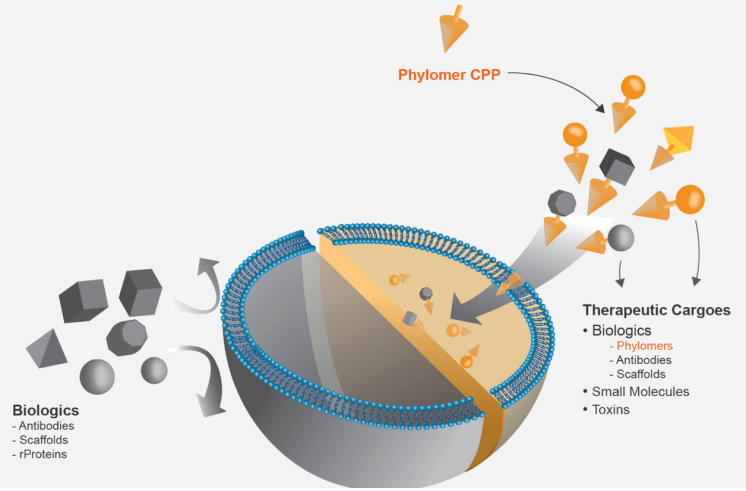
1. Phage is taken up by endosomes
2. FPP mediates phage release
3. Biotinylation of Avitag
4. Capture of biotinylated phage on Streptavidin beads

Our endosomal escape trap screen identifies FPPs that can ***escape*** the endosome allowing ***functional delivery*** of cargoes into the cytoplasm

Significant constraints in existing drug discovery approaches

The problem?

Drug discovery growth stagnating as biologics currently limited to extracellular targets (unable to enter cells)

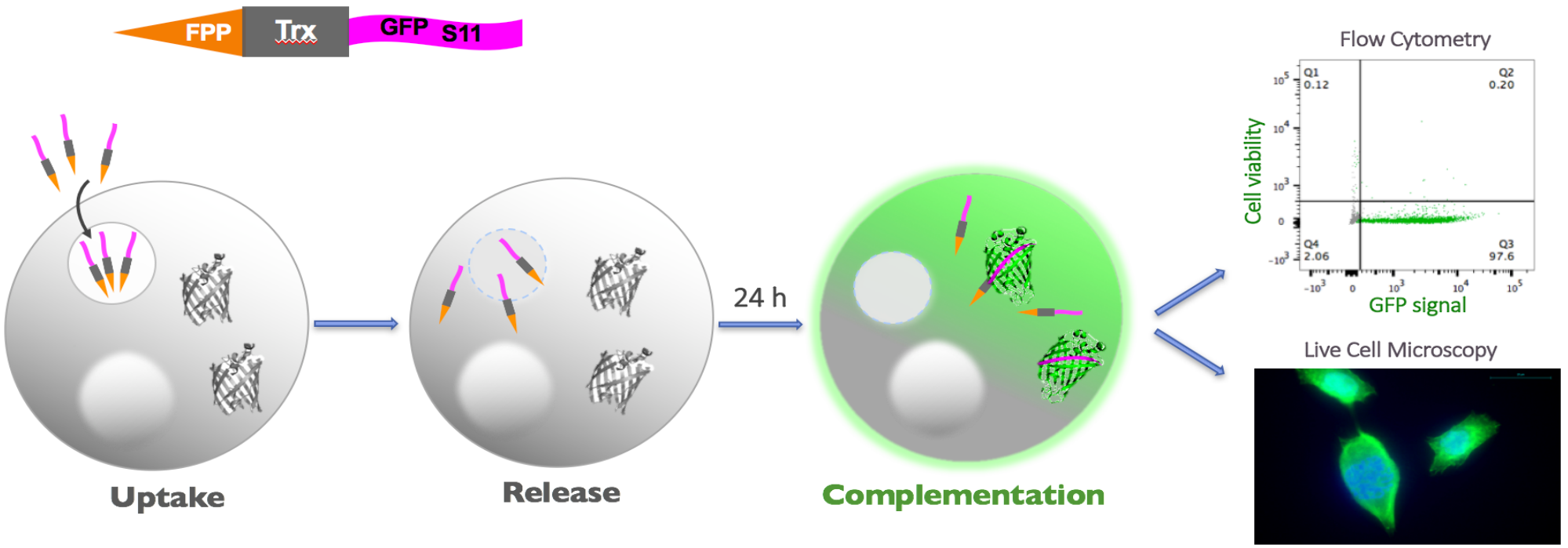


Our Functional Penetrating Peptides (FPPs) can deliver biologics into the cell

Our solution?

We can bring biologics into the cell, unlocking the potential of these powerful drugs by allowing them to reach intracellular targets

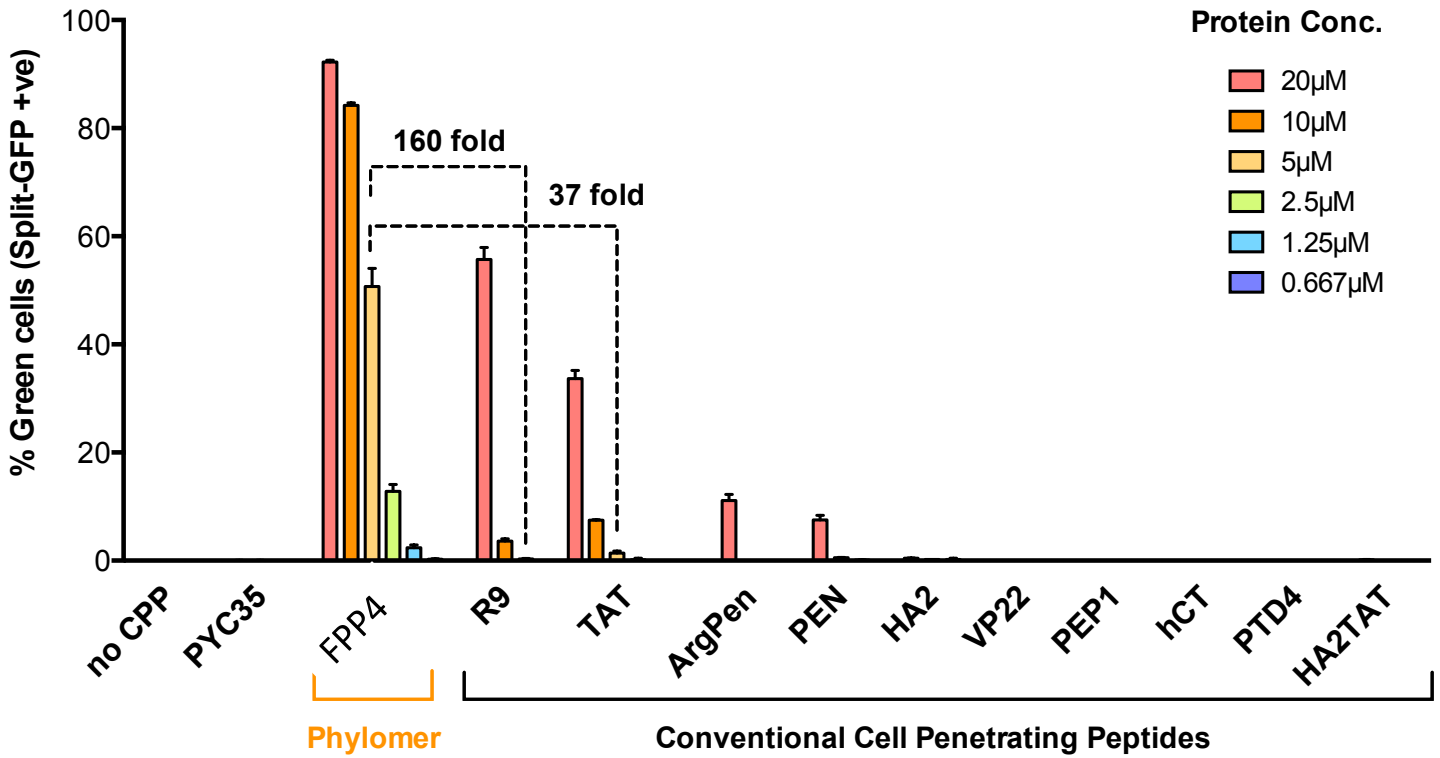
Validation of FPP endosomal escape using the split GFP complementation assay



International patent no: PCT/AU2014/050094

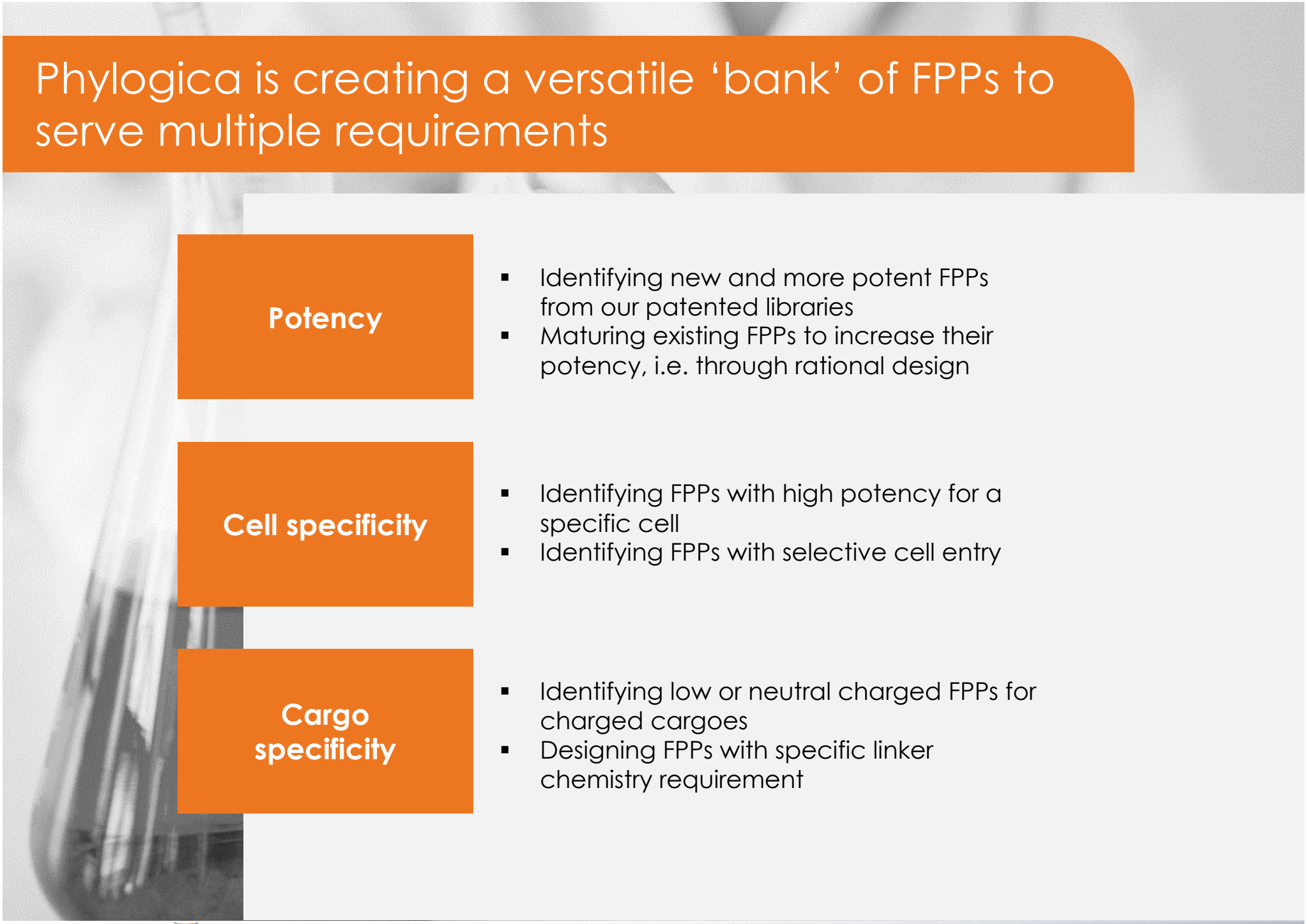
Our split GFP assay identifies FPPs that escape the endosome, to deliver cargoes to the cytoplasm

Validation of FPP endosomal escape using the split GFP complementation assay



Phylomer FPPs have superior cytoplasmic delivery compared to conventional CPPs, at lower concentrations

Phylogica is creating a versatile 'bank' of FPPs to serve multiple requirements



Potency

- Identifying new and more potent FPPs from our patented libraries
- Maturing existing FPPs to increase their potency, i.e. through rational design

Cell specificity

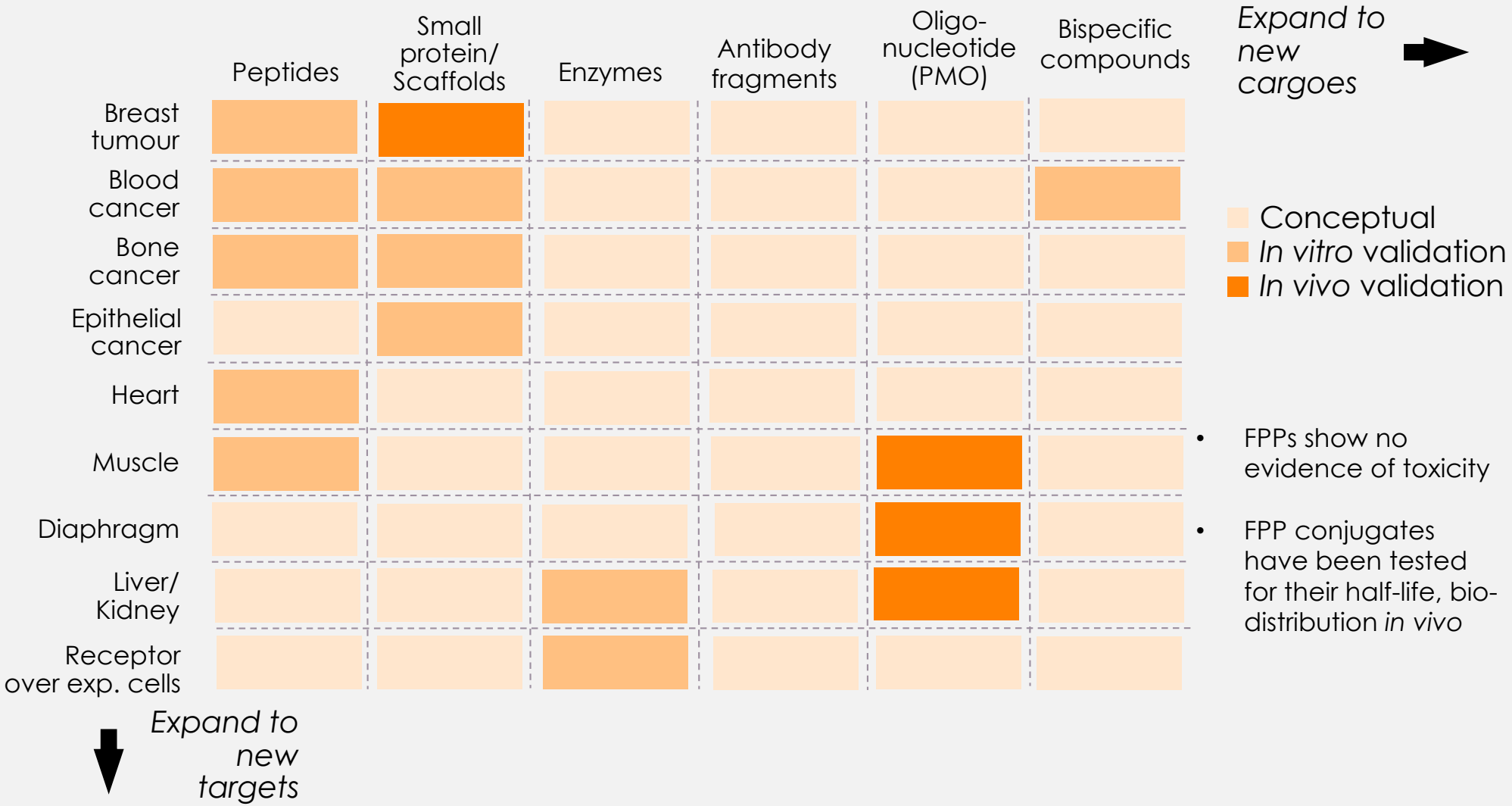
- Identifying FPPs with high potency for a specific cell
- Identifying FPPs with selective cell entry

Cargo specificity

- Identifying low or neutral charged FPPs for charged cargoes
- Designing FPPs with specific linker chemistry requirement

Phylogica is building a comprehensive matrix of FPPs to target different cargoes and cell types

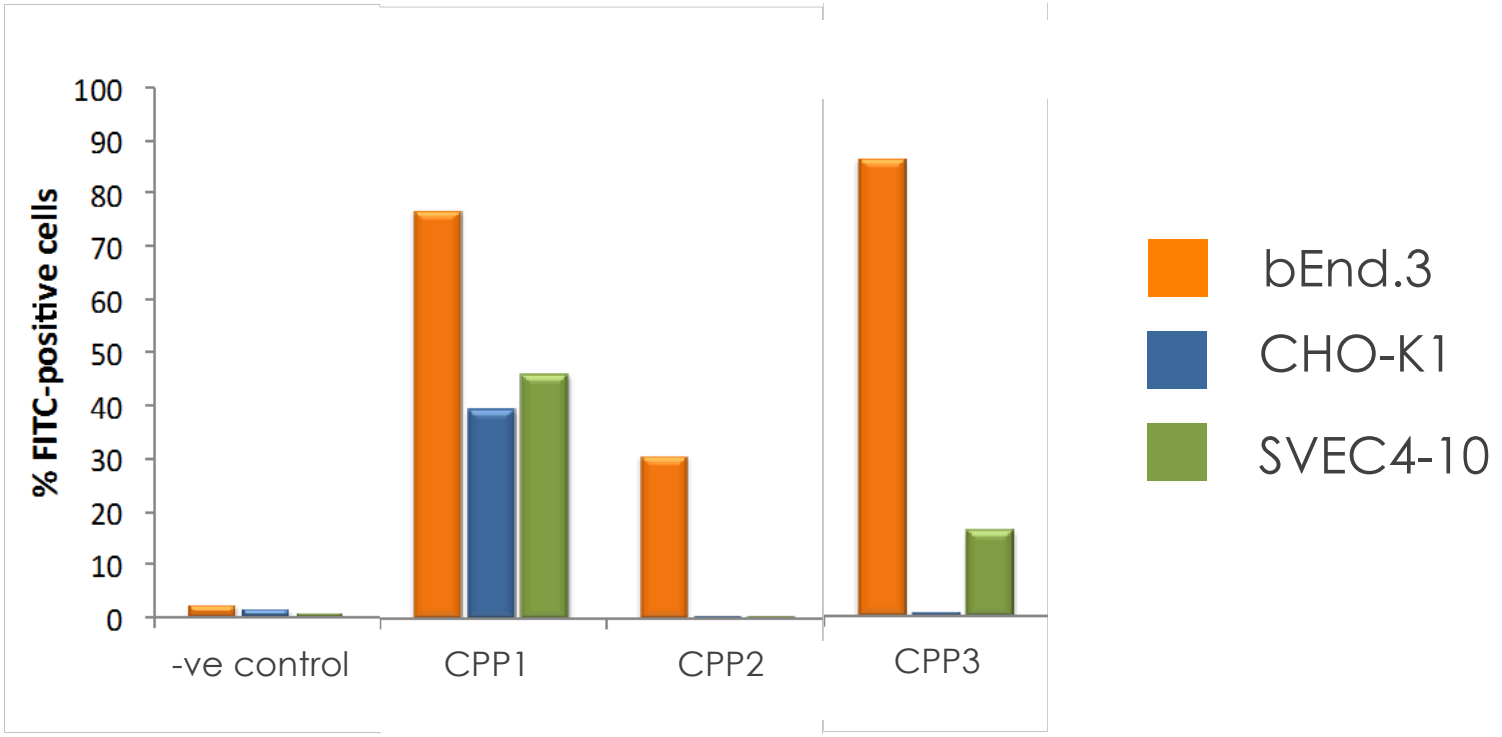
FPP validation matrix



FPPs deliver a diverse class of cargoes

Cargo Class	Cargo	Size/Charge
Toxin / large protein	Bouganin	28 kDa, pI 7.8
Small protein scaffold	Omomyc	11 kDa, pI 9.6
Enzymatic protein	β-lactamase	42 KDa, pI 5.5
Large disordered protein	PAS	50 kDa MW, 600 kDa equiv. hydrodynamic radius, pI 5.9
Peptide	Apoptotic (PAP) PPI inhibitor (DPMIα) Split protein complementation (S11 of GFP) Bcl-2 family inhibitory peptides – 26aa	17 aa, pI 10.7 15 aa, pI 8.26 30 aa, pI 6.75 26 aa, pI 6.28
Bispecifics	Bcl-2 inhibitory peptide + Omomyc scaffold	37 kDa, pI 8.02
Oligonucleotides	Exon-skipping Morpholinos	24 base pairs, neutral

Efficient delivery of Phylomer CPPs into brain endothelial cells



NOTE: These Phylomers have not been validated using Phylogica's endosomal escape validation assays

Phylomer CPPs can efficiently enter mouse brain endothelial cells, with potential applications in delivering cargoes across the blood brain barrier

FPPs show no evidence of toxicity

Toxicity in adult male C57BL/6J mice, 40mg/kg dose, daily injections for 7 days

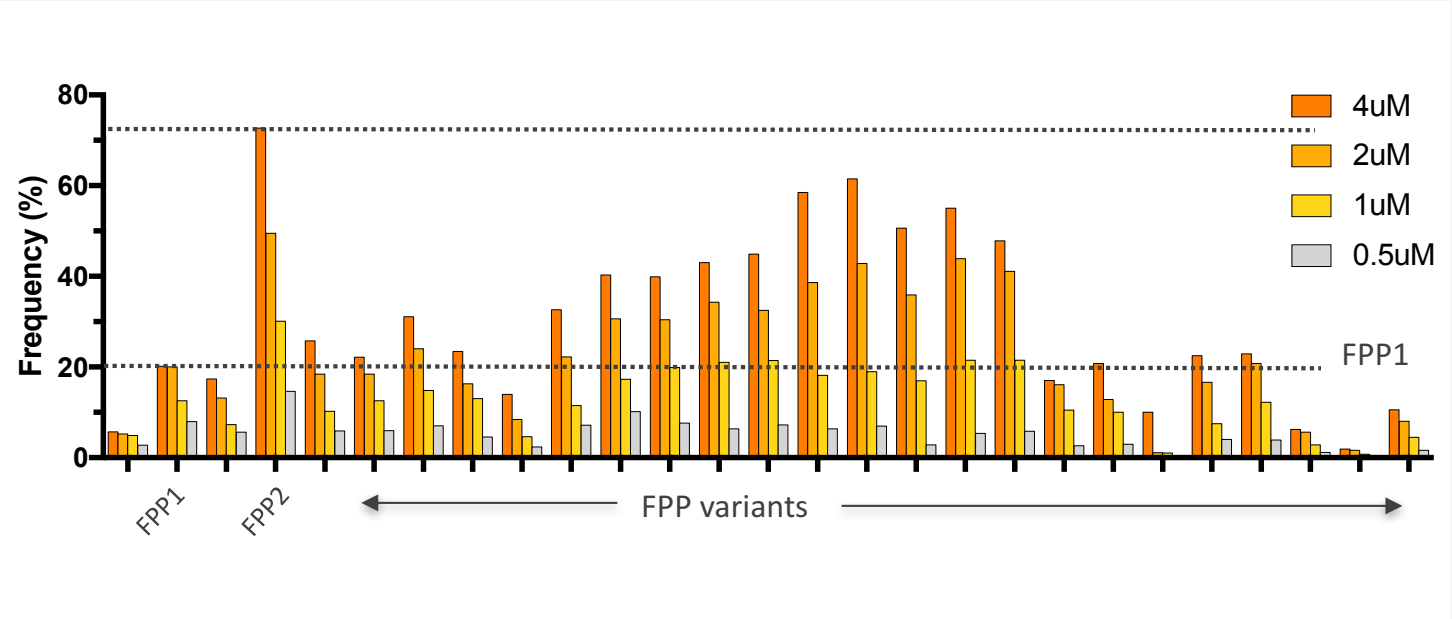
	FPP (n=6)		**Untreated** (n=4)		
	Mean	**StDev**	**Mean**	**StDev**	**Significance**
ALT, U/L	59.73	39.09	107.60	18.54	No, p=0.054
AST, U/L	84.98	69.05	81.61	44.02	No, p=0.94
Urea, mg/dL	50.99	8.30	57.06	3.24	No, p=0.21
Creatinine, mg/dL	0.33	0.05	0.48	0.09	Yes, p=0.01

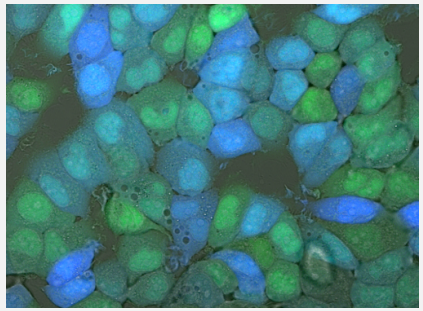
FPP1 showed no evidence of *in vivo* toxicity at 40mg/kg doses.

This is in contrast to the toxicity associated with other positively charged CPPs

FPP1 has been significantly improved upon, and new variants are being validated *in vitro*

CHO-K1 cells





FPP2 cell entry into T47D cells (4 uM protein)

- Promising maturation variants will be re-tested in the split GFP or split β-lactamase assay

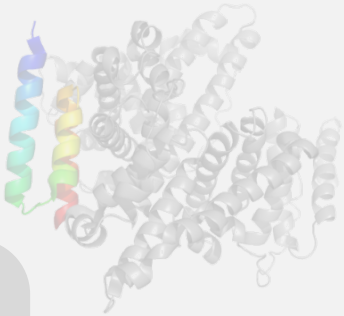
Phylogica's FPP improvement program through rational design has demonstrated the ability to enhance potency with no increase in toxicity

FPPs are compatible with engineering approaches to enhance pharmacological properties

Desired Effects

Serum half-life extension

Reduced clearance



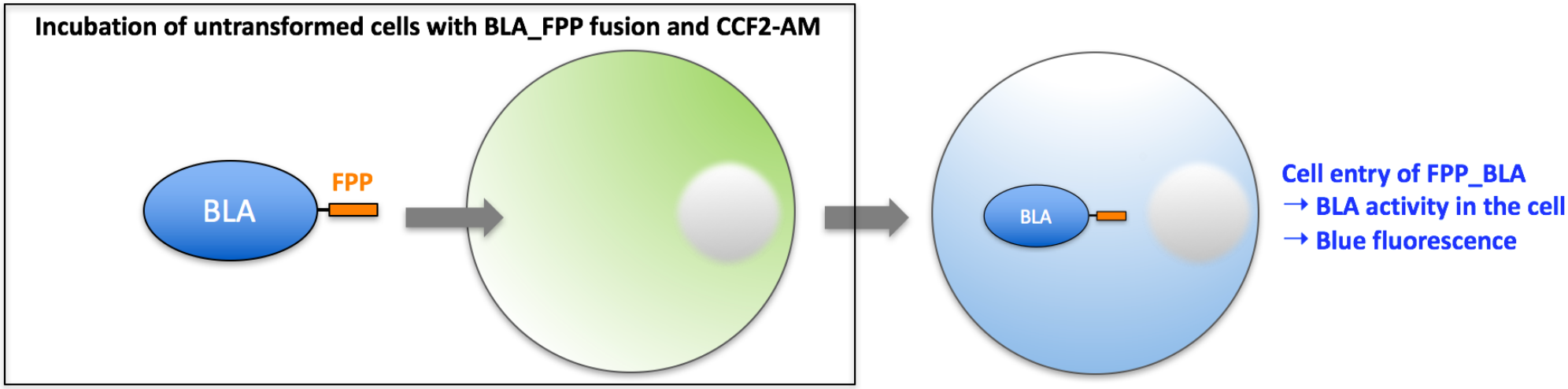
Strategies

- Increase receptor cycling
- Increase protein size and negative charge

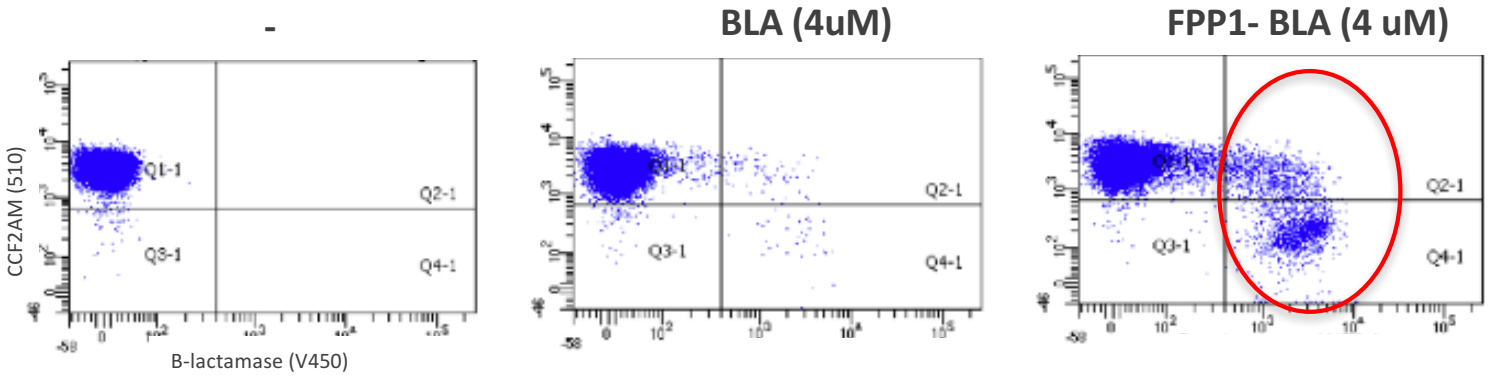
- Fc Fusion
- Albumin
- ABDCon
- PEGylation
- PASylation

FPPs can be tuned with a range of pharmacokinetic optimisation technologies to improve half-life and prolong circulatory time

Efficient delivery of an FPP-conjugated enzyme (β-Lactamase, BLA)



Blue fluorescence, CHO-K1 cells incubated with FPP1-BLA for 1 h

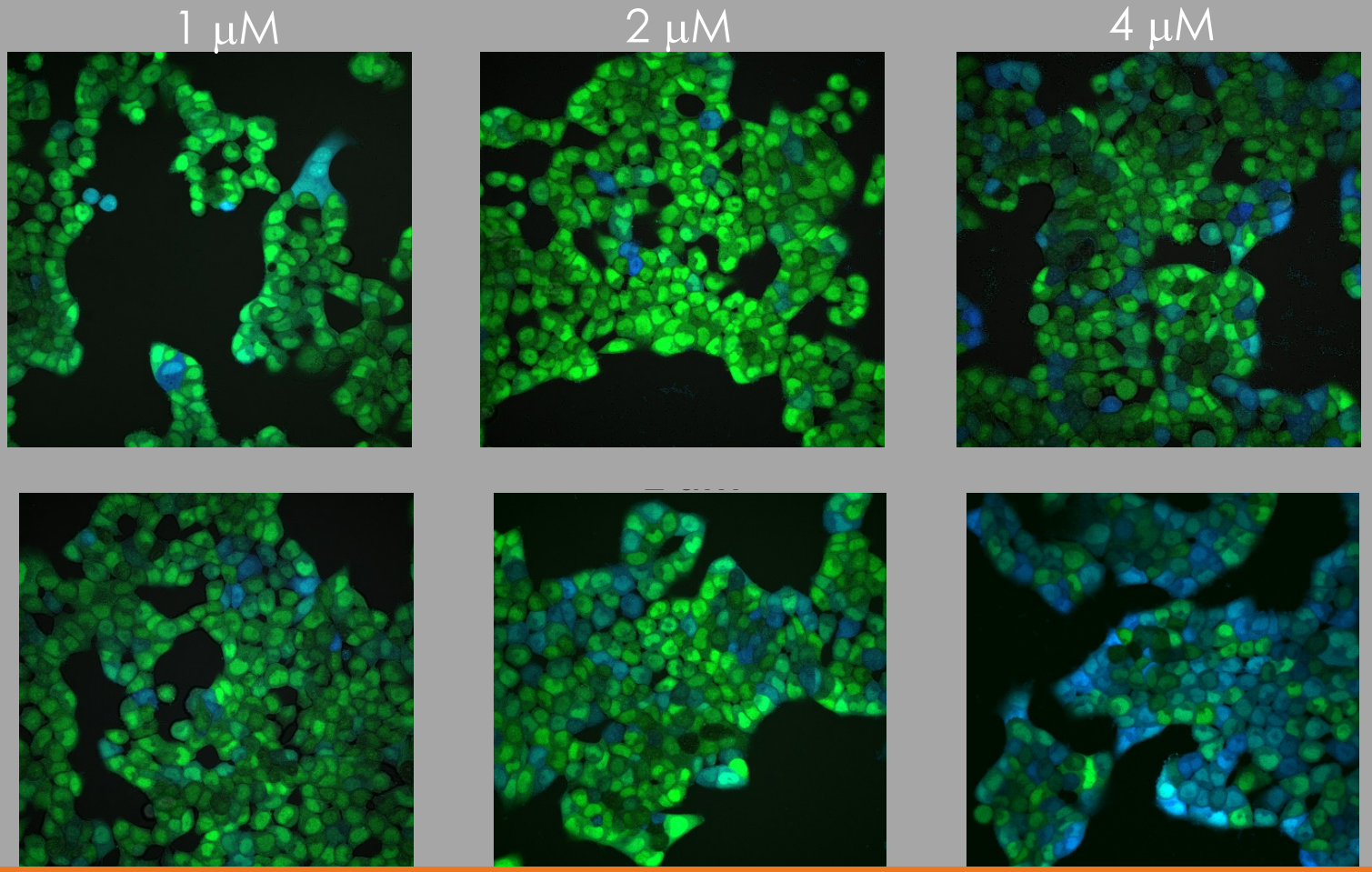


FPP-mediated cell entry

FPPs deliver functional enzymes into the cell at concentrations as low as 0.5 µM

Optimised FPPs mediate enhanced delivery of β-Lactamase into breast cancer cells

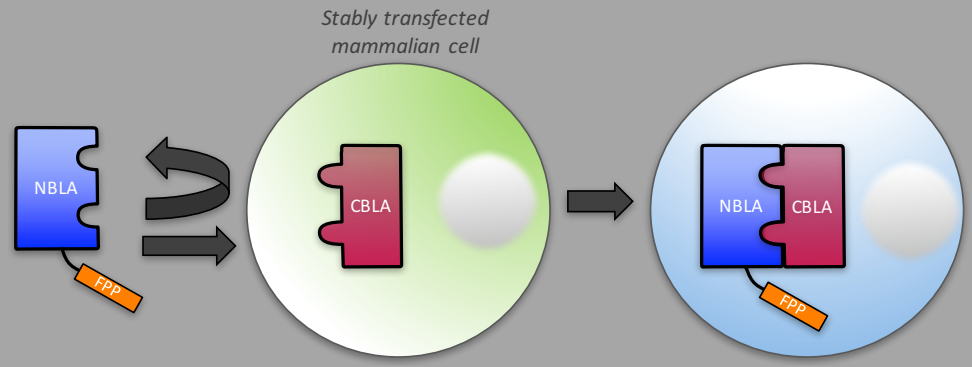
Blue fluorescence, T47D cells incubated with FPP1-BLA or optimised variant, FPP2 for 1 h



Our FPPs are constantly being improved for enhanced delivery of cargoes into a wide range of cell types

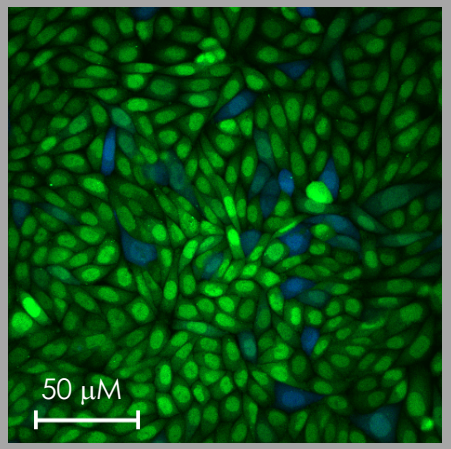
Efficient cytoplasmic delivery of proteins using a split β-Lactamase complementation assay

Blue Fluorescence; CHO-CBLA cells incubated with FPP1-NBLA (8 μM)

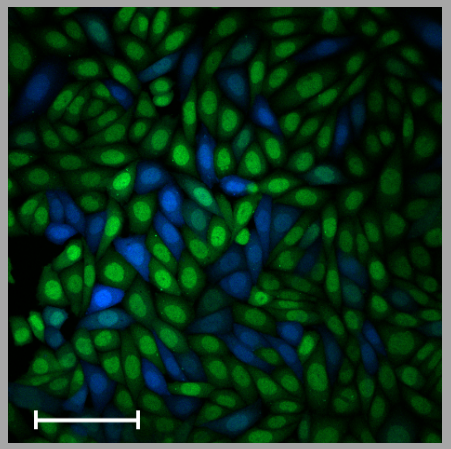


Only endosomal escape leads to β-lactamase complementation and signal development

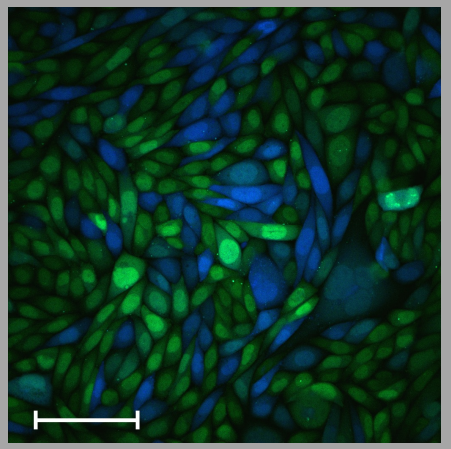
30 min



60 min



120 min



FPPs deliver functional protein into cells with efficient uptake and cytoplasmic delivery observed between 30-60 min

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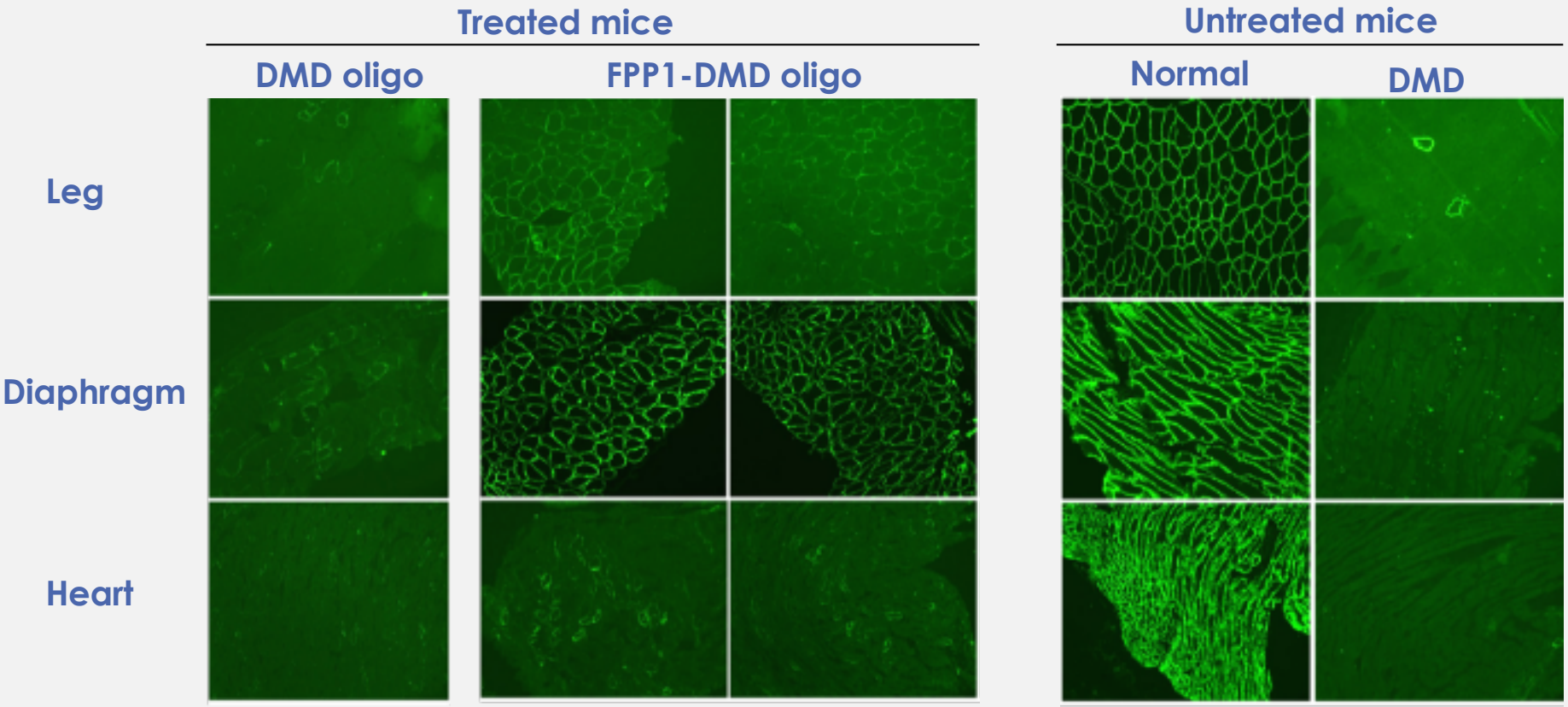
Dystrophin levels are restored by FPP-mediated delivery of DMD[1] PMO[2] *in vivo*

Dystrophin levels and muscle architecture, C57BL/10ScSnmdx mice



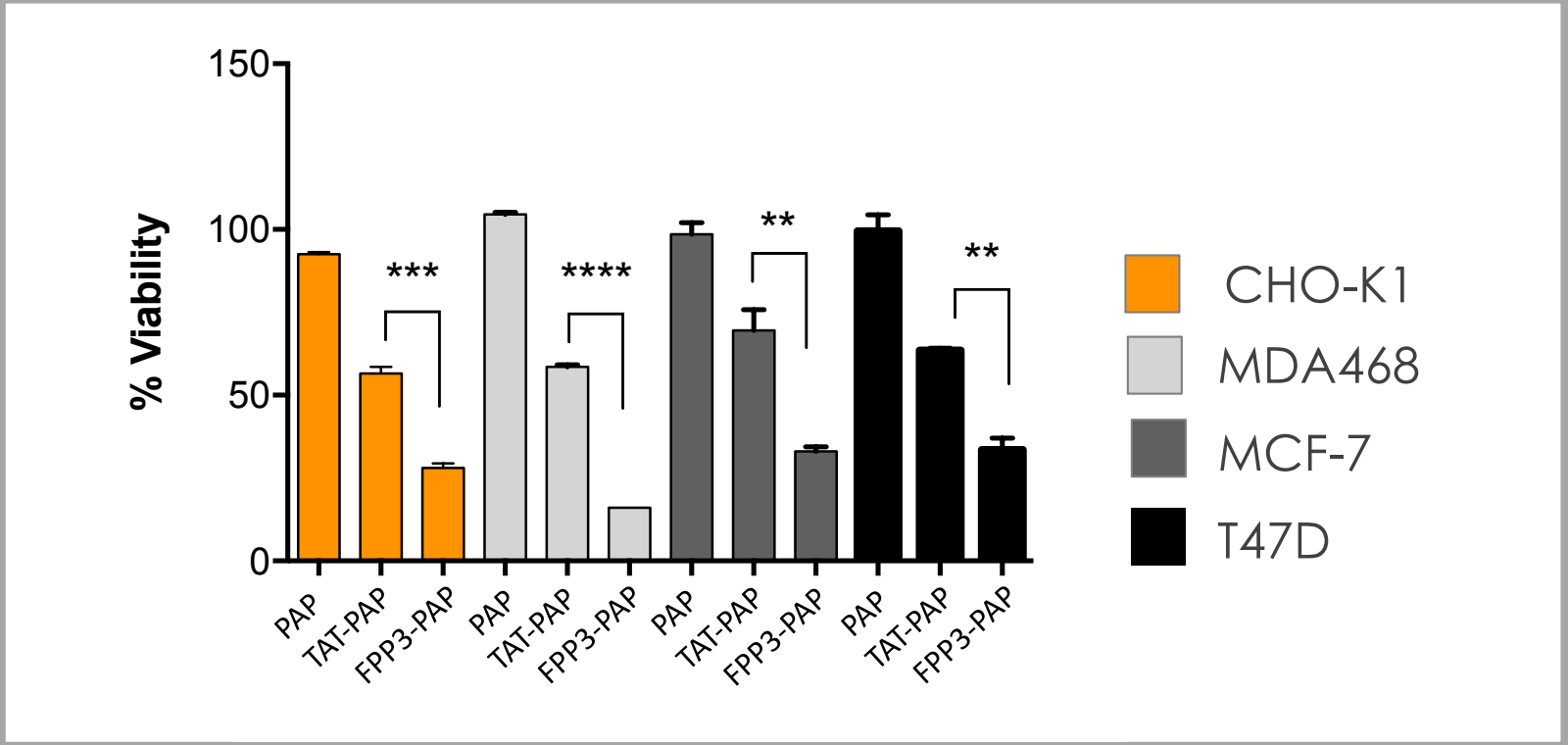
Collaborator: Sue Fletcher, Centre for Comparative Genomics

Initial tests with Phylogica's FPP1 showed improvement over 'naked' PMOs in DMD mice, while also showing low toxicity

[1]DMD: Duchenne muscular dystrophy, [2]PMO: Phosphorodiamidate Morpholino Oligomer

FPP-delivered pro-apoptotic peptide (PAP) significantly impact cell viability in a range of cell lines

Cell viability after 24 h



FPP3-conjugated PAP outperforms naked PAP and PAP fused to TAT in a panel of breast cancer cell lines and in CHO-K1 cells

Phylogica's Oncology Pipeline harnesses our FPP technology to reach intracellular targets

- Phylomer screens against validated and clinically relevant oncology targets
  - cMyc, N-Myc, Stat5 and YB1
- Validated hits already exceed potency of gold standard inhibitors
- Stat5 and YB 1 collaborations with Dana Farber Institute, Harvard Medical School

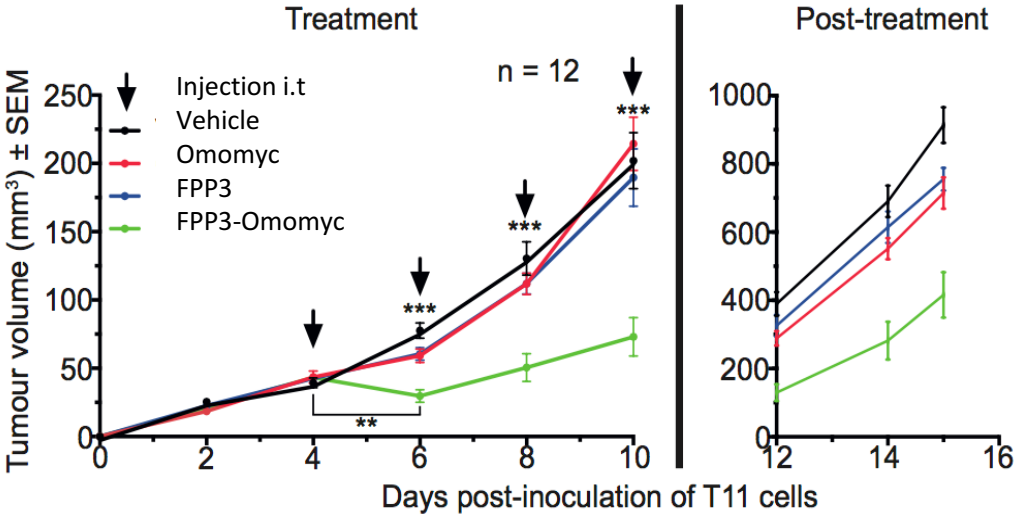
Program	Potential Targeted Indications*	Hit ID	Hit to Lead Validation In Vitro	Hit to Lead Validation In Vivo	Lead Selection/ Optimisation	Preclinical/ IND enabling
Myc	AML, Breast Cancer (TNBC), Neuroblastoma	✔	✔	✔	progressing	
STAT5	AML, CML	✔	✔	progressing		
YB1	AML, Breast Cancer (TNBC)	✔	✔	progressing		
FPP**	Intracellular Payloads	✔	✔	✔	*progressing*	

* current shortlisted indications only

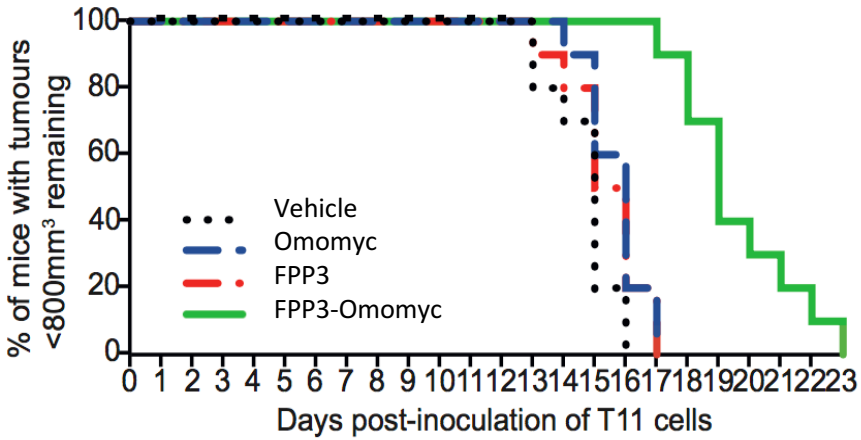
** Multiple diverse FPP-payload constructs at various stages (includes external collaborations)

FPP-Omomyc inhibits breast cancer cell growth *in vivo*

Tumour volume, T11 triple negative breast cancer graft in mice



Animals with tumours, T11 triple negative breast cancer graft in mice



Collaborator: Pilar Blancafort, Harry Perkins Institute

- FPP3-Omomyc significantly inhibits breast cancer cell growth
- FPP3 and Omomyc alone showed no significant effects on tumour growth
- Tumour growth was inhibited for days after cessation of treatment

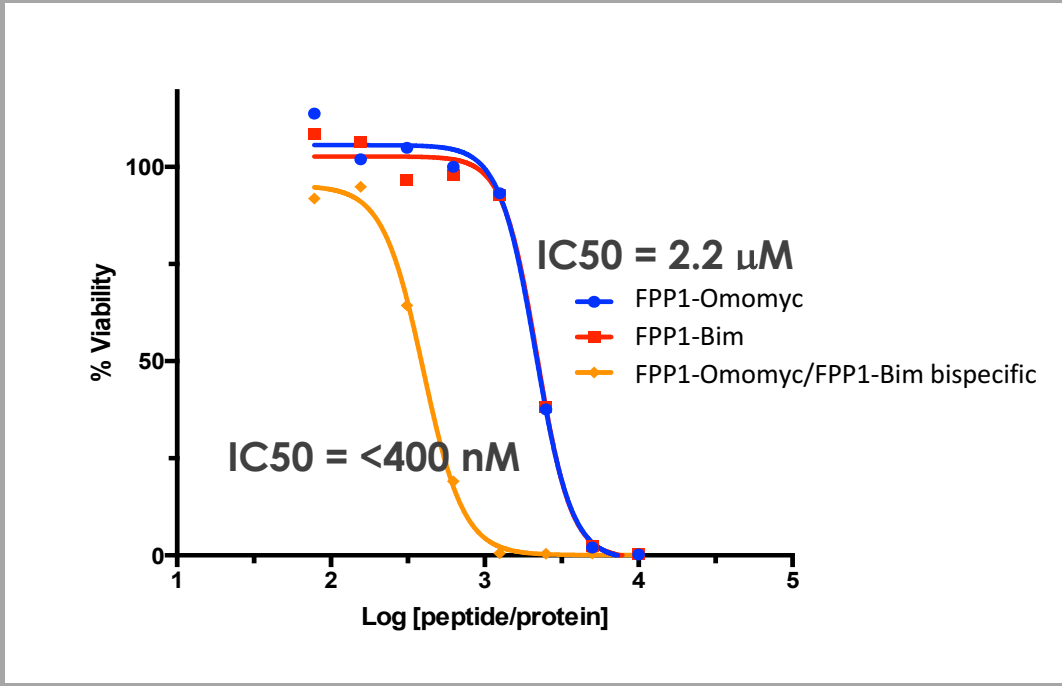
FPP-Omomyc is active across multiple cell types

Cell line	Disease	Cell Line Characteristics
T47D	Breast cancer	p53 mut$^{(hetero)}$, Myc^{+++}
MDA-MB-468	Breast cancer	p53 mut$^{(hetero)}$, triple -ve
SUM159	Breast cancer	Basal, Triple -ve
B1.15 (mouse)	Breast Cancer	Basal, Brca-/-
A1.8 (mouse)	Breast Cancer	Basal, Brca-/-
T11 (mouse)	Breast cancer	Basal, Triple -ve, P53-/-
PyMT (Mouse)	Breast cancer	Luminal/basal
Saos-2	Osteosarcoma	p53 null
14169	NUT midline carcinoma	Bet inhibitor sensitive
EμMyc #560 (mouse)	B lymphoma	Myc driven
AMO-1	Plasmacytoma	Myc overexpressing
HL-60	Acute Myeloid Leukaemia	-

FPP-Omomyc is inhibitory in breast cancer, osteosarcoma, NUT midline cancer, B lymphoma, plasmacytoma and myeloid leukaemia cells with a range of Myc dependencies

Potent activity of bi-specific compound targeting BCL/MCL and MYC in EμMyc lymphoma cells

Cell viability after 24 h, EμMyc murine lymphoma cells



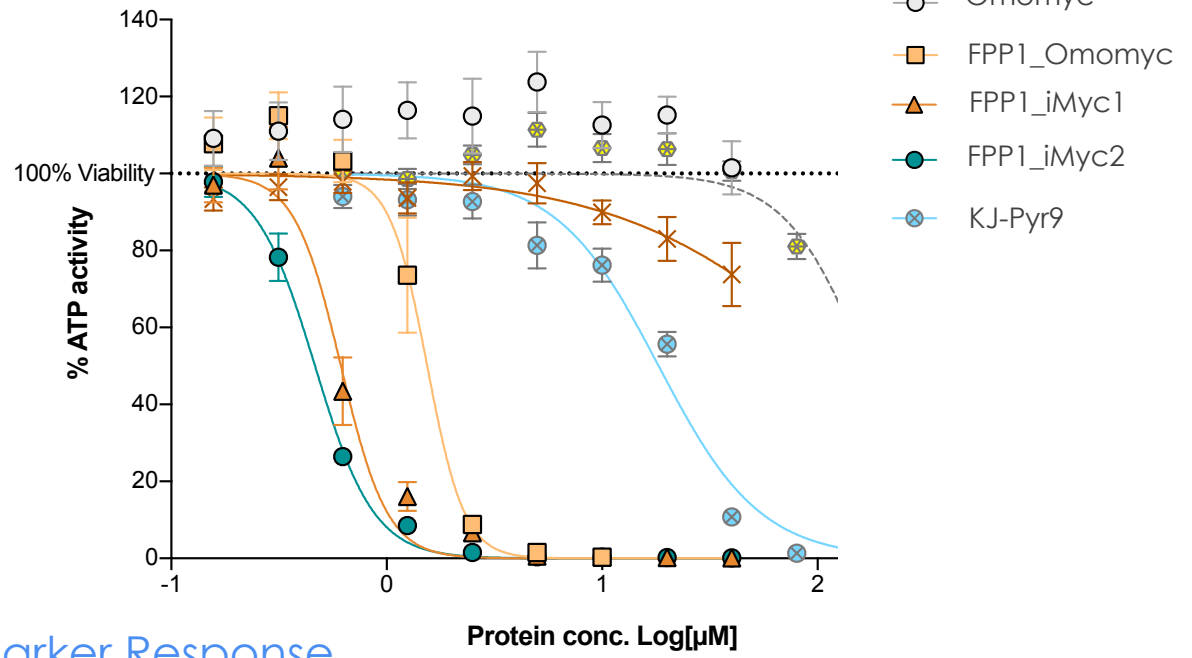
- The IC_{50} of FPP1-Bim-Omomyc-FPP1 is less than 400 nM

Collaborator: Doug Fairlie, ONJCRI

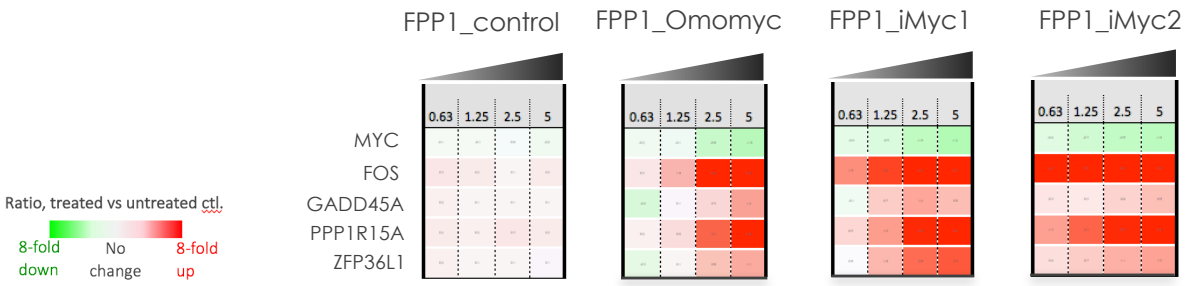
iMyc outperforms Omomyc and small molecule MYC inhibitors in AMO-1 human myeloma cells

Phylogica's first generation iMyc phylomers lead to functional inhibition of MYC and have ***higher potency*** than Omomyc and small molecule inhibitors of Myc

ATP Activity (%) after 24 h



Biomarker Response



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High affinity primary 'iMyc' Phylomers against human c-MYC

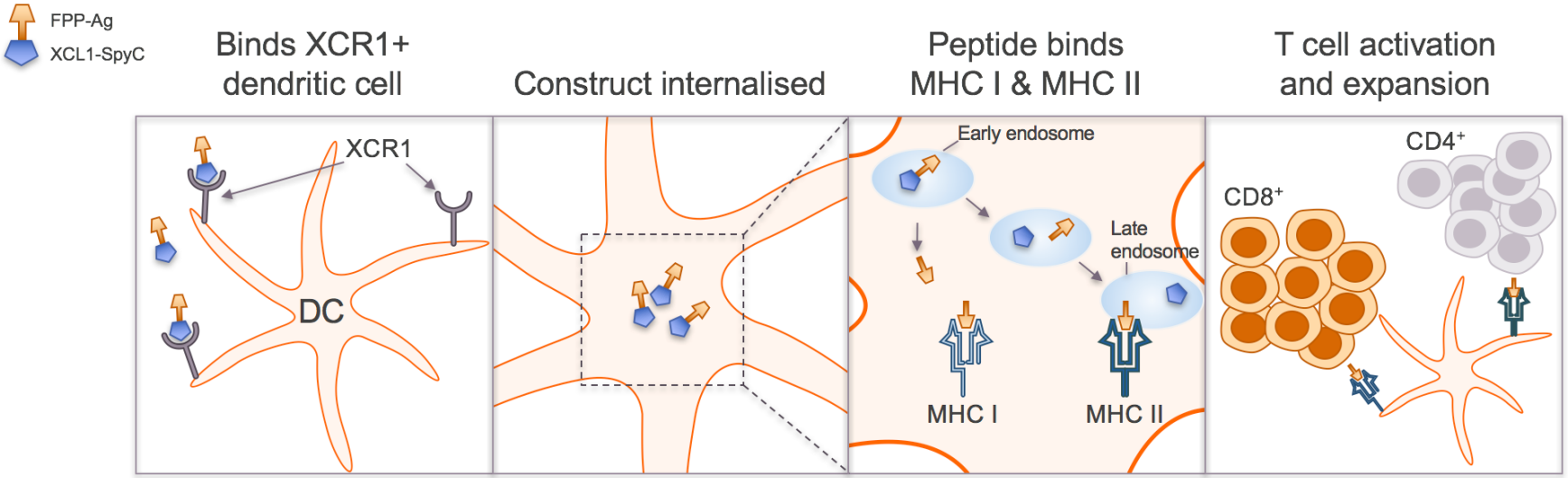
Human c-MYC Binding Affinity; kD determined using Octet® Systems

	kD (nM) (Mean)	kD (nM) (SD)
MAX	47.1	11.2
iMyc1	30.4	4.3
iMyc2	176.2	107.9
Omomyc	191.5	34.5

(n > 3)

Phylogica's first generation iMyc phylomers have target binding affinities comparable to natural ligand (Max) and Omomyc protein

FPP efficiently targets cross presenting dendritic cells for an effective peptide vaccine



XCL1 target vaccine to XCR1 on XCR1⁺ DCs

CPP internalisation via endocytosis:
- MHC II = endosomal processing
- MHC I = cytosolic processing

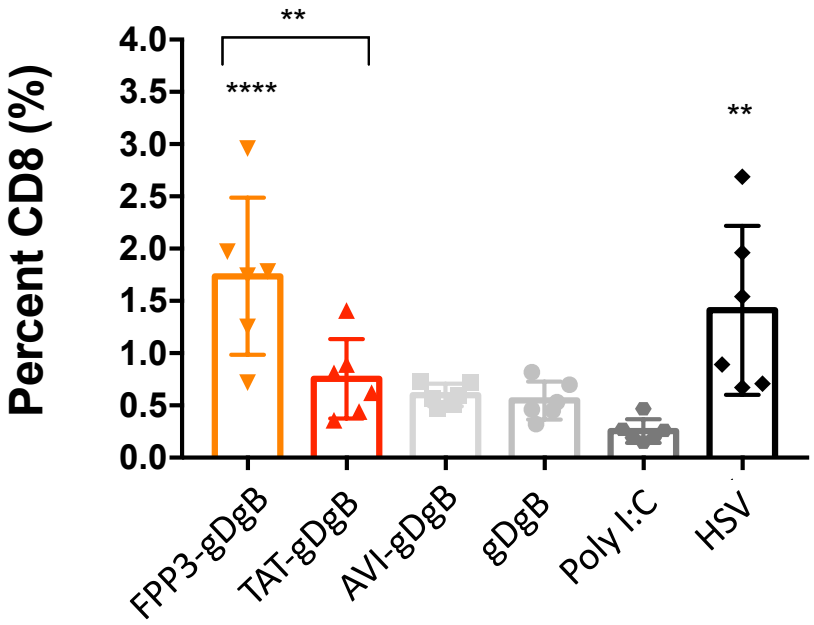
T cell expansion:
- CD8⁺ gBT.I T cells (MHC I)
- CD4⁺ gDT.II T cells (MHC II)

Collaborator: Jason Waithman, Telethon Kids Institute

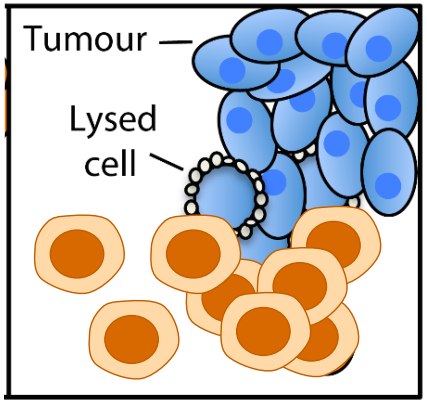
- FPP3 and XCR1 ligand facilitate internalisation into cells
- Only endosomal escaping CPPs will result in CD8+ T cell expansion via MHC I loading

FPP delivered antigen leads to greater expansion of CD8+ T cells compared to TAT

CD8+ T cells (%), mice primed with FPP3-Ag or TAT-Ag for 14 days. Analysis of T cells 7 days post-challenge



CD8+ T cells attack tumor



Collaborator: Jason Waithman, Telethon Kids Institute

- CD8+ T cell expansion is evidence of cytosolic processing of antigen via MHC-I
- The FPP peptide vaccine approach primes CD8+ T cells to identify tumors and destroy them

Partnering Strategy

Helping customers add value to their existing drugs …

Genentech
A Member of the Roche Group

Roche

PHORENOST
DRUGGING THE UNDRUGGABLE

Pfizer

MedImmune

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

… and partnering with academia to enhance the value of our library

HARVARD MEDICAL SCHOOL

Murdoch UNIVERSITY

LA TROBE UNIVERSITY

Brunel University London

The University Of Queensland AUSTRALIA | IMB
Institute for Molecular Bioscience

Perkins
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Olivia Newton-John
Cancer Research Institute

Agency for Science, Technology and Research
SINGAPORE

DANA-FARBER CANCER INSTITUTE

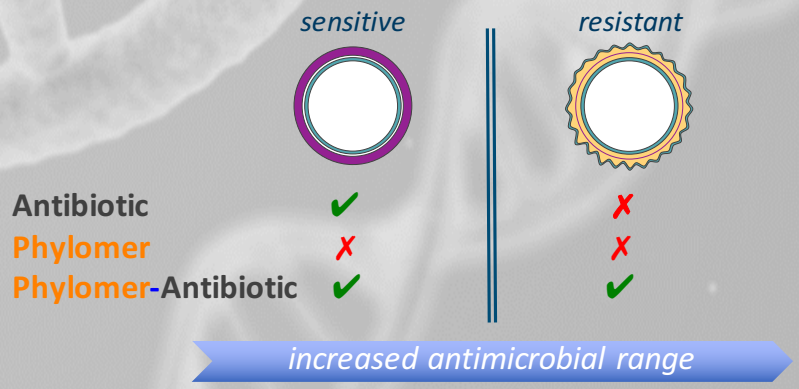
Antimicrobials

The Problem: Antimicrobial resistance is one of the 3 most important health problems

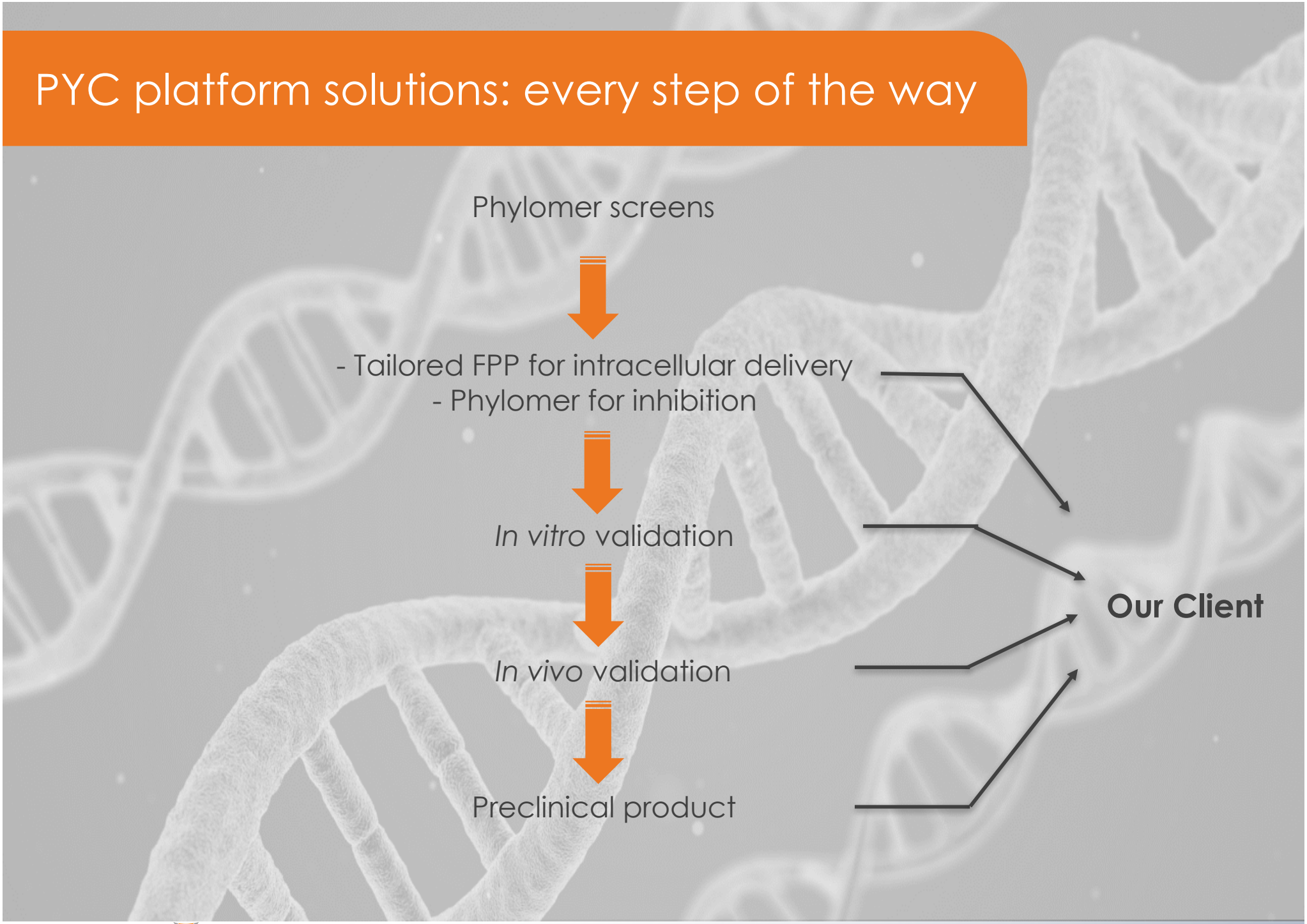
Our Solution: Phylogica's diverse platform and proprietory cell penetrating peptide discovery technology is being harnessed to discover novel antibiotics

Genentech
A Member of the Roche Group

- Our collaboration aims at the isolation of Phylomers that can help killing multi-drug resistant "super bugs"
- Phylomers are expected to increase the potential to kill bacteria which can cause pneumonia, urinary tract infections, meningitis and sepsis in people with a weakened immune system



PYC platform solutions: every step of the way



Phylogica adds value to customer drugs