Using novel cell penetrating Phylomer peptides to access intracellular targets with biologics

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PHYLOGICA

BREAKTHROUGH PEPTIDE THERAPEUTICS

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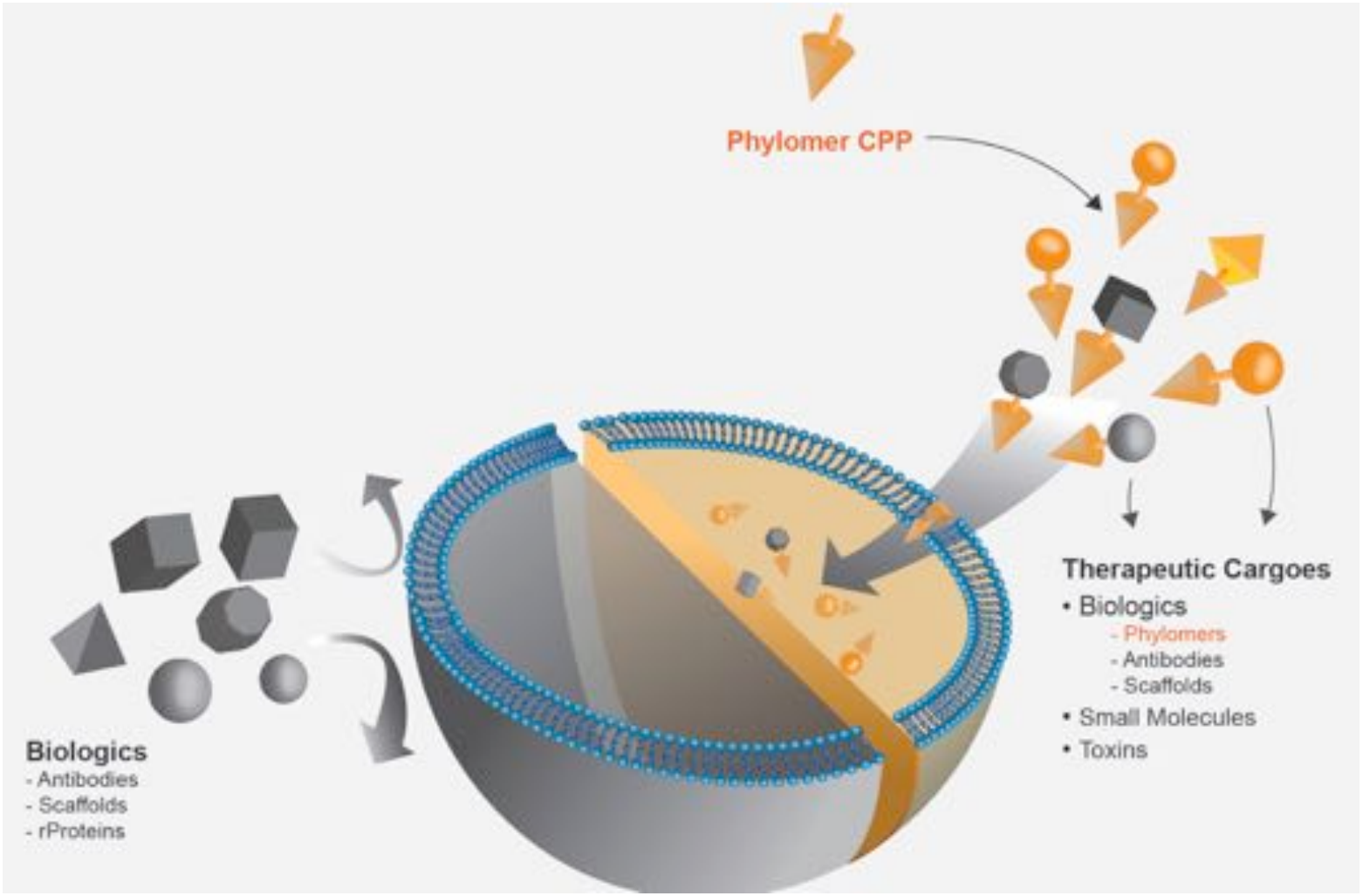
Phylogica: unique capabilities for intracellular discovery and delivery of biologics drugs



Potential to expand the druggable intracellular landscape by >10-fold with Phylomer *Functional Penetrating Peptides (FPP)* - Phylogica's proprietary cell penetrating peptides.

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About Phylogica

- ASX Listed company (ASX:PYC)
  - Based in Perth, Western Australia with 22 Scientists and market cap. of ~A$50M
  - Founded by Telethon Kids Institute of WA and Fox Chase Cancer Centre in Philadelphia

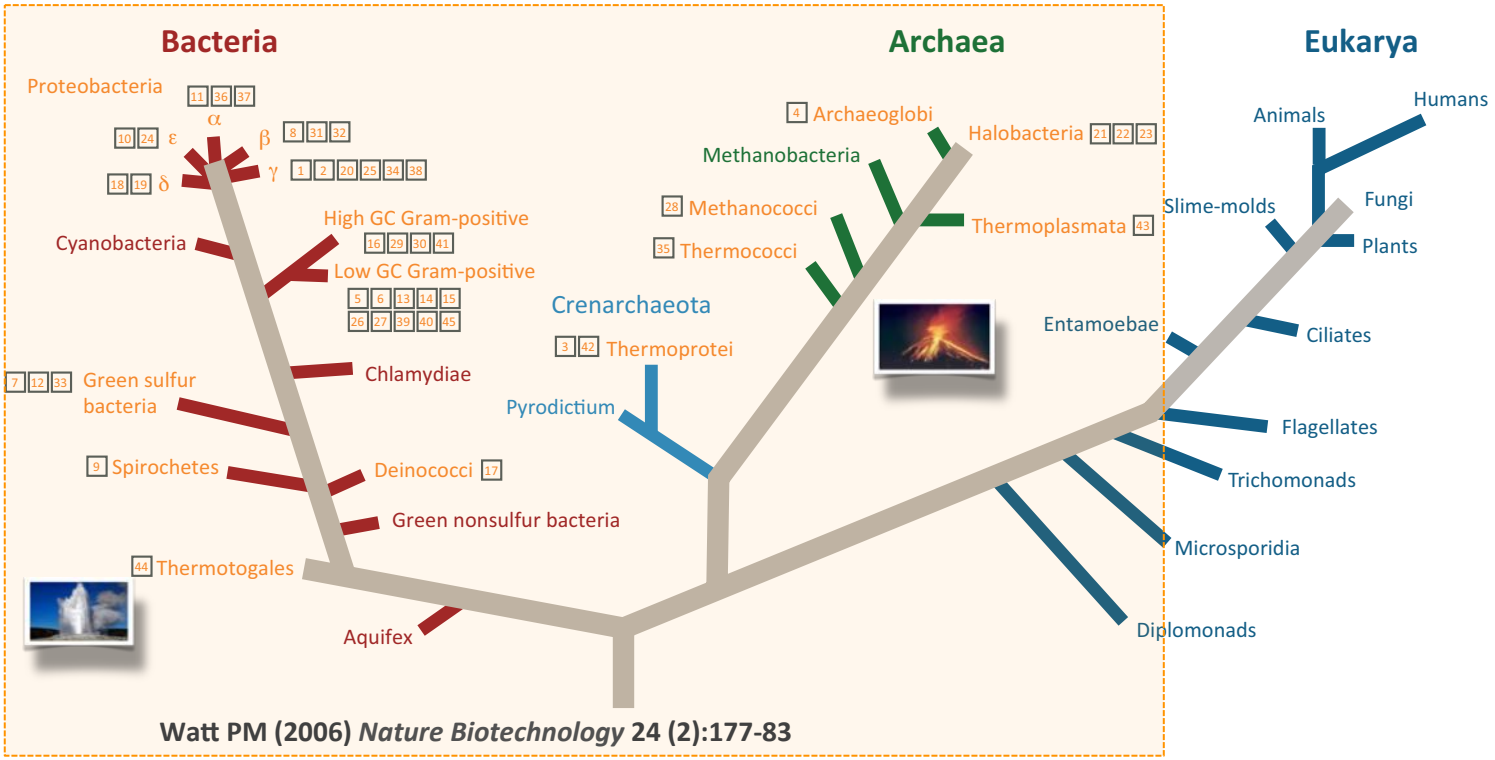
- Owns unique proprietary class of peptide therapeutics (Phylomers®)
  - Most structurally diverse source of peptides available for drug discovery (hundreds of billions of Phylomers derived from thousands of fold families)

- Current internal focus is on 3 key areas
  1. **Superior intracellular delivery** of peptide drugs against intracellular targets using **proprietary class of cell-penetrating peptides ("FPPs")**
  2. Advancing **proprietary intracellular oncology payloads** against intractable targets
  3. Validated platform for discovery

- Discovery alliances
  - past/present - Roche, Pfizer, MedImmune, Janssen and Genentech

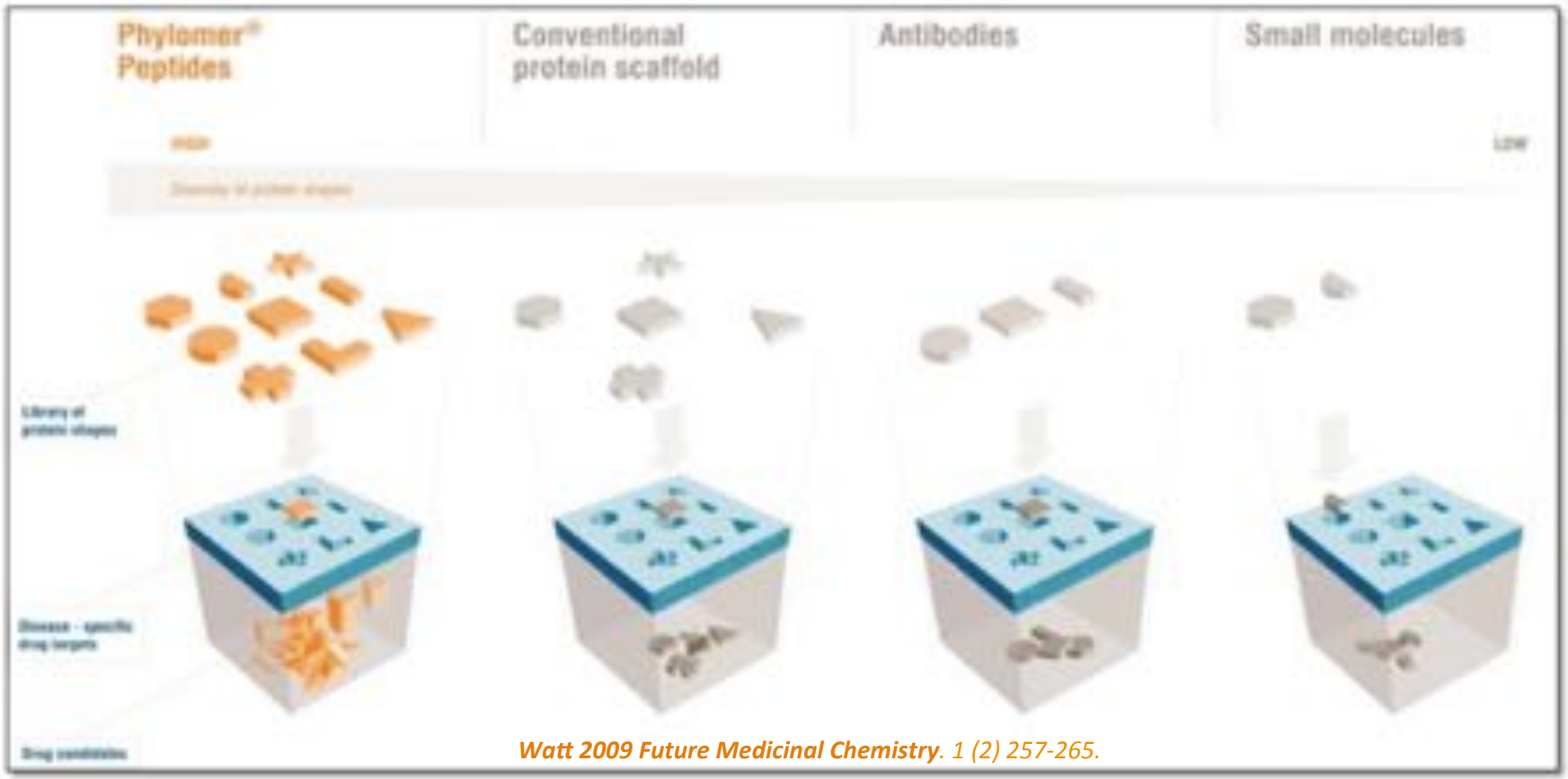
Phylomers: peptides from parts of biodiverse proteins

- Encoded by >35 biodiverse microbial genomes (derived from volcanoes, geysers and undersea vents)
- Rich source of diverse natural secondary/tertiary structures
- Average size ~30 amino acid residues
- Libraries encode hundreds of billions of distinct peptides



Watt PM (2006) *Nature Biotechnology* 24 (2):177-83

More structures for better hits against more targets

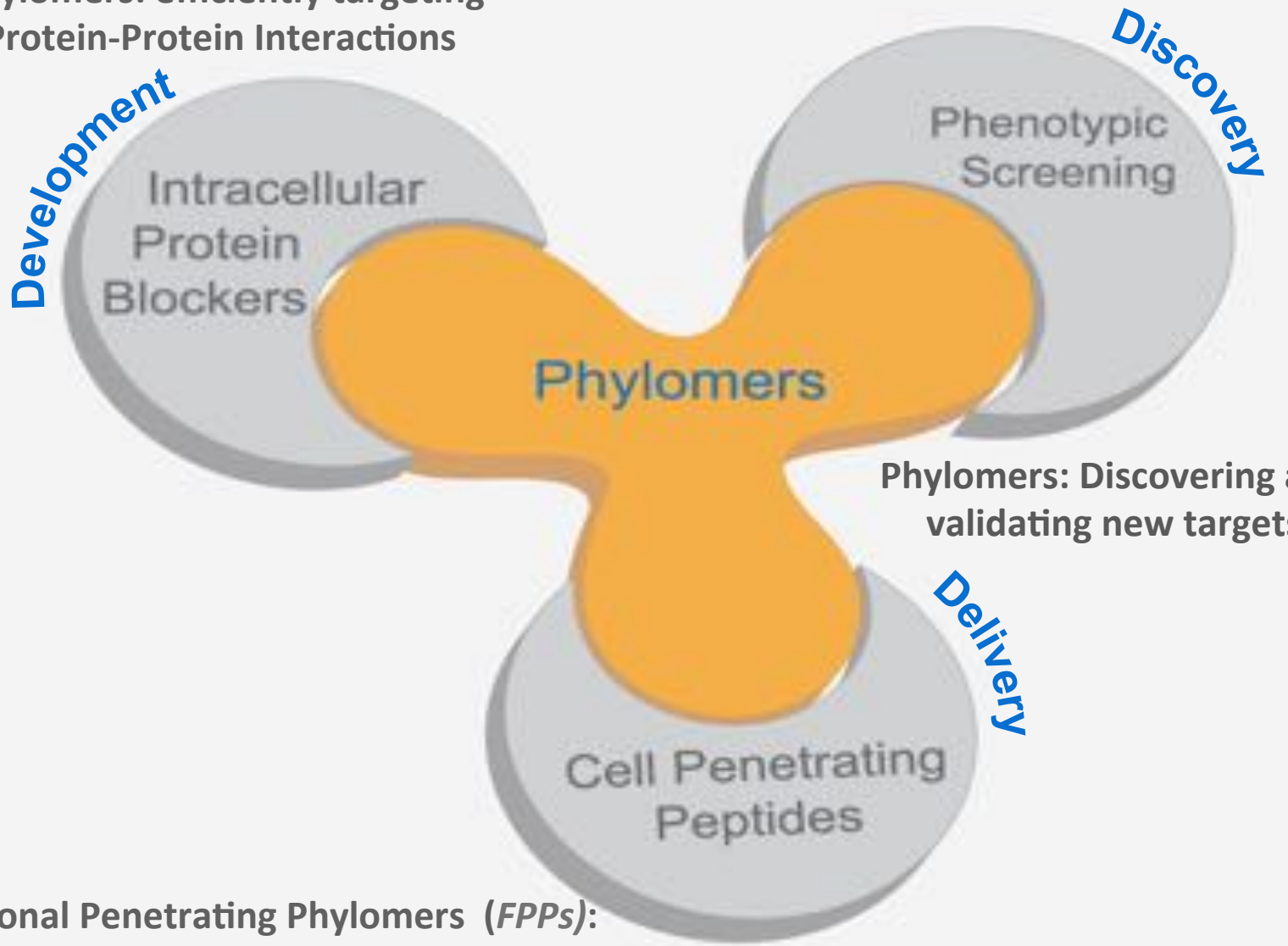


Watt 2009 Future Medicinal Chemistry. 1 (2) 257-265.

- Phylomer libraries comprise thousands of unique structural families
- Phylomer screens allow the target to 'choose' the scaffold from thousands of folds
- High structural diversity allows for a higher quantity and quality of hits

Phylomer peptides have complementary capabilities

Phylomers: efficiently targeting Protein-Protein Interactions



Phylomers: Discovering and validating new targets

Functional Penetrating Phylomers (*FPPs*): Efficiently delivering biologics to cells

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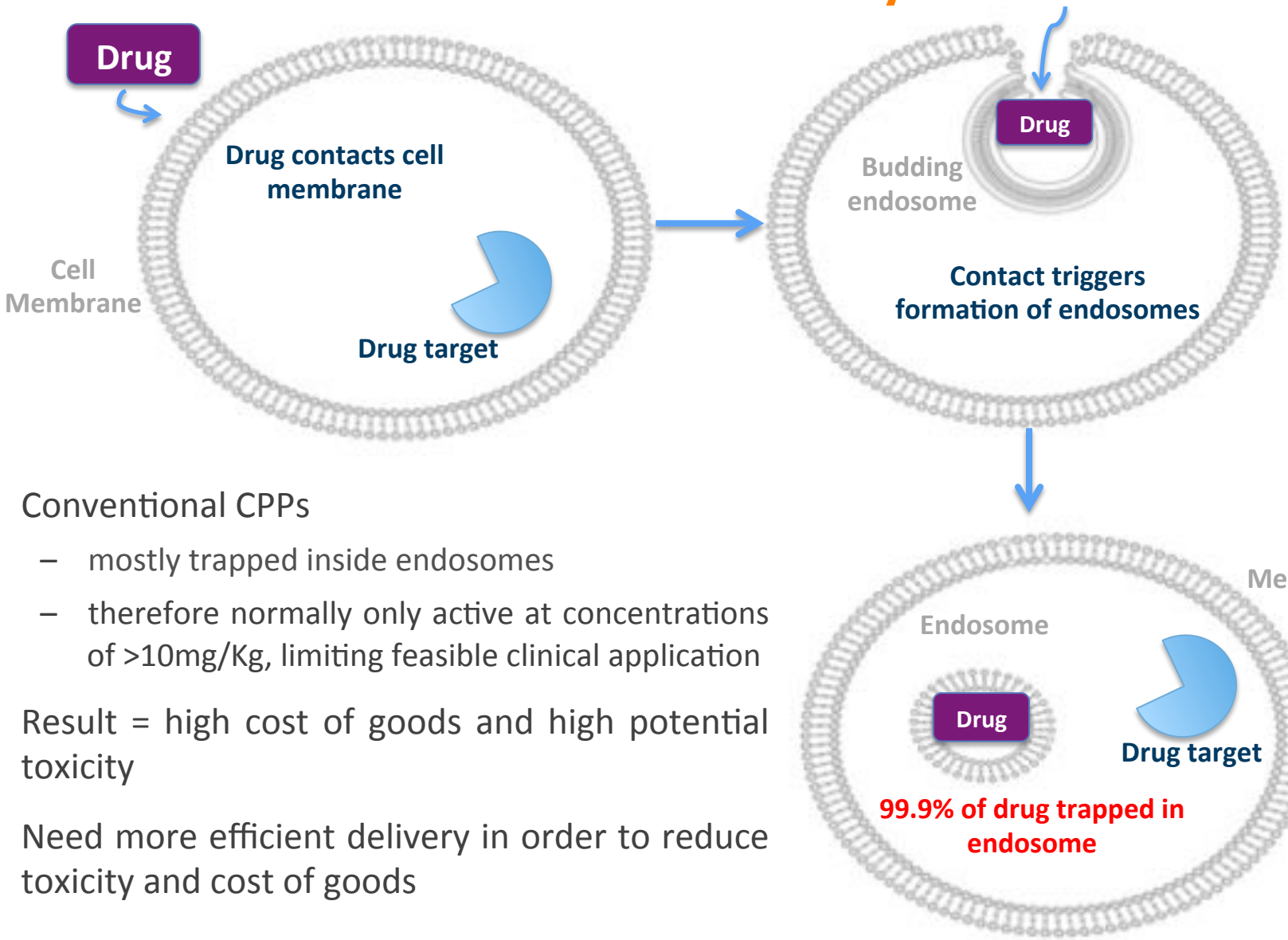
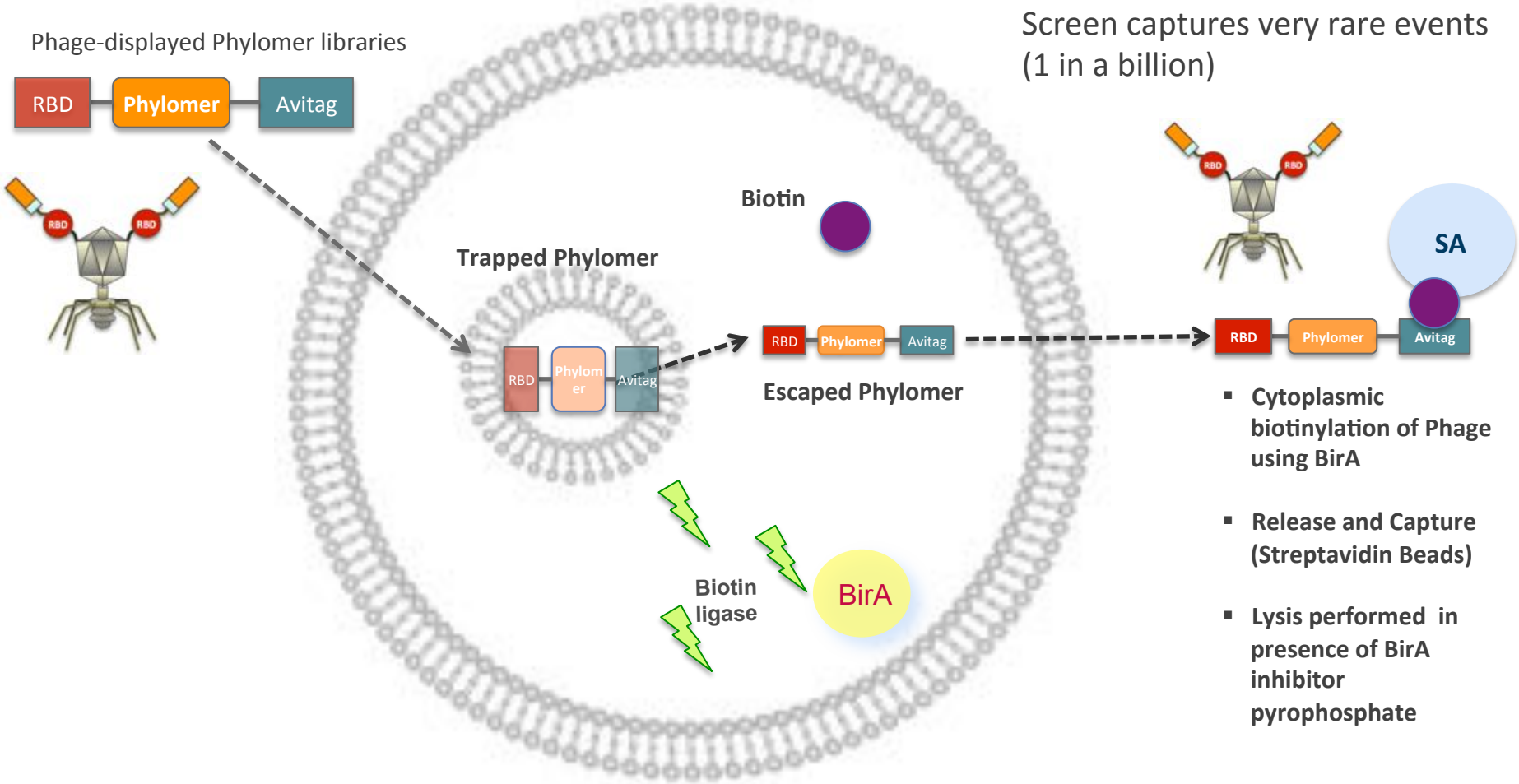
Biologics drugs are trapped within endosomes resulting in inefficient delivery



- Conventional CPPs
  - mostly trapped inside endosomes
  - therefore normally only active at concentrations of >10mg/Kg, limiting feasible clinical application
- Result = high cost of goods and high potential toxicity
- Need more efficient delivery in order to reduce toxicity and cost of goods

Phylomer FPP - cargo sequences are able to enter cells and escape the endosome



- Phylogica has developed an “Endosomal Escape Trap” screen which directs cargoes(“payloads”) into endosomes via receptor mediated endocytosis

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Phylomer FPPs are able to deliver diverse cargo classes

Examples of cargoes delivered with FPP01 or its derivatives (FPP1.1, FPP1.2):

Cargo Class	Cargo	Size/Charge	IC50*	**MED
Toxin / large protein	Bouganin	28kDa, pI 7.8	20nM	ND
Small protein scaffold	Omomyc	11kDa, pI 9.6	0.7-5µM	ND
Enzymatic protein	β-lactamase	42 KDa, pI 5.5	ND	ND
Large disordered protein	PAS	50kDa MW, 600kDa equiv. hydrodynamic radius, pI 5.9	ND	5µM
Peptide	Apoptotic (PAP) PPI inhibitor (DPMIα) Split protein complementation (S11 of GFP) Bcl-2 family inhibitory peptides – 26aa	17aa, pI 10.7 15aa, pI 8.26 30aa, pI 6.75 26aa, pI 6.28	1.7µM 8µM ND 1.6µM	 1.25µM 1.25µM
Bispecifics	Bcl-2 inhibitory peptide + Omomyc scaffold	37kDa, pI 8.02	190nM	156nM
Oligonucleotides	Exon-skipping Morpholinos	24 base pairs, neutral	ND	50nM

*IC50s tested in various cell lines **Minimal Effective Dose ND (Not determined)

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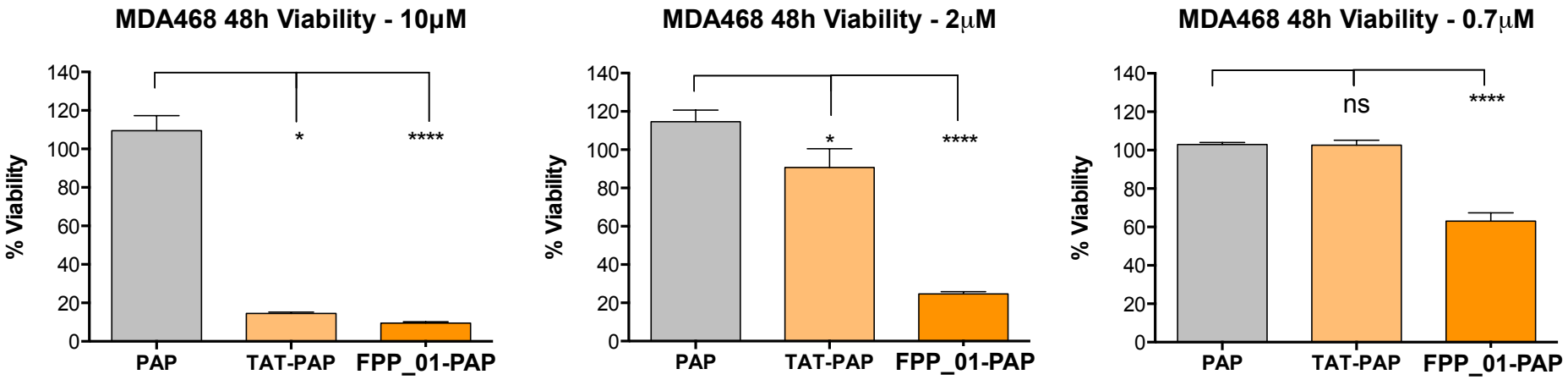
FPP delivery of Pro-Apoptotic Peptide (PAP) into cells demonstrates superiority over TAT at low concentrations

- Pro-apoptotic peptide PAP domain $(KLAKLAK)_2$ induces intrinsic apoptosis[1]
  - Decreased proliferation of triple negative breast cancer cell line (MDA-MB-468)

PHYLOMER FPP – GAS– **$(KLAKLAK)_2$ CARGO**



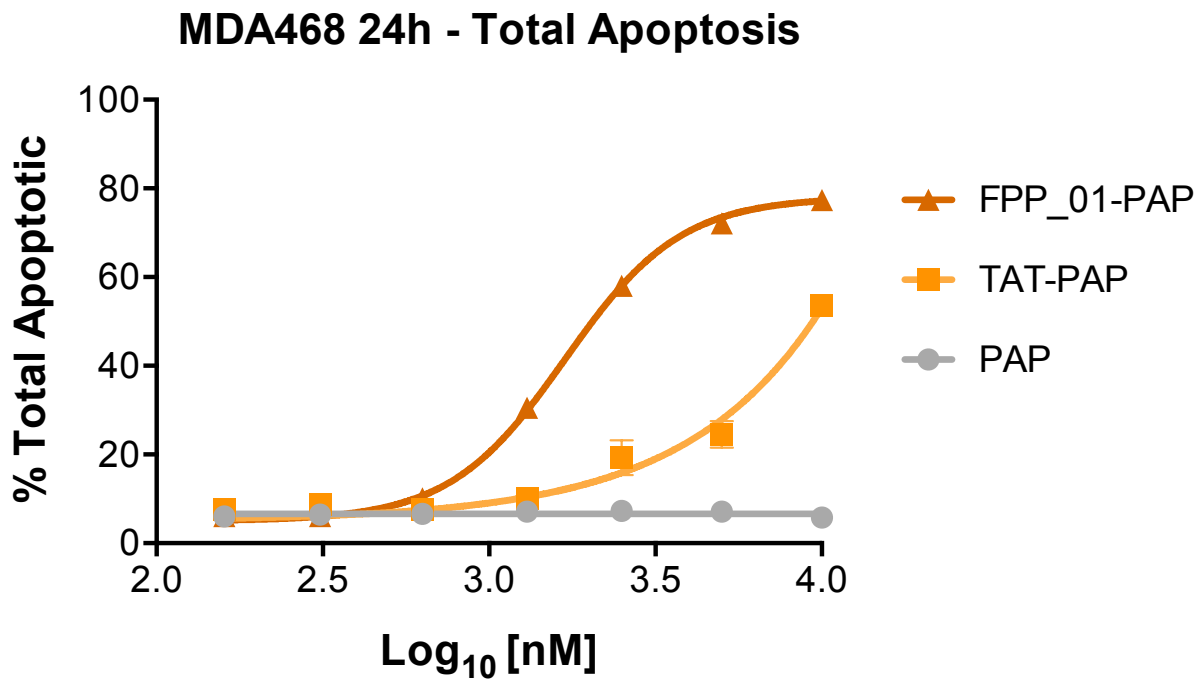
- FPP_01-PAP more potent than TAT-PAP, especially at lower concentrations
- At high concentrations cationic CPPs enter cells by alternative pathway[2]
- At lower concentrations only the FPP remains functional

1. Fantin et al., Cancer Res 2005;65:6891-6900

2. Verdurmen et al., J. Controlled Release 147 (2010) 171–179

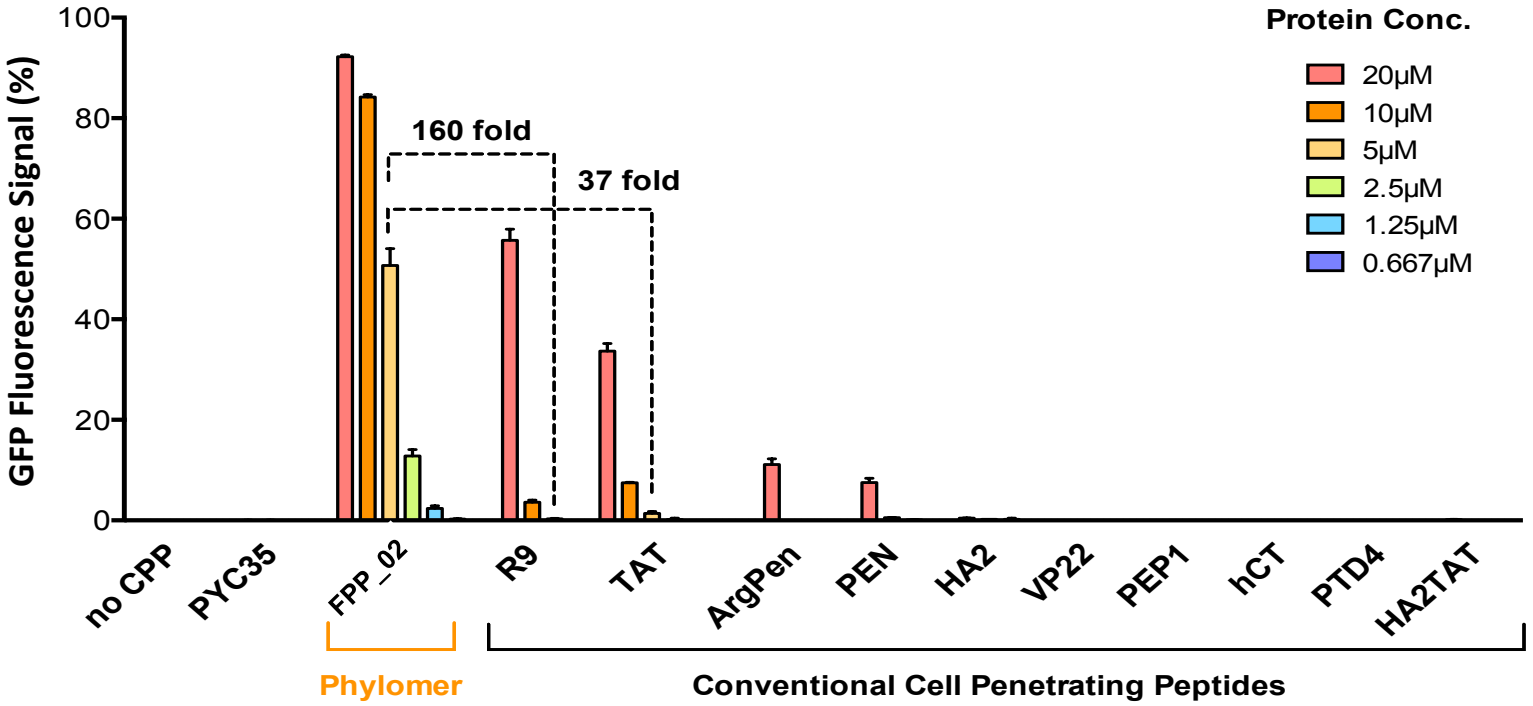
Higher potency achieved by FPP-PAP vs TAT-PAP

- Potent functional activity of a pro-apoptotic peptide (PAP)
  - Increased apoptosis – Measured by % Annexin V staining



	PAP	TAT-PAP	FPP-PAP
IC50 (µM)	Not converged	>10µM	1.7µM

Split GFP assay shows greatly superior FPP uptake and cytoplasmic delivery versus other CPPs in live cells



- Uptake and endosome escape can be measured in live cells by both flow cytometry and microscopy of split GFP complementation
  - more detail on methodology shown below
- **FPPs are best-in-class when compared to conventional CPPs** – especially at lower concentrations and with further scope for optimisation

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FPP mediated delivery of biologics into diverse cell types

Disease	Cell/Tissue type	Cargoes delivered
Breast cancer (*in vitro* and *in vivo*)	• Breast tumour epithelial (T47D, MDA-MB-468, murine T11)	Pro-apoptotic peptide (PAP) PPI inhibitor (DPMIα) Protein scaffold (Omomyc) Phylomer peptides (iMyc)
Blood cancers (*in vitro* and *in vivo*)	• B cell lymphomas (murine EμMyc, Ramos) • Multiple myeloma (H929) • Acute myeloid leukemia (HL-60) • Acute lymphoblastic leukemia (MOLT4)	Protein scaffold (Omomyc) Bcl-2 inhibitory peptides Phylomer peptides (iMyc)
Osteosarcoma (*in vitro*)	• Osteocarcoma (SJSA-1)	Pro-apoptotic peptide (PAP)
Melanoma (*in vivo*)	• T cells targeted and non-targeted	T cell neoantigen peptide vaccine
Heart disease (*in vitro*)	• Murine cardiac myocytes (ex vivo)	Peptide (Ca2+ channel inhibitor)
Spinal Muscular Atrophy Muscular dystrophy (*in vitro* and *in vivo*)	• Murine tissues - tibialis anterior muscle, diaphragm, heart and liver • Murine myoblasts (ex vivo) • Human fibroblasts	Oligonucleotides (exon-skipping Morpholino's)

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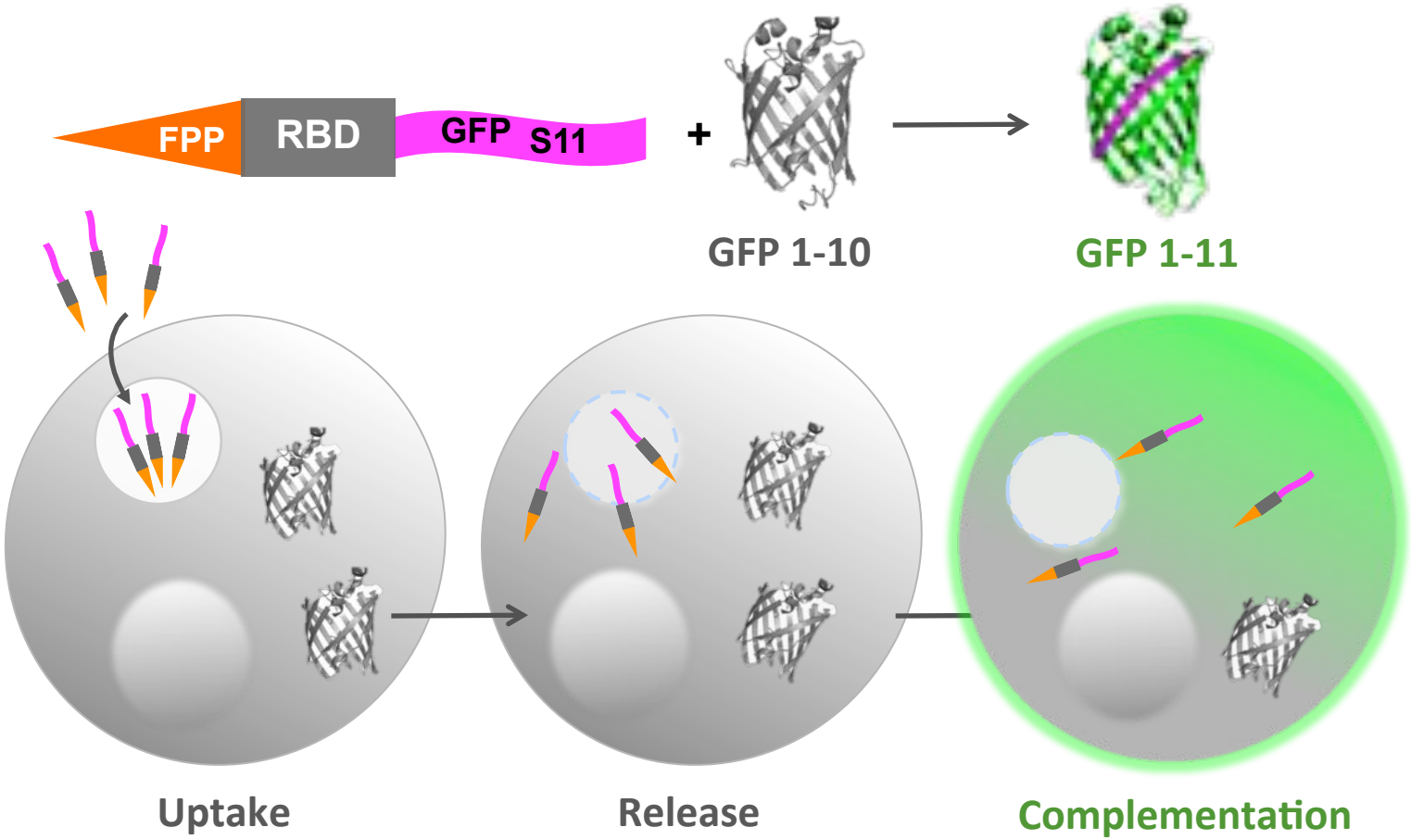
Proprietary Split-GFP complementation assay developed to validate endosomal escape of penetrating Phylomer fusions

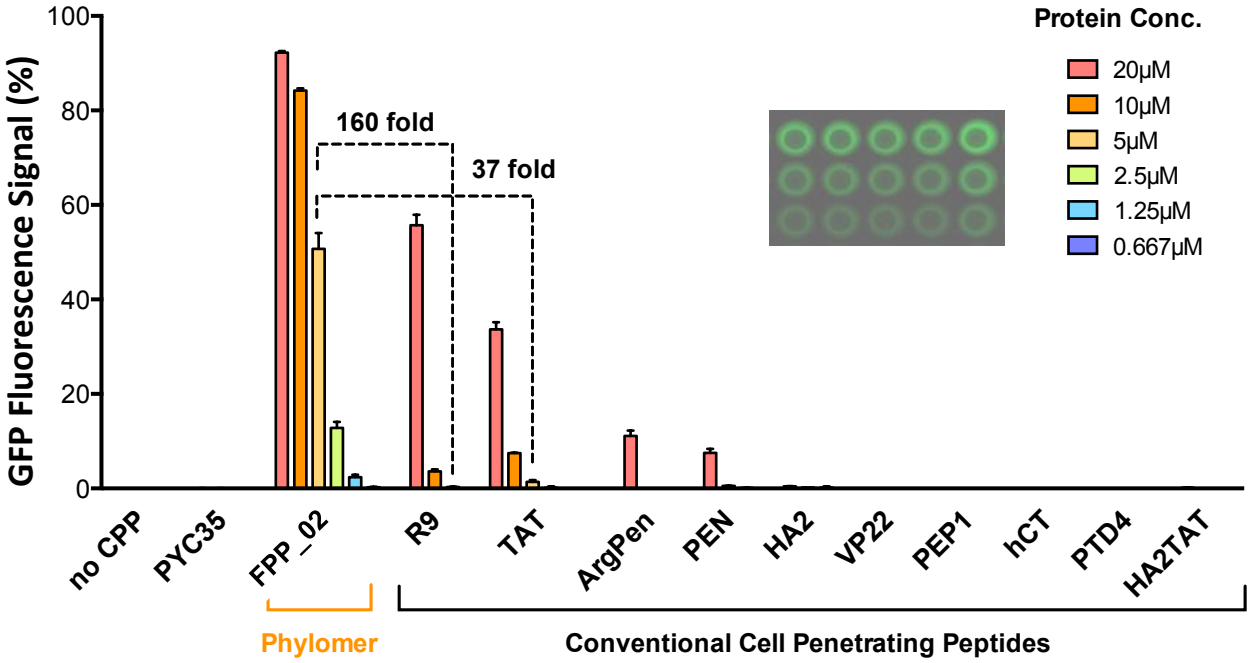
- Only biologics delivered to the cytoplasm can fluoresce in this assay

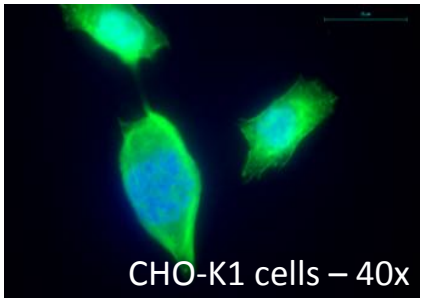


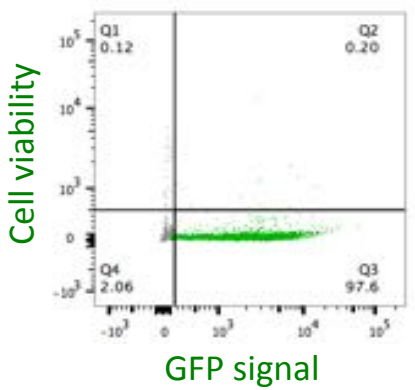
International patent no: PCT/AU2014/050094

Milech *et al.*, (2015) *Scientific Reports* 5:18329

Split GFP assay shows greatly superior FPP uptake and cytoplasmic delivery vs other CPPs in live cells







- Uptake and endosome escape can be measured in live cells by both flow cytometry and microscopy of split GFP complementation
- Inactive CPP fusions still capable of complementing GFP fluorescence *in vitro*
- **FPPs are best-in-class when compared to conventional CPPs** – especially at lower concentrations and with further scope for optimisation

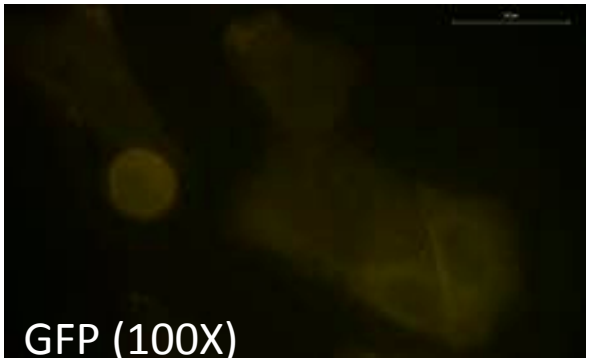
Split GFP microscopy confirms endosomal escape

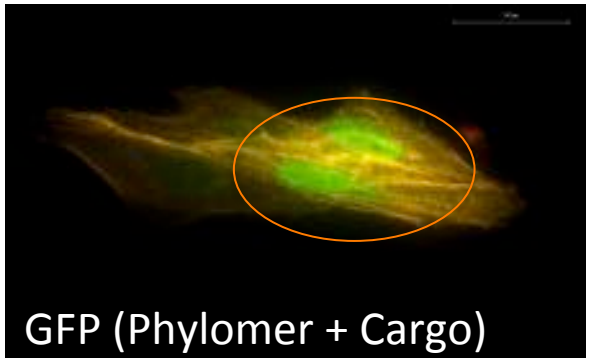
No FPP Phylomer

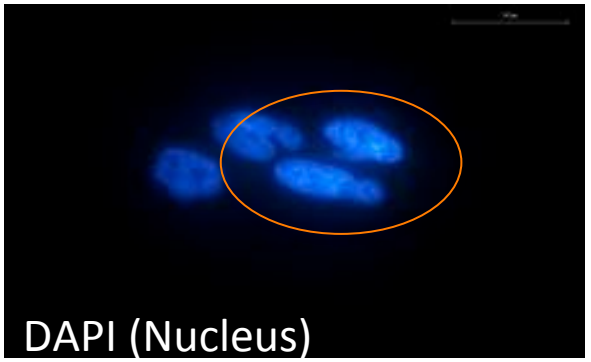
With FPP Phylomer

With FPP Phylomer

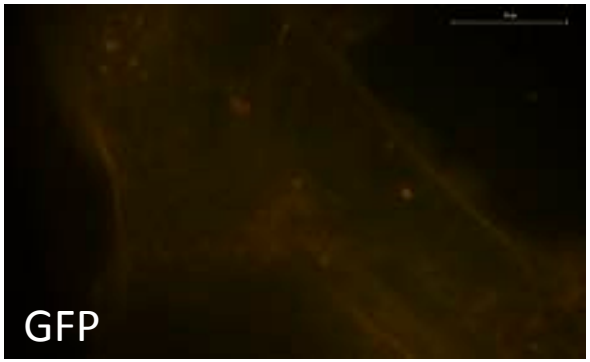
Low Receptor

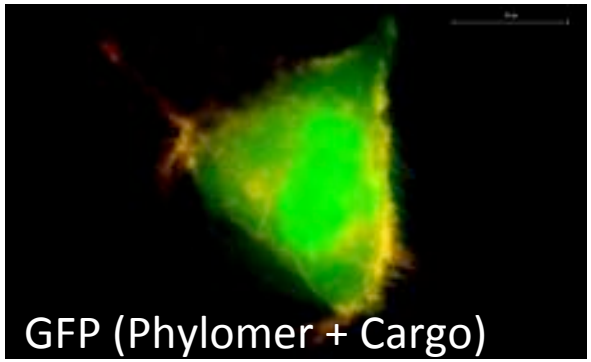


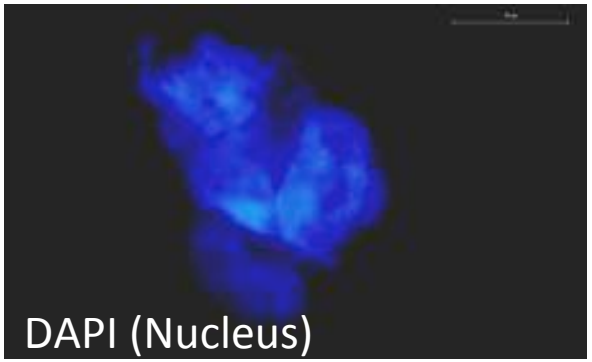




High Receptor





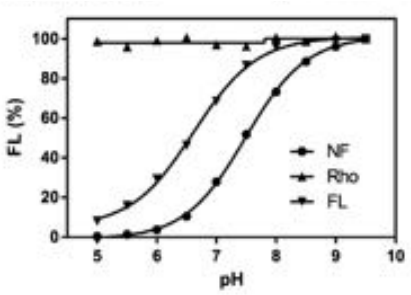


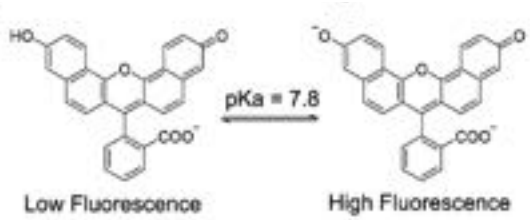
- Endosomes are much larger than the nuclear pore (5.3nM)
- Cargoes remaining trapped in endosome not visible and can't reach nucleus
- DAPI staining confirms co-localisation with GFP-labelled FPP construct in nuclei

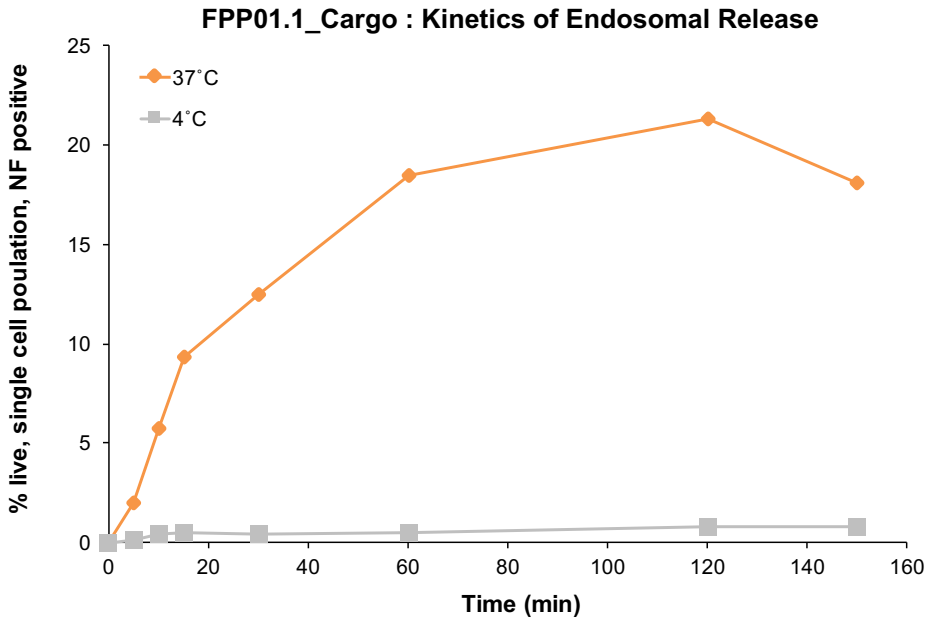
FPP allows rapid cell uptake and endosomal release

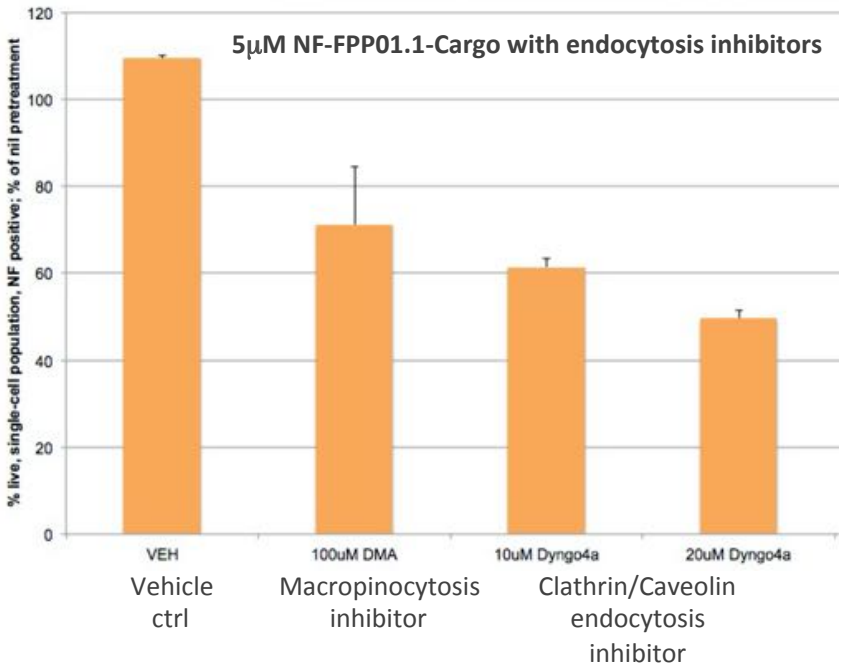
- Use pH sensitive Naphthofluorescein (NF) dye which only fluoresces after endosomal escape (at pH above 6.5)[1]
- Most delivery occurs within 1hr and is temperature (energy) dependent

[1] *Qian et al., Chem.Commun.* 51 (2015) 2162





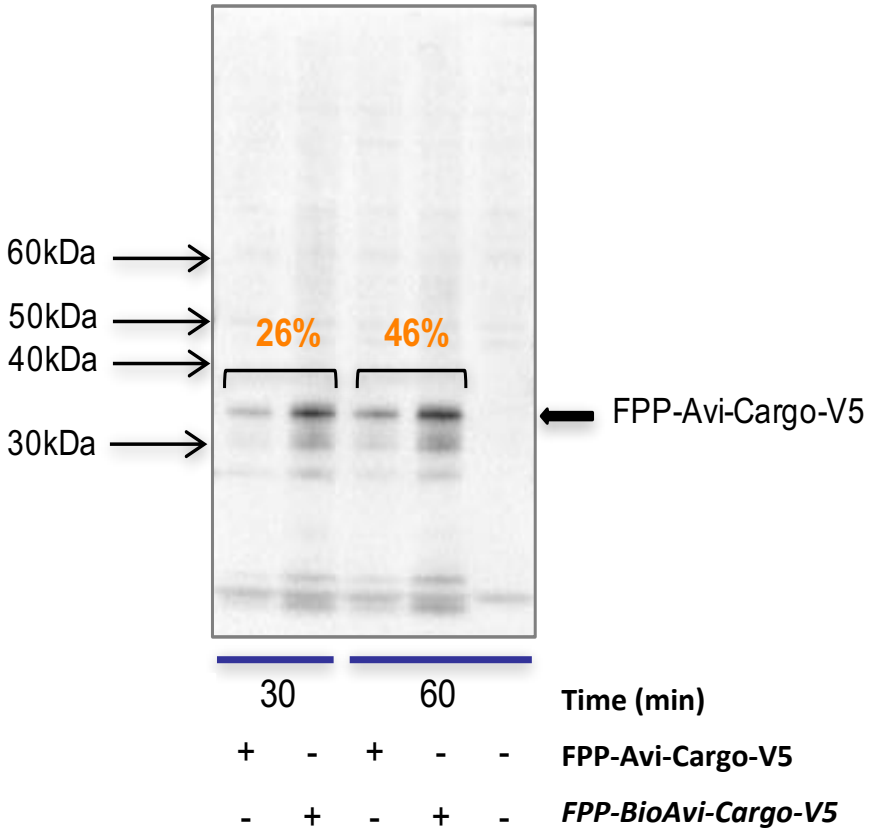




[1] *Qian et al., Chem.Commun.* 51 (2015) 2162

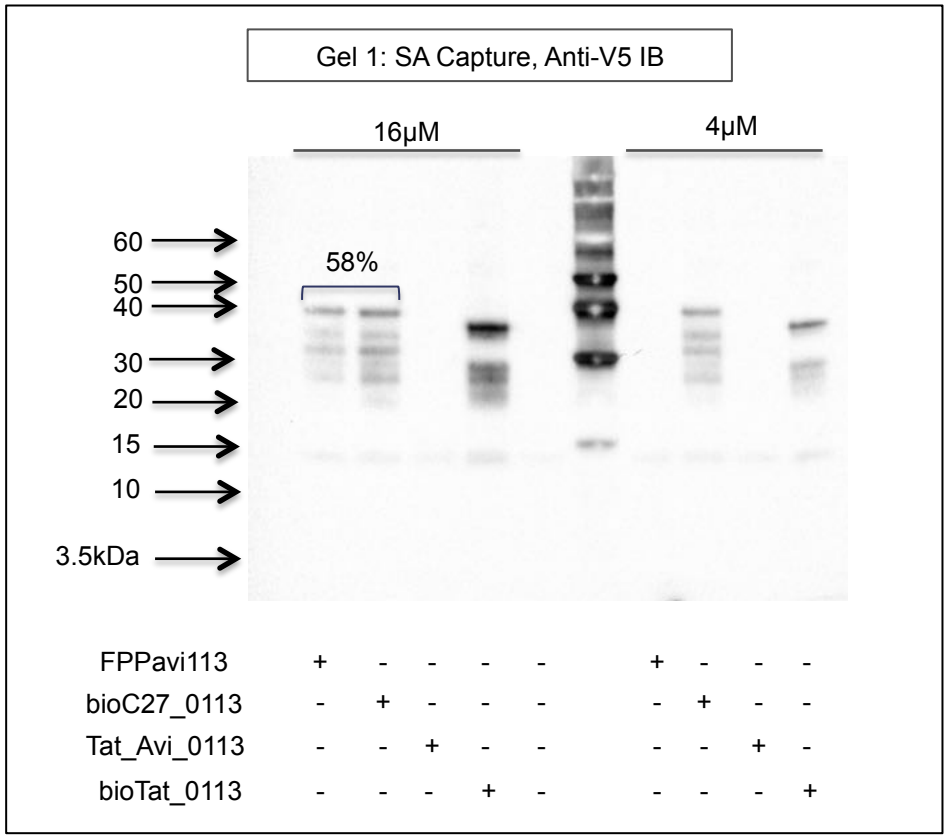
A biochemical assay using BirA expressing cells confirms efficient endosomal escape of FPP-cargo

Constructs +/- Biotinylation added to HEK293-BirA cells @ 15µM



- Pull down Western blot assay
- Compared pre-biotinylated construct (FPP-BioAvi-Cargo-V5) with unbiotinylated FPP-Avi-Cargo-V5
- Ratio of two constructs reflects degree of endosome escape
- Rapid uptake and biotinylation of FPP-Avi-Cargo construct in less than 1hr

Negligible endosomal release detected for TAT fusion compared to 58% release for FPP fusion

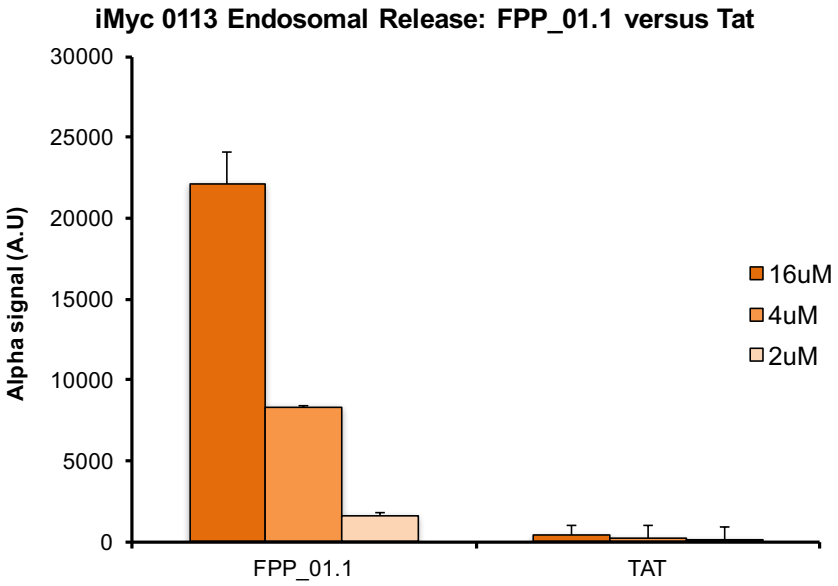


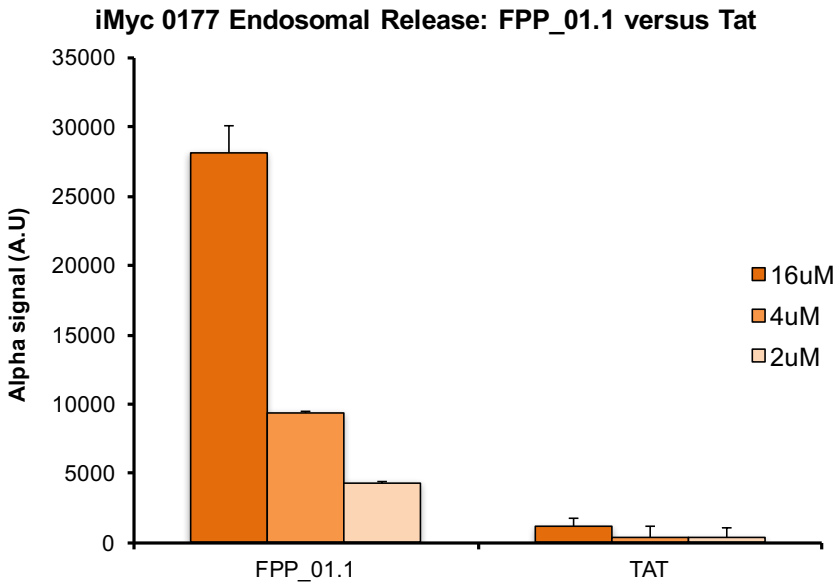
Comparing endosomal escape of Tat and FPP using Pull-down of biotiylated Avitag and Western blotting

- 16 and 4µM FPP-iMyc113 versus Tat_iMyc113 (1hr incubation) compared to pre-biotinylated peptide (HEK293 BirA cells)

FPP permits far greater endosomal release than TAT

- Protein conjugates applied to HEK293 BirA cells for 60min
- Cell lysates assessed for dual-tagged conjugate that has escaped the endosome (sensitive Streptavidin/V5 AlphaLISA proximity assay)

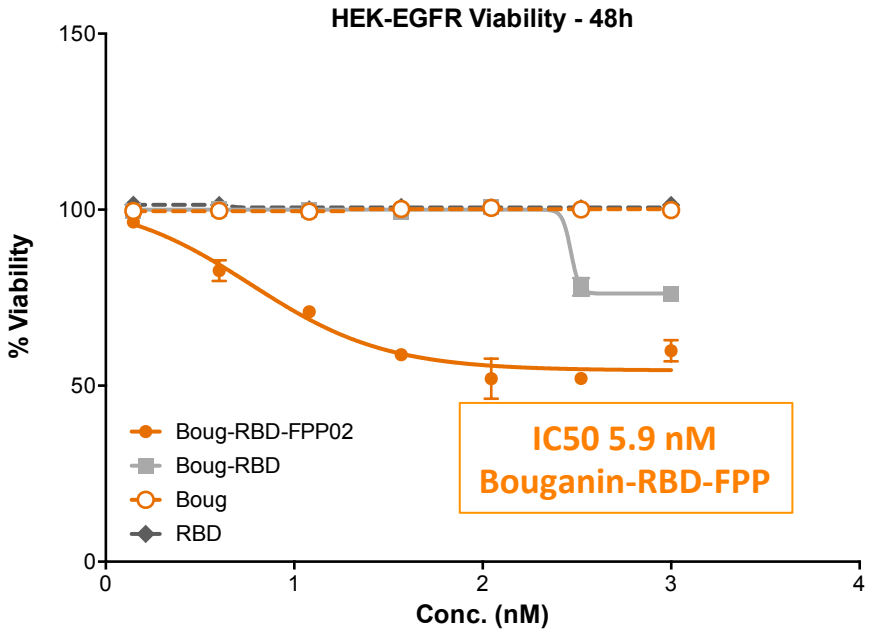


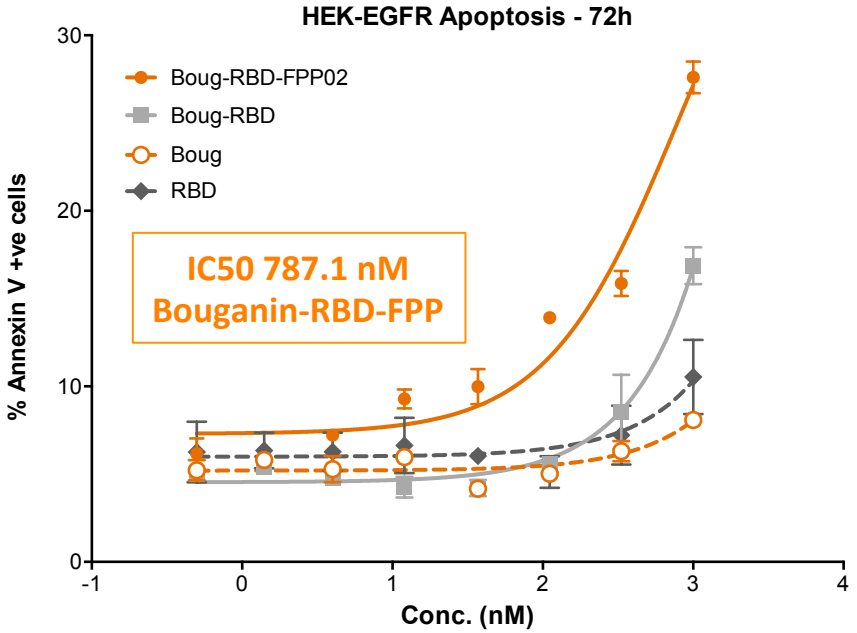


- FPP_01.1 conjugates of 2 different iMyc cargoes (0113 and 0177) demonstrate greater endosomal release than equivalent Tat conjugates at all concentrations tested

FPP can enhance potency of cargo delivered via receptor medicated endocytosis

FPP-cargo size 50KDa

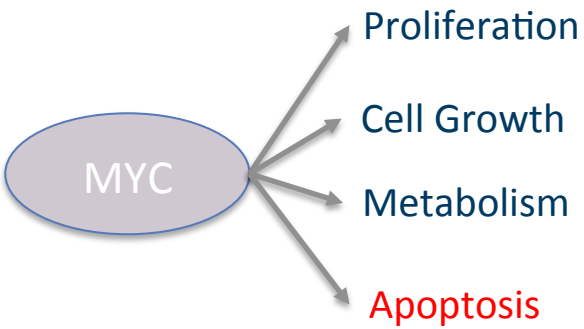




- Addition of a receptor binding domain to Bouganin toxin (only functional in cytoplasm) increases its toxicity due to receptor mediated endocytosis
- Addition of FPP to the RBD further increases potency of Bouganin toxin into the low nanomolar range

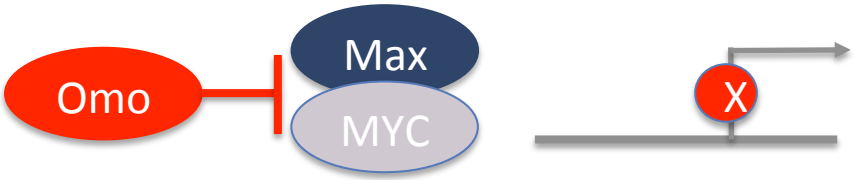
Using the validated MYC inhibitor Omomyc as a model cargo for FPP delivery

- **MYC:** Amplified/overexpressed in most human cancers



- MYC: non redundant role in cancer – associated with addiction

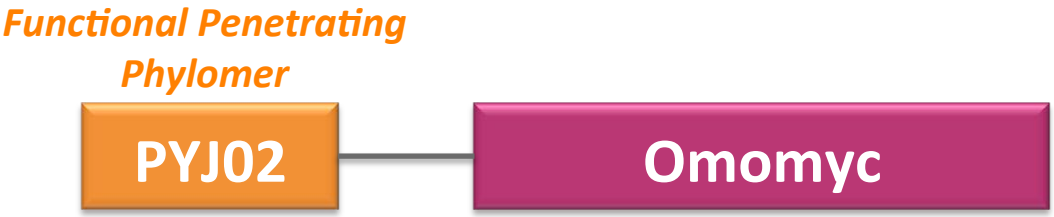
- OmoMyc: 92 aa peptide derived from bHLHZ domain of cMyc[1,2]
  - Omomyc eradicates existing tumours – eg. lung, pancreas and brain



1. Soucek et al. (1998) Oncogene 17, 2463–2472; 2. Soucek et al. (2013) Genes Dev. 27, 504-513

Delivering Omomyc using Phylogica's FPP

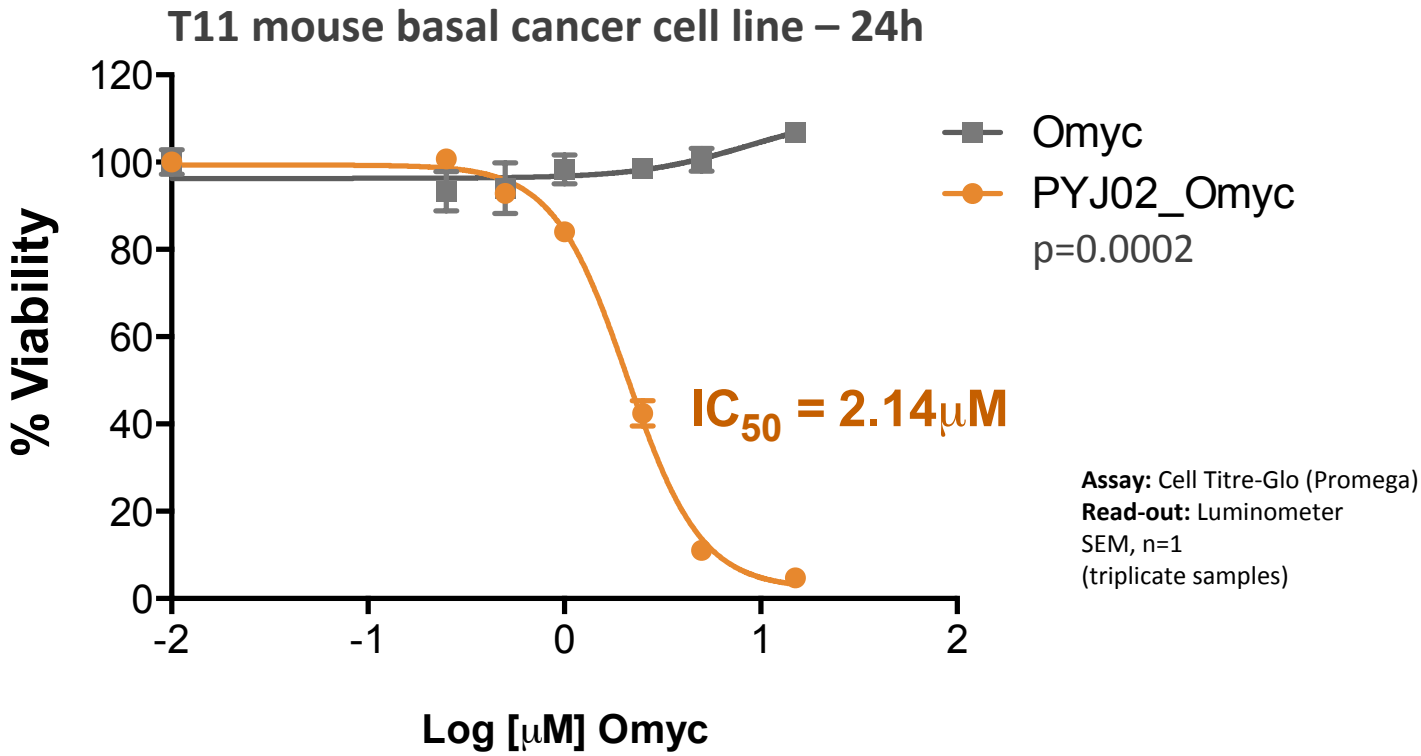
- Linked a Phylomer cell penetrating peptide (FPP PYJ02) to Omomyc, the most effective known Myc inhibitor when expressed in cells



- Omomyc protein has very low potency due to very poor cell penetration
- Tested for activity in a the T11 basal breast cancer cell line resistant to conventional drugs and in Eμ-Myc lymphoma cells
- Potency measured by assessing proliferation, viability and apoptosis.

FPP delivery of Omomyc reduces viability of resistant breast cancer cells

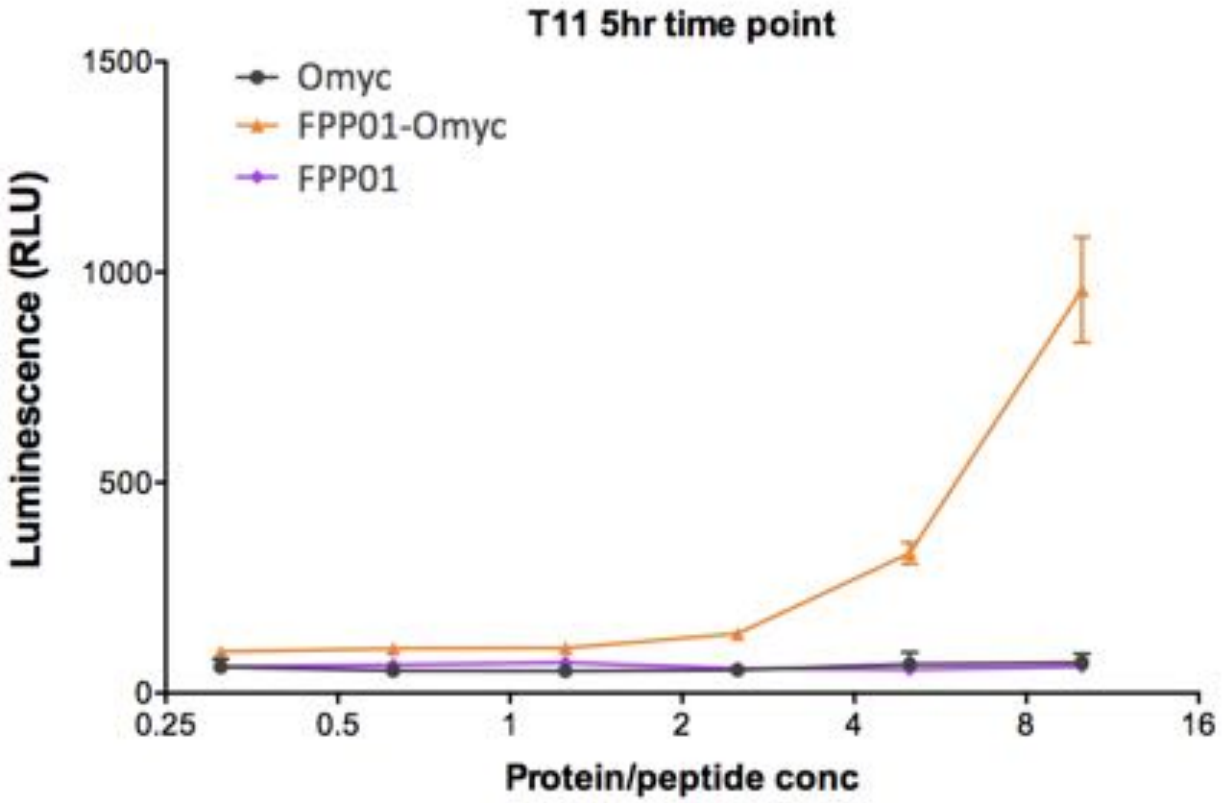
- Delivery of FPP-Omomyc *(PYJ02-Omyc)* into aggressive multi-drug resistant mouse basal cancer cell line in-vitro, used in a syngeneic mouse model



Assay: Cell Titre-Glo (Promega)
Read-out: Luminometer
SEM, n=1
(triplicate samples)

Assoc. Prof. Pilar Blancafort
Harry Perkins Institute, Perth Western Australia

FPP delivery of Omomyc results in apoptosis of cancer cells



- Caspase assay shows increased apoptosis in FPP01-Omyc treated cells only
- FPP-01 itself had no apoptotic activity

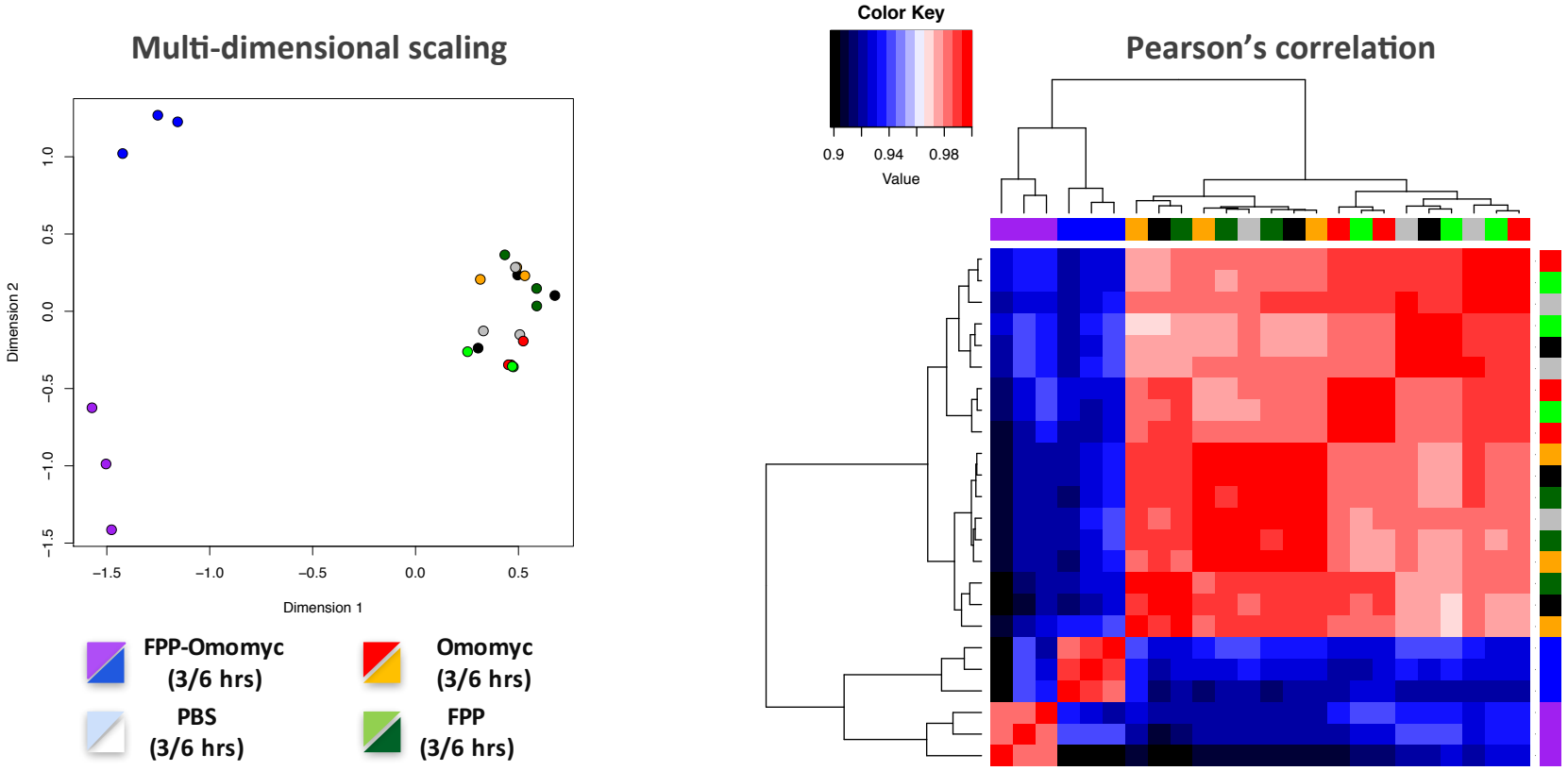
FPP-Omomyc shows potent activity in multiple Myc-driven cancer cell lines

Cell line	Disease	Cell line characteristics	FPP_01-Omyc (IC_{50} (µM))
T47D	Breast cancer	p53 $mut^{(hetero)}$, Myc^{+++}	4.5
MDA-MB-468	Breast cancer	p53 $mut^{(hetero)}$, triple -ve	1.7
SUM159 *	Breast cancer	Basal, Triple -ve	1.1
B1.15 (mouse) *	Breast Cancer	Basal, Brca-/-	1.1
A1.8 (mouse) *	Breast Cancer	Basal, Brca-/-	1.2
T11 (mouse) *	Breast cancer	Basal, Triple -ve, P53-/-	2.1
PyMT (Mouse) *	Breast cancer	Luminal/basal	1.0
MCF10A *	Immortalised tissue	Epithelial breast	>15
Saos-2	Osteosarcoma	p53 null	4.4
14169	NUT midline carcinoma	Bet inhibitor sensitive	0.7
EµMyc #560 (mouse)	B lymphoma	Myc driven	2.1

- *MCF10a cells are telomerase transformed and not Myc dependent
- Best in-class potencies for direct Myc inhibition with unoptimised FPPs

* Assoc. Prof. Pilar Blancafort; Cancer Epigenetics Lab, Harry Perkins Institute

Global gene expression profiling



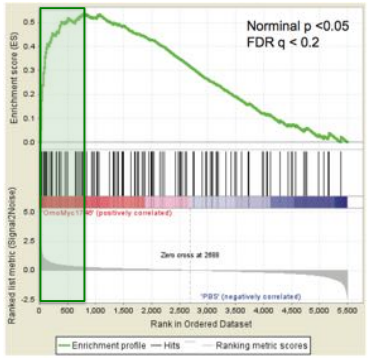
- FPP-Omomyc treated samples cluster uniquely and distinctly away from control groups on total RNA-seq dataset (normalised)
  - Multi-dimensional scaling analysis
  - Pearson's correlation analysis

Gene set enrichment analysis: Myc pathway

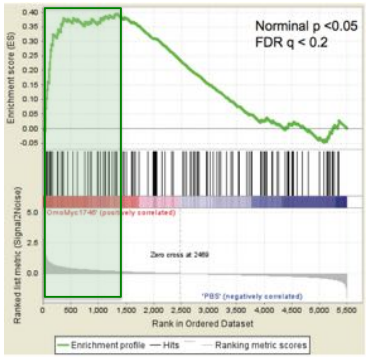
- Differentially regulated genes enriched for a priori defined set of activated and repressed Myc pathway genes

  - Zeller *et. al.*,(2003) Genome Biology 4: R69.
  - Savino et al., (2011) *PLoS ONE*, 6(7), e22284

Myc repressed genes – activated by FPP-Omyc



3 h

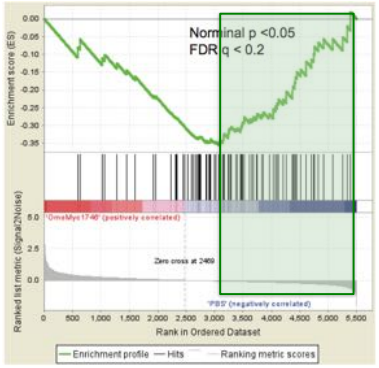


6 h

Symbol	Gene
CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)
NDRG1	N-myc downstream regulated gene 1
MYC	v-myc myelocytomatosis viral oncogene homolog (avian)
CD47	CD47 molecule
CDKN1B	cyclin-dependent kinase inhibitor 1B (p27, Kip1) **[3 h only]**

Myc activated genes – repressed by FPP-Omy

FPP-Omomyc 3hrs: no significant enrichment for Myc-activated genes

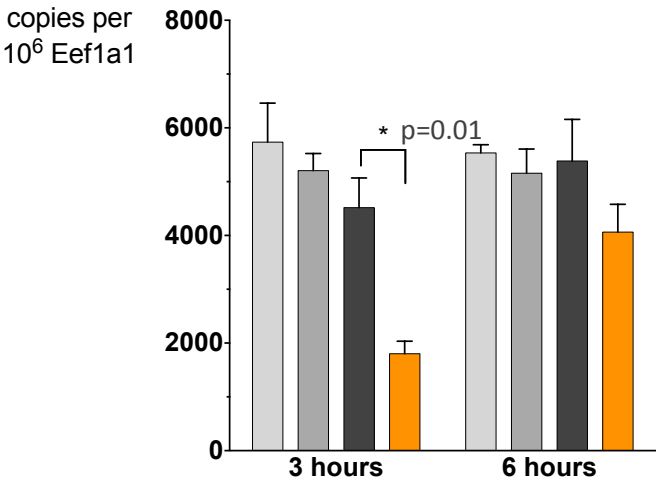


6 h

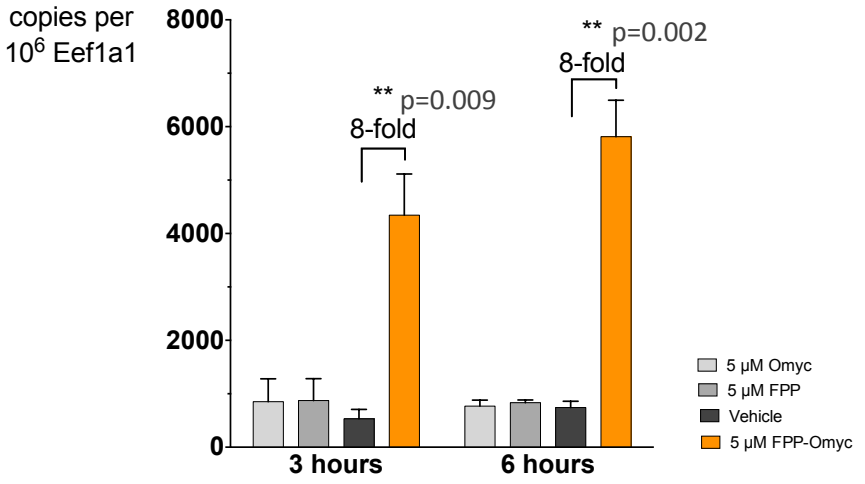
Symbol	Gene
E2F1	E2F transcription factor 1
CCNB1	cyclin B1
CDC25A	cell division cycle 25A
CDK4	cyclin-dependent kinase 4
DKC1	dyskeratosis congenita 1, dyskerin

Modulation of Myc-pathway target genes

Tfap4 mRNA expression levels by ddPCR (normalised to Eef1a1)



p21 mRNA expression levels by ddPCR (normalised to Eef1a1)



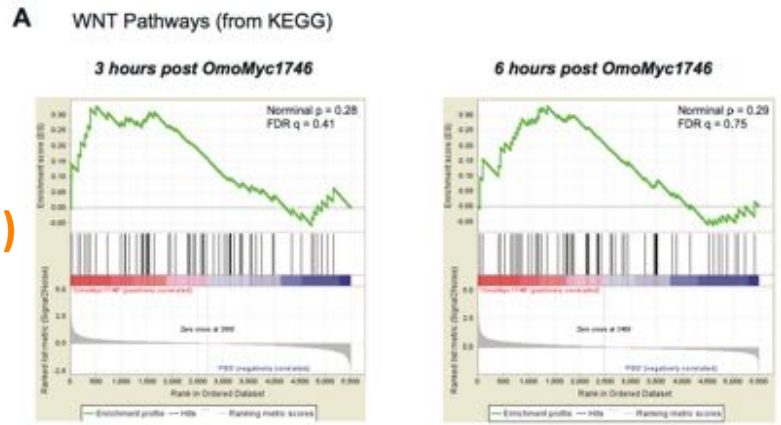
SEM, n=1
(triplicate samples)

- Treatment of T11 cells with FPP-Omomyc for 3 or 6 hrs
- FPP-Omomyc induces *p21* (*WAF1*) via inhibition of *AP4* expression
  - Expression measured by digital droplet RT-PCR, relative to expression of house-keeping gene *Eef1a1*
  - Treatment: no effect on expression of *Myc*-independent *Eef1a1*

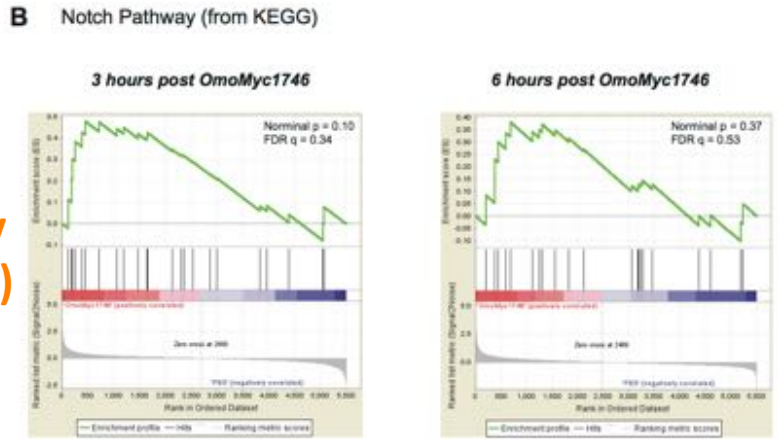
Gene set enrichment analysis: FPP-Omomyc doesn't significantly affect other pathways (Notch and Wnt)

- No evidence for off-target regulation of other pathways unrelated/upstream of Myc

WNT Pathway (no correlation)



Notch Pathway (no correlation)



GSEA of WNT and Notch from KEGG
(http://www.genome.jp/kegg/)pathways

- 9 WNT and 7 Notch gene sets
- 12/16 show no enrichment
  - P value > 0.1
  - FDR > 0.25

- Shows specificity of Omomyc response for the Myc pathway

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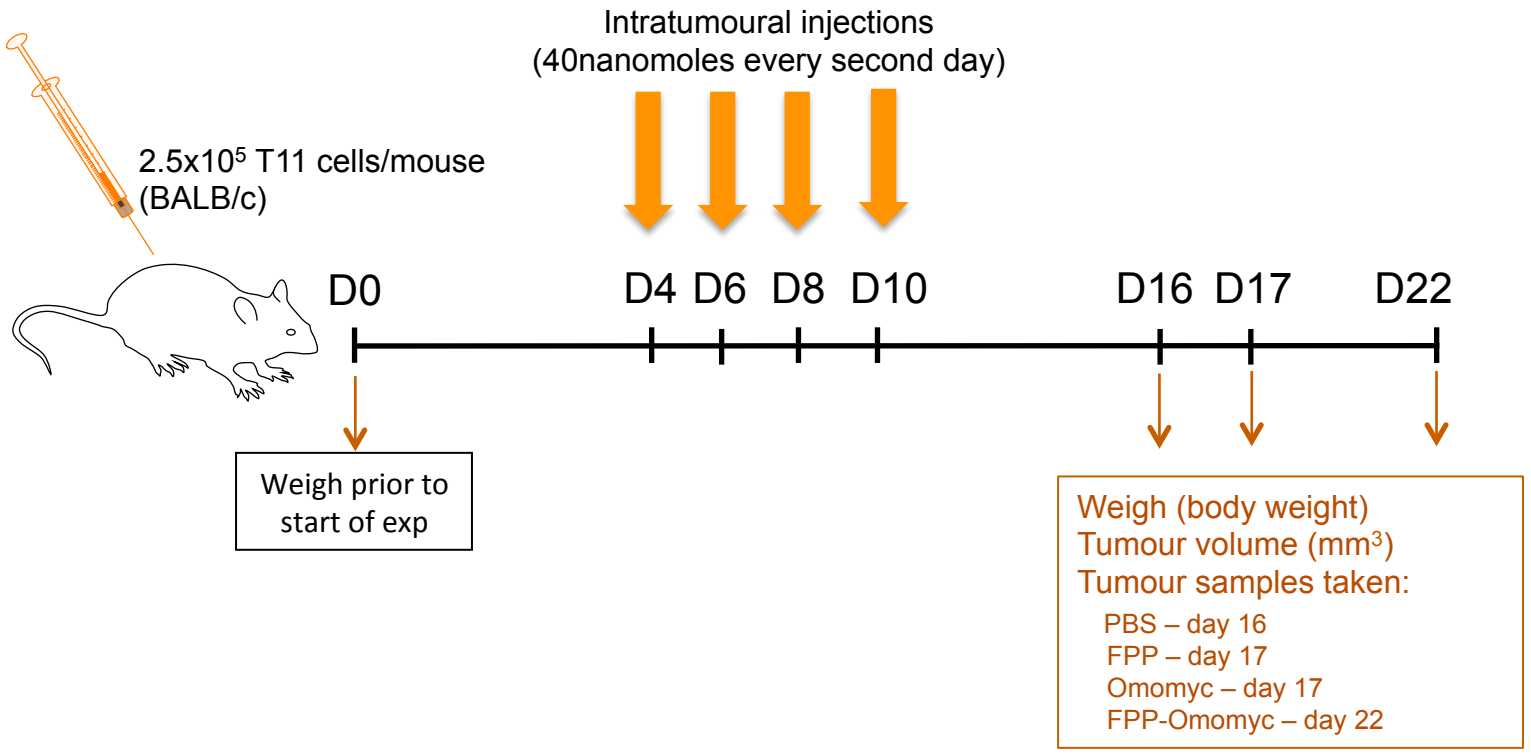
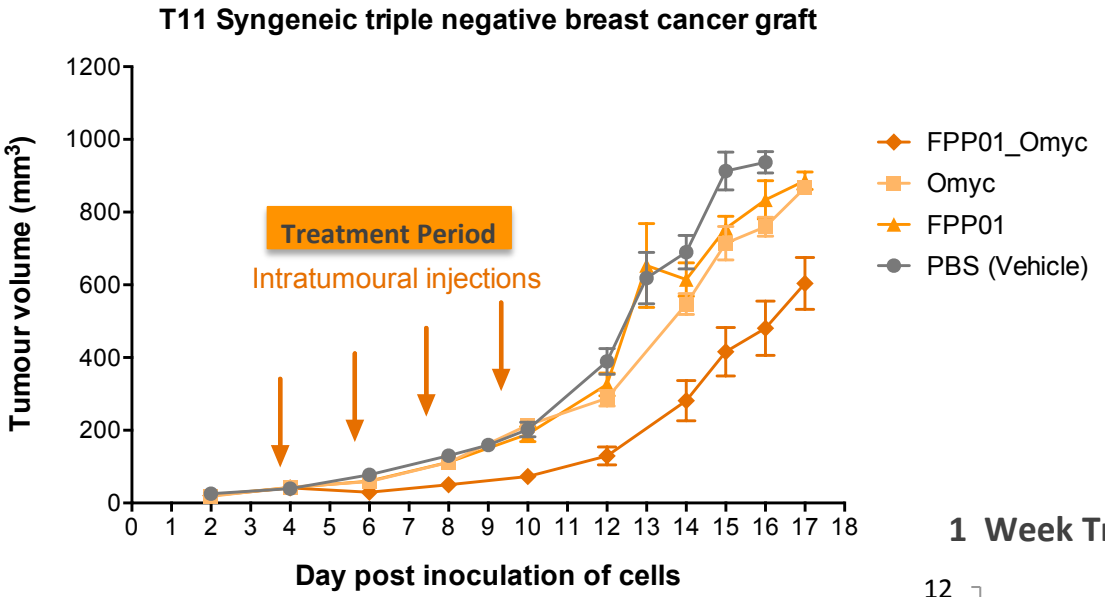
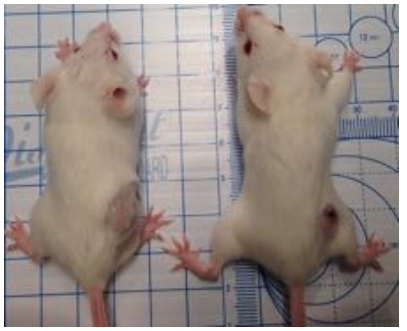
Protocol for syngeneic allograft breast cancer model: *intratumoral* delivery

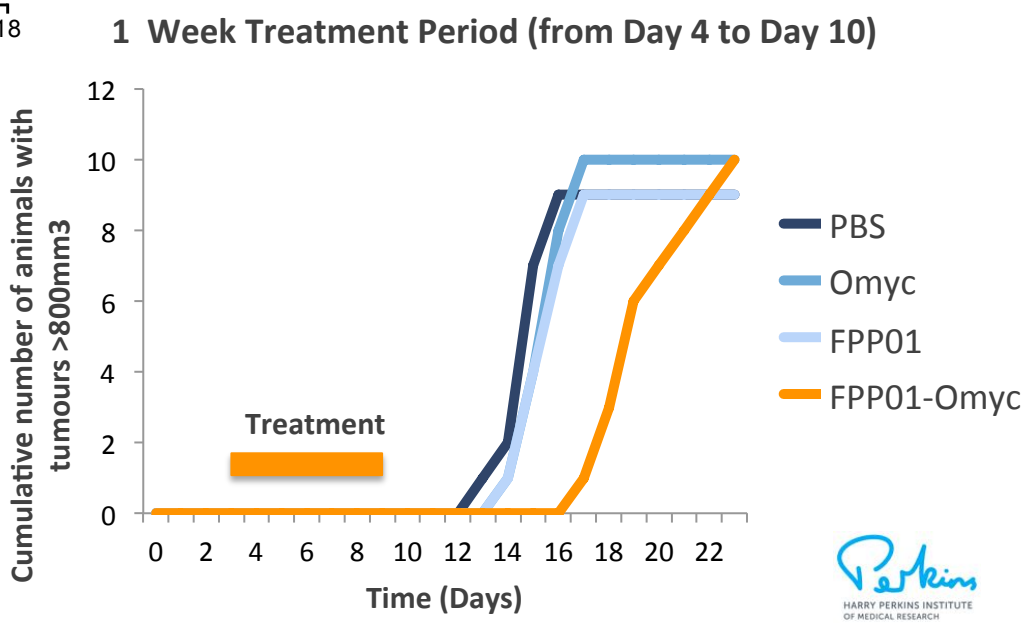


Intratumoral FPP-Omomyc inhibits growth in basal breast cancer cells (T11) in immunocompetent mice

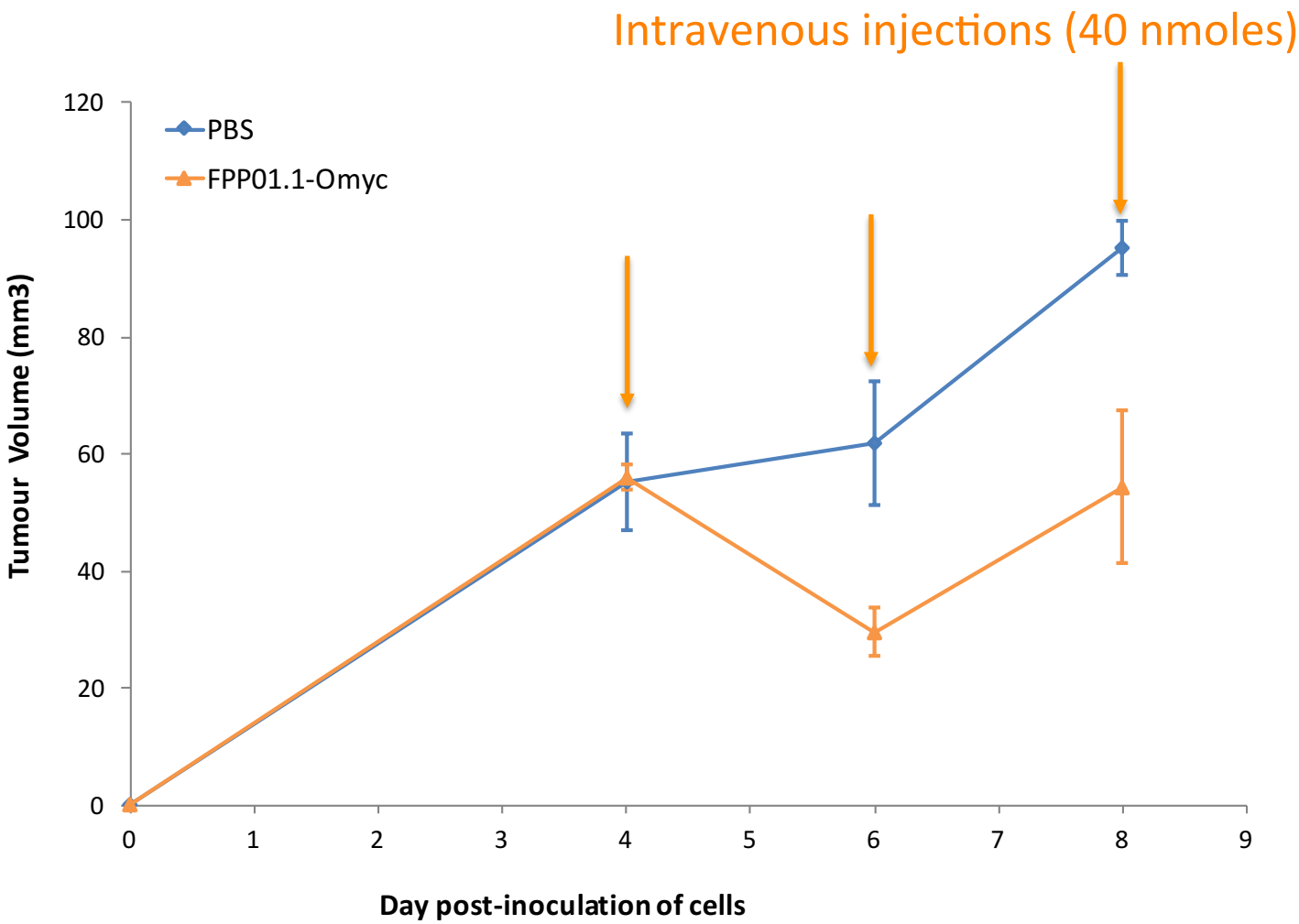




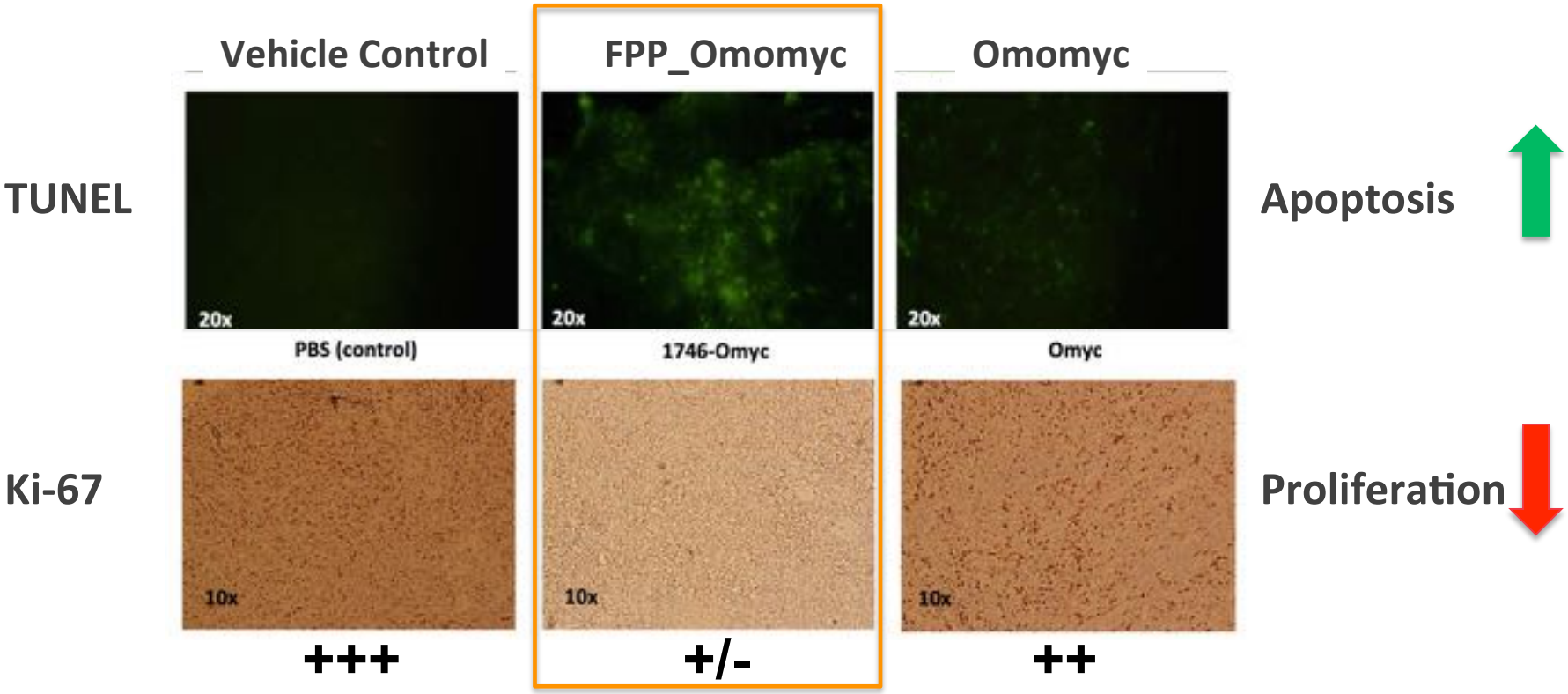
- 40nmol intratumoral injections of FPP-Omomyc, once every 2 days
- FPP, Omomyc and PBS controls showed no effects on tumours
- Growth of tumours was inhibited for days after cessation of treatment



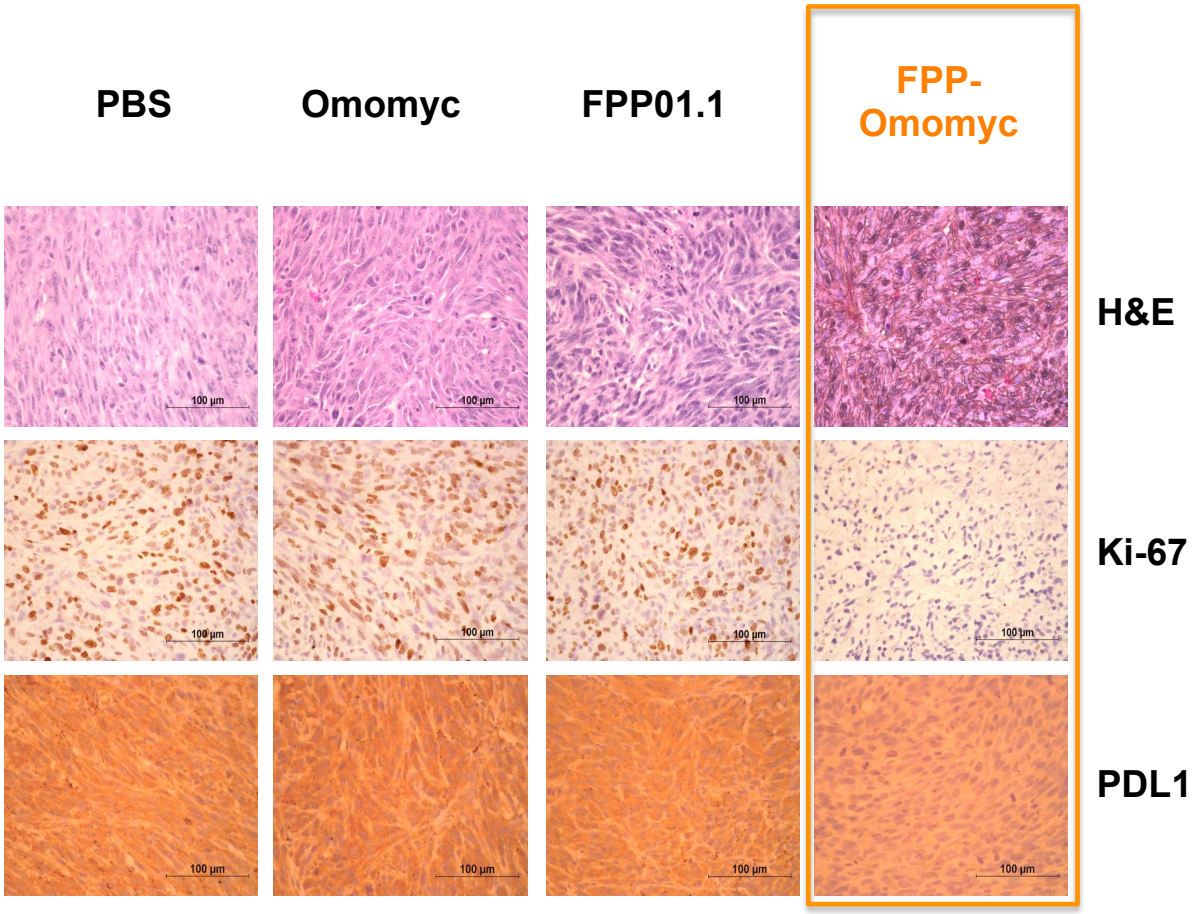
FPP-Omomyc inhibition of T11 tumour engraftment: *intravenous* delivery



Tumour Immunohistochemistry:
FPP-Omomyc induces apoptosis and blocks proliferation



Tumour Immunohistochemistry: FPP-Omomyc decreases PDL1 (Myc target gene)



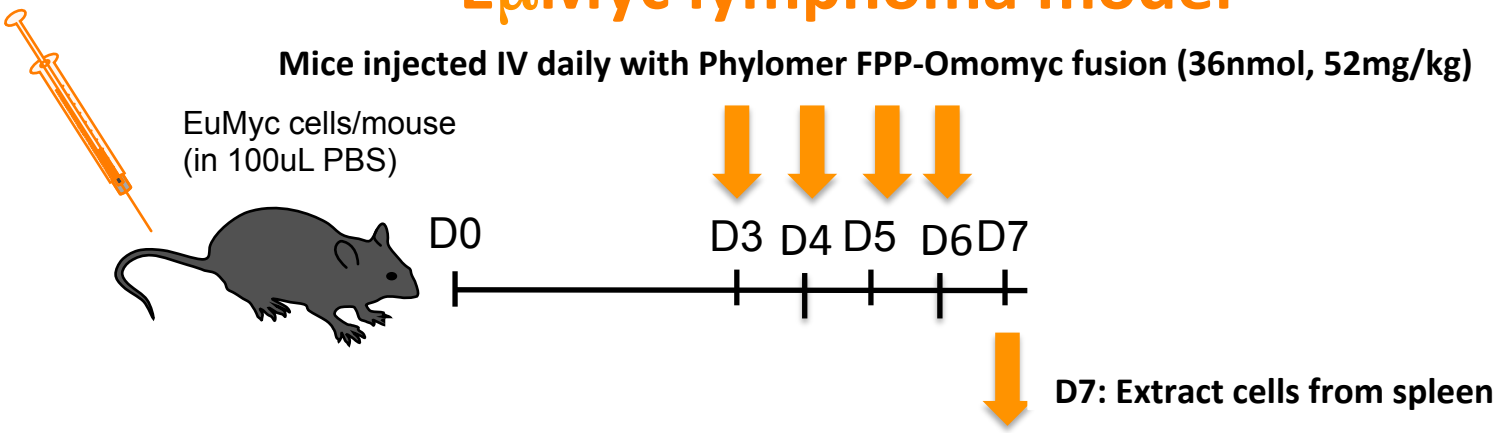
- Increased cell death, decreased proliferation & PDL1 expression in tumours treated with FPP-Omomyc versus FPP, Omomyc or vehicle controls
- Potential immuno-oncology implications*

Pilar Blancafort

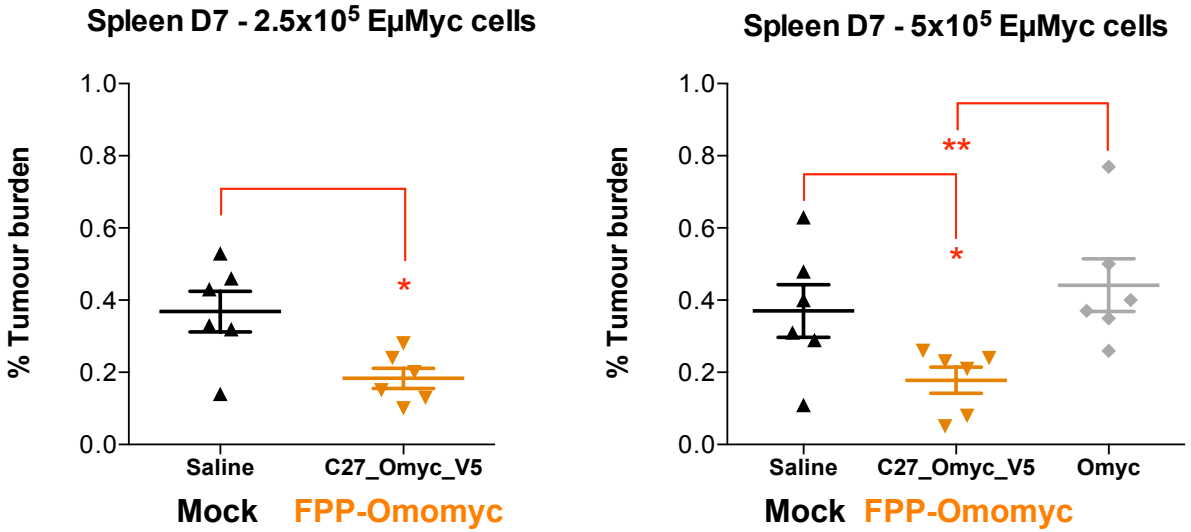
HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

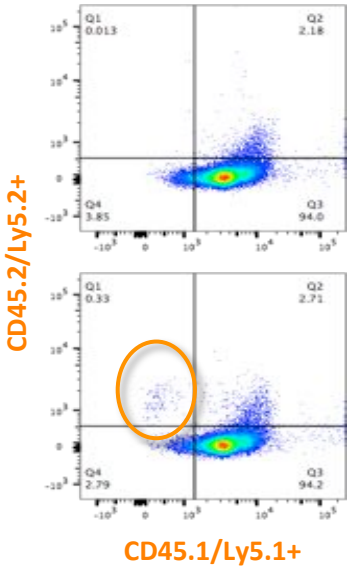
*Casey, et al. (2016). MYC regulates the antitumor immune response through CD47 and PD-L1, *Science* 10.1126/science.aac9935

Evidence of efficacy following *intravenous* delivery in EμMyc lymphoma model



Measure labelled EμMyc lymphoma cells (CD45.2/Ly5.2+) in spleen by flow cytometry at Day 7



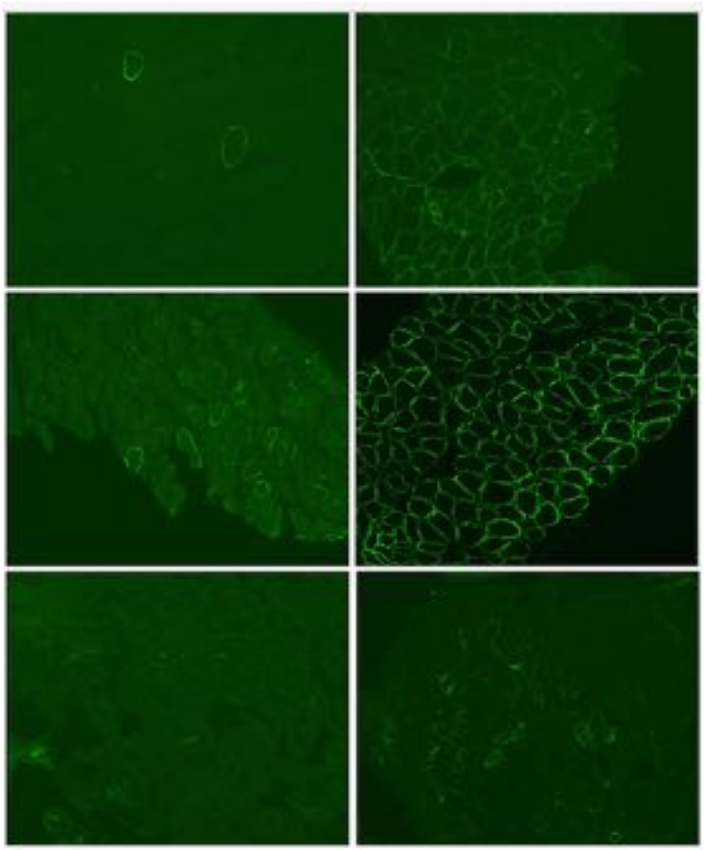


- **4 daily injections of FPP-Omomyc show reduced accumulation of lymphoma cells in spleen**

Enhanced delivery *in vitro* of antisense morpholino oligonucleotides using FPPs: DMD Model

- Morphilino antisense oligo (AO) targeting dystrophin gene (mutated in Duchenne muscular dystrophy; DMD)
- DMD oligo is designed to induce exon skipping (Δ23) in muscle cells to produce a shorter, yet functional dystrophin protein
- Phylomer FPP-DMD oligo caused greater exon skipping in mouse muscle cells at lower doses than alternative CPPs (e.g. PepK) which are toxic
- Evidence of increased levels of dystrophin protein with FPP-DMD oligo in a variety of muscles

FPP enhances dystrophin protein levels in muscles
Mouse DMD animal model



CENTRE FOR COMPARATIVE GENOMICS

- ~4 day old mdx mice treated with five IP injections of 4 nmoles of FPP-PMO
- Muscle tissue sections stained for Dystrophin protein 2 weeks after last injection
- FPP significantly enhanced function of PMO to increase dystrophin levels

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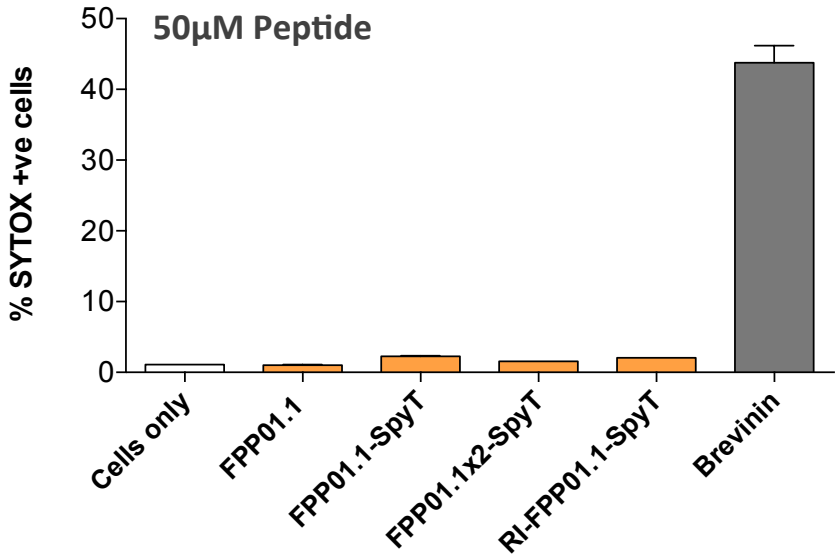
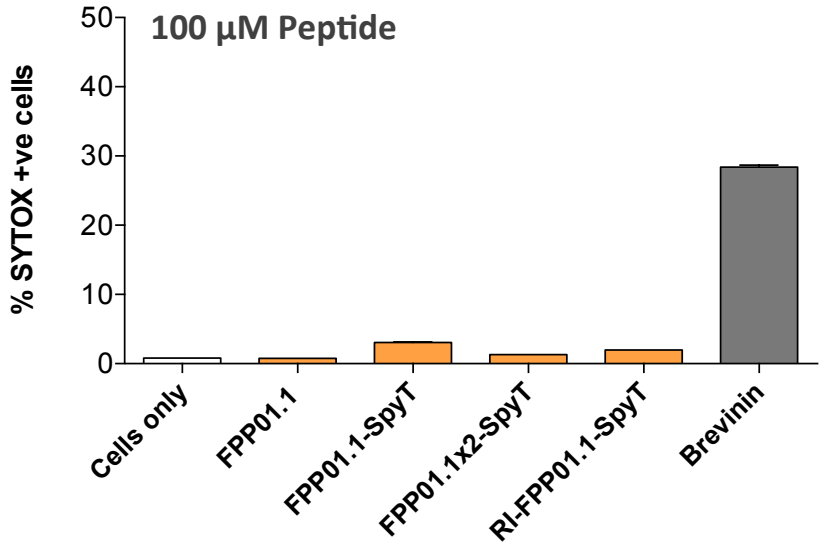
- Company and Technology Overview
- FPP Delivery Platform
  - Enables endosomal escape
  - Compatible with wide range of biologics cargoes
  - Outperforms other intracellular delivery technologies
  - Functional in multiple tissues
  - Demonstrable evidence of action
  - Evidence of in vivo efficacy
  - Promising initial safety signals
- Oncology Programs - Myc, Stat5, YB1
- Collaboration Opportunities and Summary

FPP peptide not cytotoxic (membrane integrity assay)

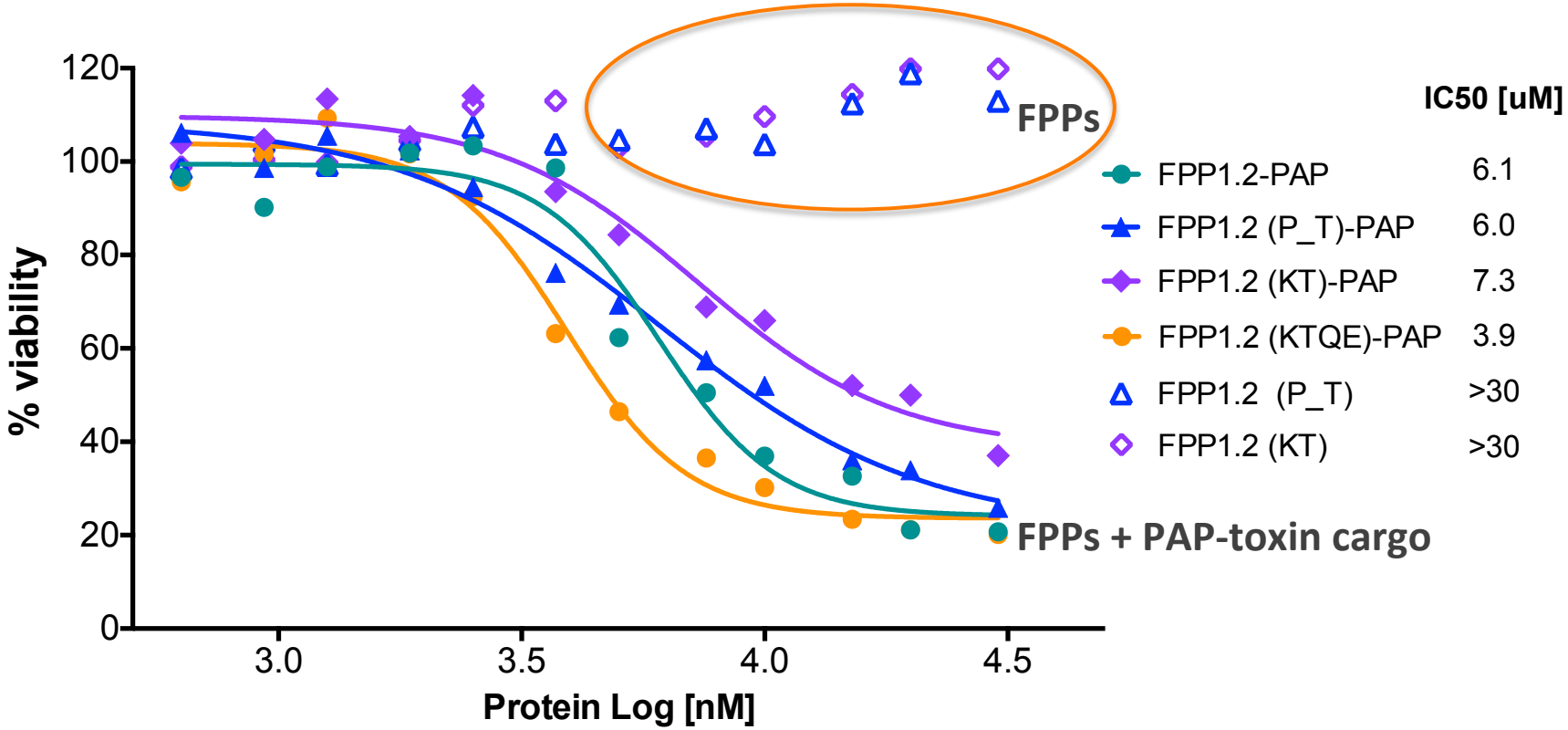
- Phylomer FPPs are non-toxic – even at 100µM
- Positive control: Peptide with known human cytotoxicity (haemolysis)
  - Brevinin an AMP from the skin of the frog, *Rana brevipoda porsa*

Membrane permeability staining of HEK293T cells after 24 h using Sytox red





FPP peptide not cytotoxic (reduction potential assay)



- CHO-K1 cells
- Presto blue viability assay (measures reducing potential of live cells)
- Assay repeated independently multiple times without evidence of FPP toxicity

Additional promising safety signals

- **No evidence of *in vivo* toxicity**
  - We routinely inject 200µM of FPP-fusion proteins or peptides i.v., i.p., and intratumorally into mice with no toxic side effects observed
  - Mice have received up to 6 doses (4 x i.v. + 2 x i.p. over 6 days)

- **No evidence of immunogenicity from *in silico* and *ex vivo* studies**
  - T-cell epitope in silico scanning shows that no predicted immunogenic epitopes are present in FPP01
  - *Ex vivo* studies from human T-cell proliferation assays predict low immunogenicity of a range of Phylomers

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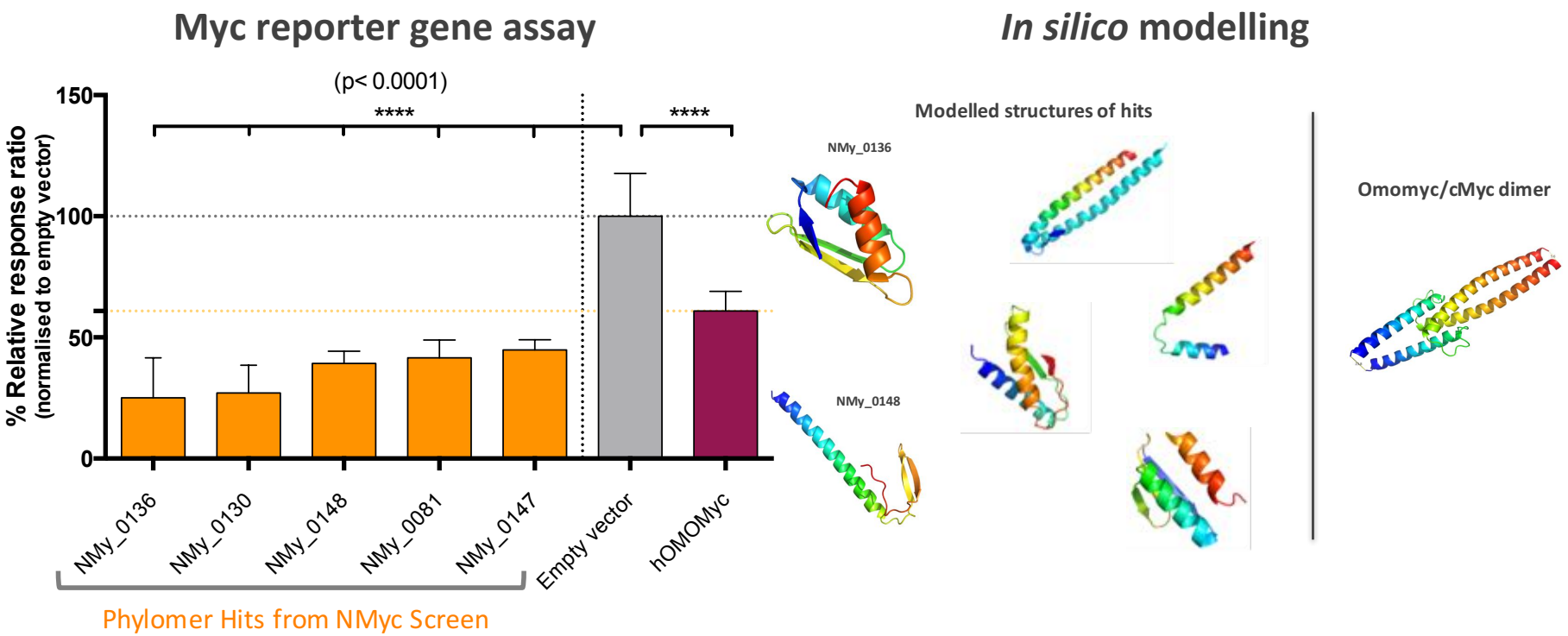
Phylogica's Intracellular Oncology Pipeline

- 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

Program	Target Indications	Discovery	Functional Validation	Preclinical
Myc	Lymphoma, AML, Breast cancer			
Stat 5	AML, Breast Cancer			
YB1	AML, Breast Cancer			

Multiple Phylomer Hits (iMyc) Targeting MYC

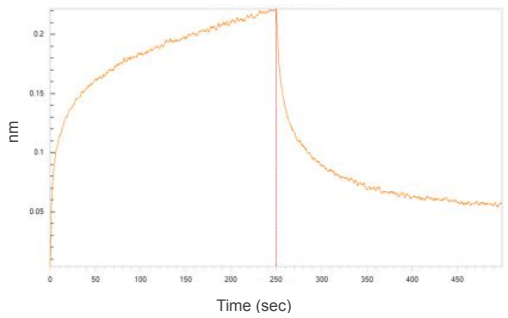


- Multiple active hits identified against *N-Myc* and *c-Myc* (bHLH motif)
- Some iMyc hits comparable or better than Omomyc in repression of reporter gene activity (Nanoluciferase) and in killing Myc-addicted cells
- Hits modeled as rich in helices & structurally diverse (e.g. coiled-coil like)

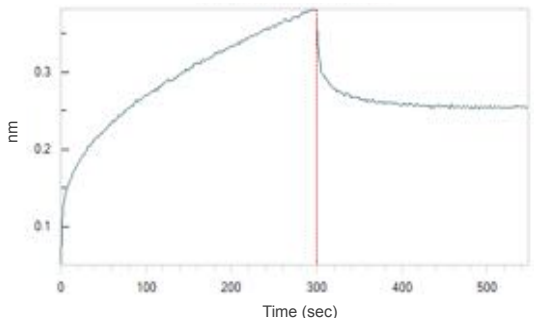
High affinity primary ‘iMyc’ Phylomers against Myc

- Primary hits before any sequence maturation can exhibit target binding affinities comparable to natural ligand (Max) and Omomyc protein
  - Binding affinities determined by Bio-Layer Interferometry

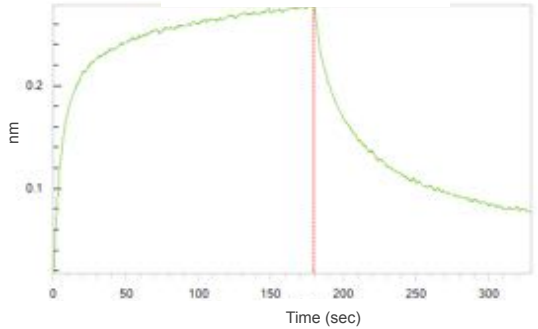
NMy_0113
345 ± 187 nM



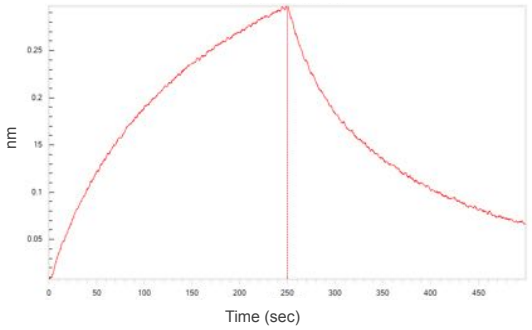
NMy_0114
166 ± 16.3 nM



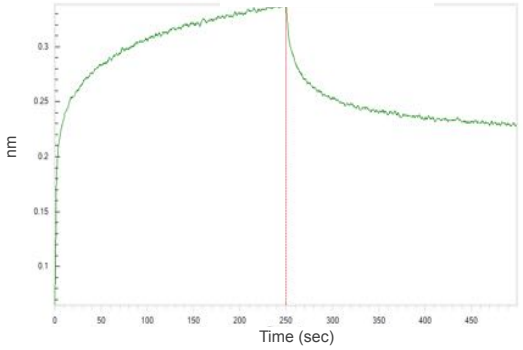
cMB_0177
30.4 ± 4.3 nM



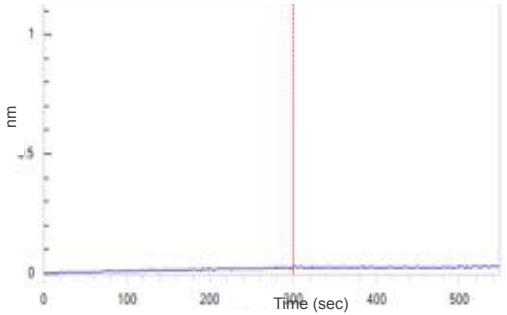
Max
43.2 ± 9.6 nM



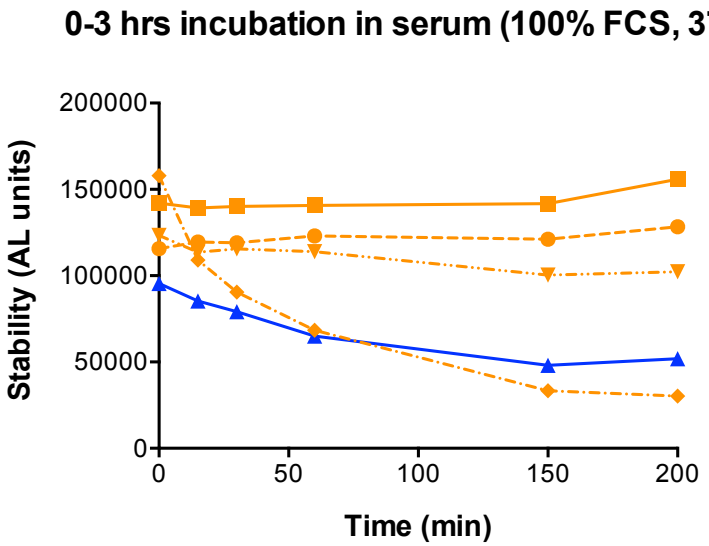
Omomyc
175 ± 75 nM

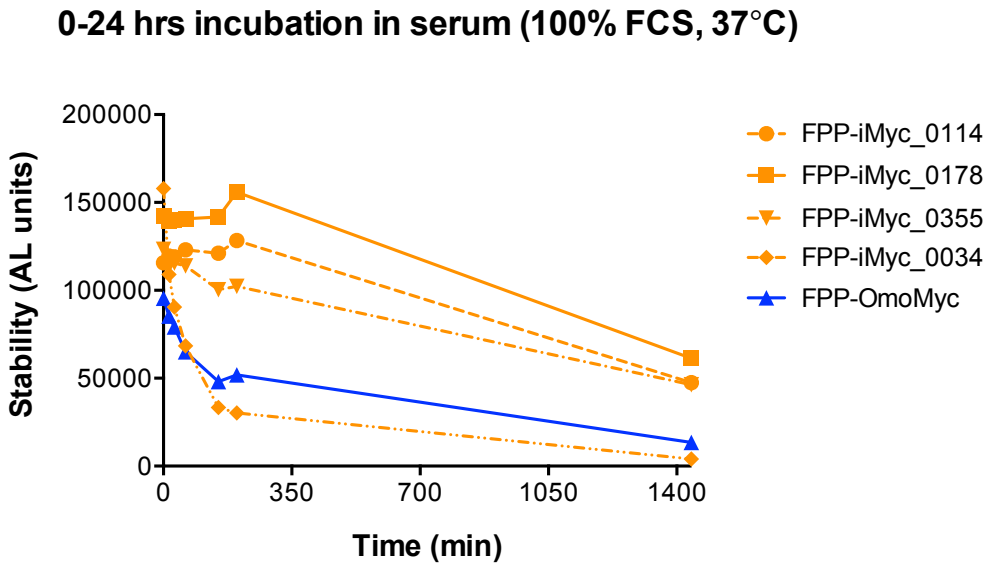


ScaffoldControl (SpyC)



FPP-iMyc conjugates are stable over hours in serum



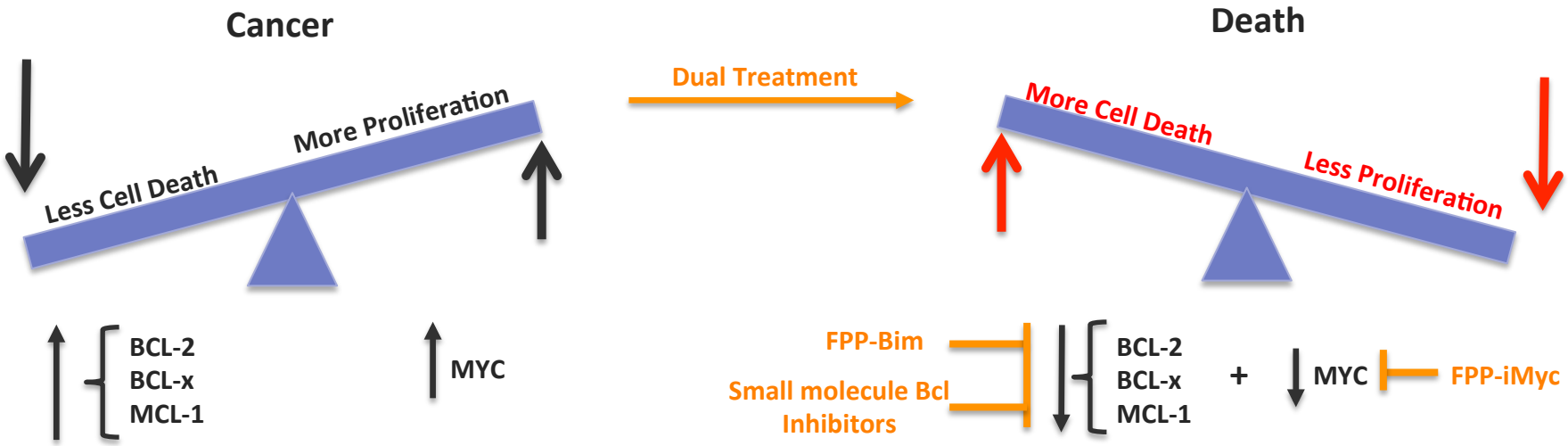


% of top FPP-iMyc hits remaining at 24h

NMy0114	cMB0177	NMy0109	NMy0112	NMy0105	Omyc
66.7	66.9	89.2	63.8	63.1	62.1

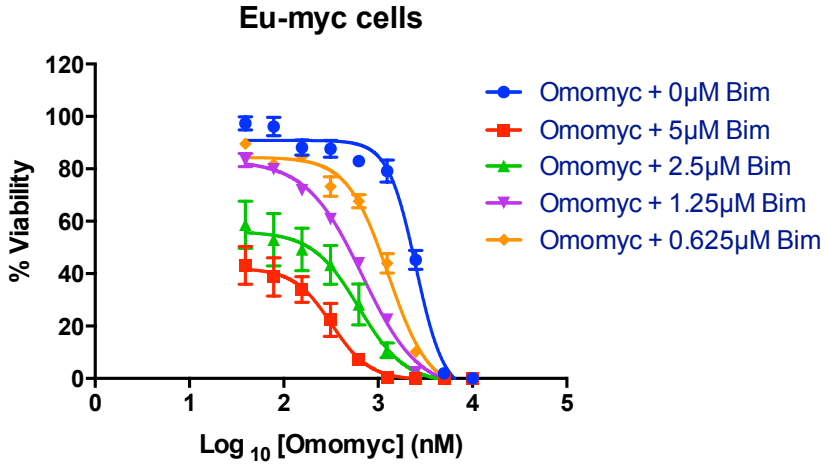
- Screening for full-length conjugates using dual epitope tags (AlphaLISA)
- Samples incubated in 100% (not heat treated) FCS at 37˚C for up to 24 hrs
- FPP-iMyc and FPP-Omomyc are relatively stable in 50% fresh serum
- Some FPP-iMyc conjugates show greater stabilities than FPP-Omomyc

Synergistic targeting of Myc and prosurvival proteins



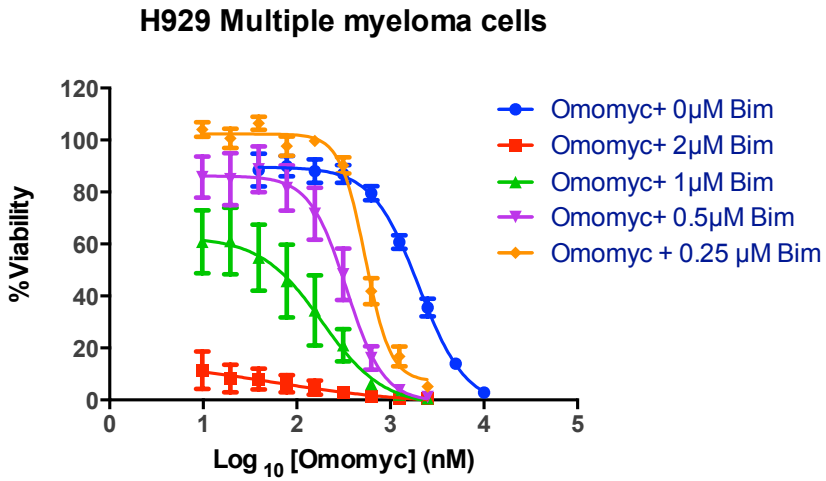
- Strategic opportunity for synergistic intervention using Phylomers
  - Phylomers targeting MYC can be combined with other FPP delivered cargoes or with small molecules
  - FPP-Bim targets all pro-survival proteins: BCL-2, BCL-x and MCL-1

Addition of FPP-Bim synergistically achieves nanomolar potencies with FPP01-spyC-Omomyc



Eu-myc (Burkitt's Lymphoma model) cells

[FPP-Bim]	0	5uM	2.5uM	1.25uM	625nM
IC50	2.5 uM	321 nM	626 nM	683 nM	1.3 uM

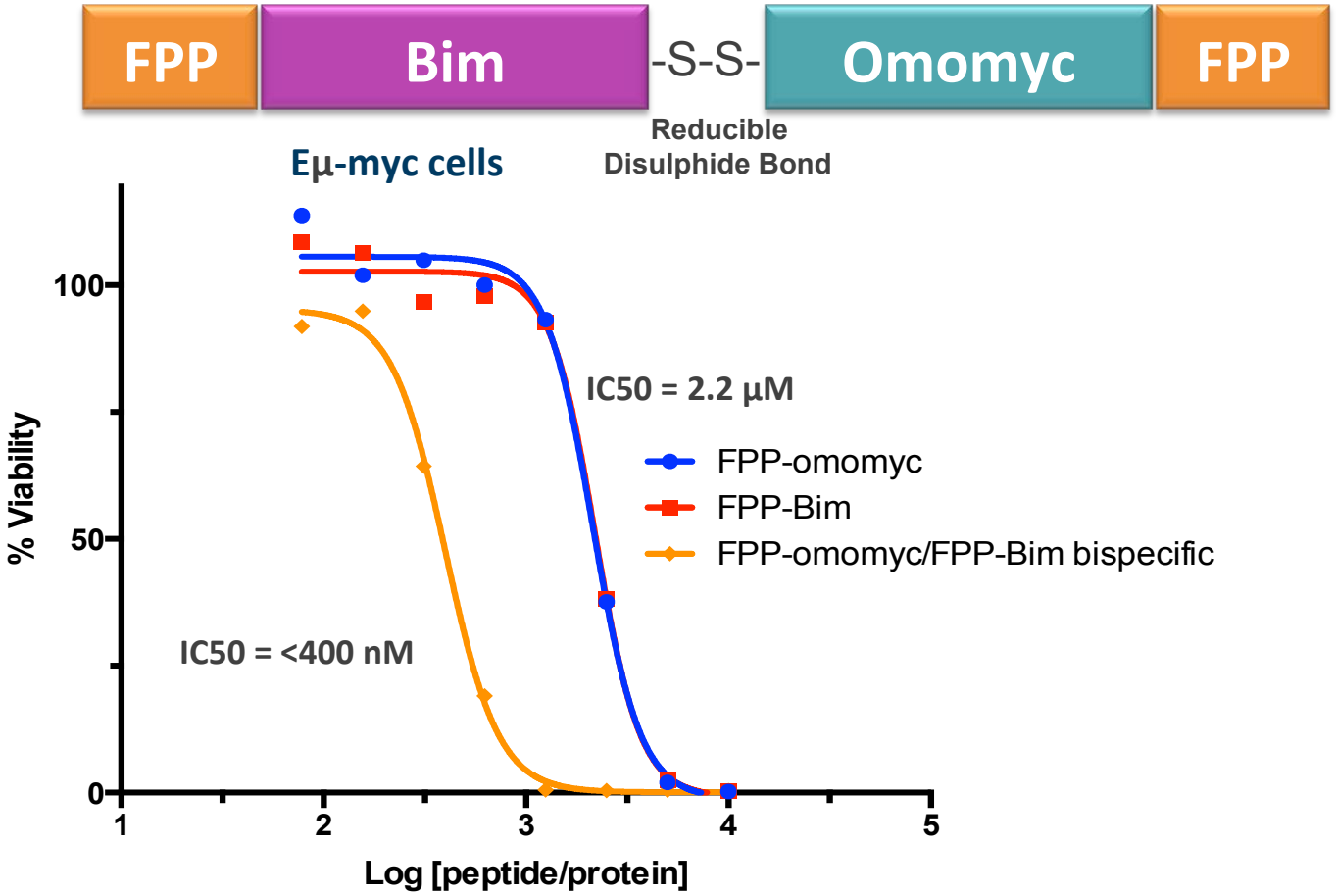


H929 Multiple Myeloma cells

[FPP-Bim]	0	2 uM	1uM	500nM	250nM
IC50	2.0 uM	ND	186 nM	340 nM	539 nM

- FPP-Omomyc potencies of 321nM and 186nM in different cell lines, achieved in synergy with FPP-Bim

Potent activity of a single compound FPP-Bim-Omomyc-FPP bispecific in EμMyc lymphoma cells



- IC_{50} of FPP-Bim-*Omomyc*-FPP is less than 400nM in EμMyc cells
- IC_{50} of FPP-Bim-*Omomyc*-FPP is 243nM in H929 MM cells (not shown)

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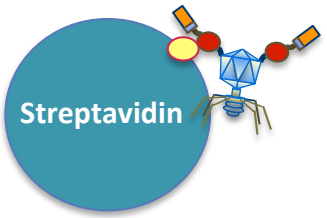
Phylogica is open to alliances with Pharma

- Phylogica's business model is open to alliances at any stage:
  - Discovery alliances
  - Alliances around our internal programs
- Open to multiple licensing structures:
  - License existing FPPs for particular cargoes or targets
  - Develop customised and proprietary FPP exclusively for partner's use
- We can deliver your biologics cargo into a wide range of cell types*
- We can help hit your intracellular target of interest with Phylomers as cargoes
- Open to partnering on our existing programs (Myc, STAT5, YB1)

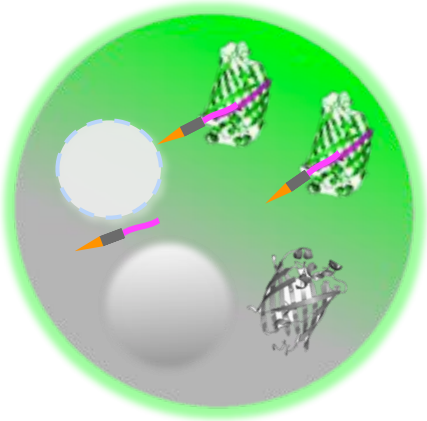
**Phylogica's recent discovery alliances have focused on intracellular delivery technology*

Expanding the intracellular landscape for novel biotherapeutics with Phylomer FPP technology

Novel endosomal escape trap for detection of efficient CPPs



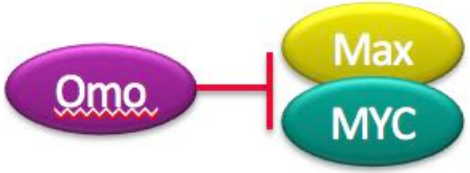
Validation of hits as best-in-class for cytoplasmic delivery, using an avitag Western blot and the Split GFP assay



Using new functional Phylomer CPPs to facilitate efficient delivery of biologic payloads

In-house oncology program with proprietary payloads targeting several key oncoproteins: cMyc, N-Myc, STAT5, YB1

Proof of *in vivo* FPP efficacy: reduced tumour burden in mice treated with FPP-Omomyc in two different animal models



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