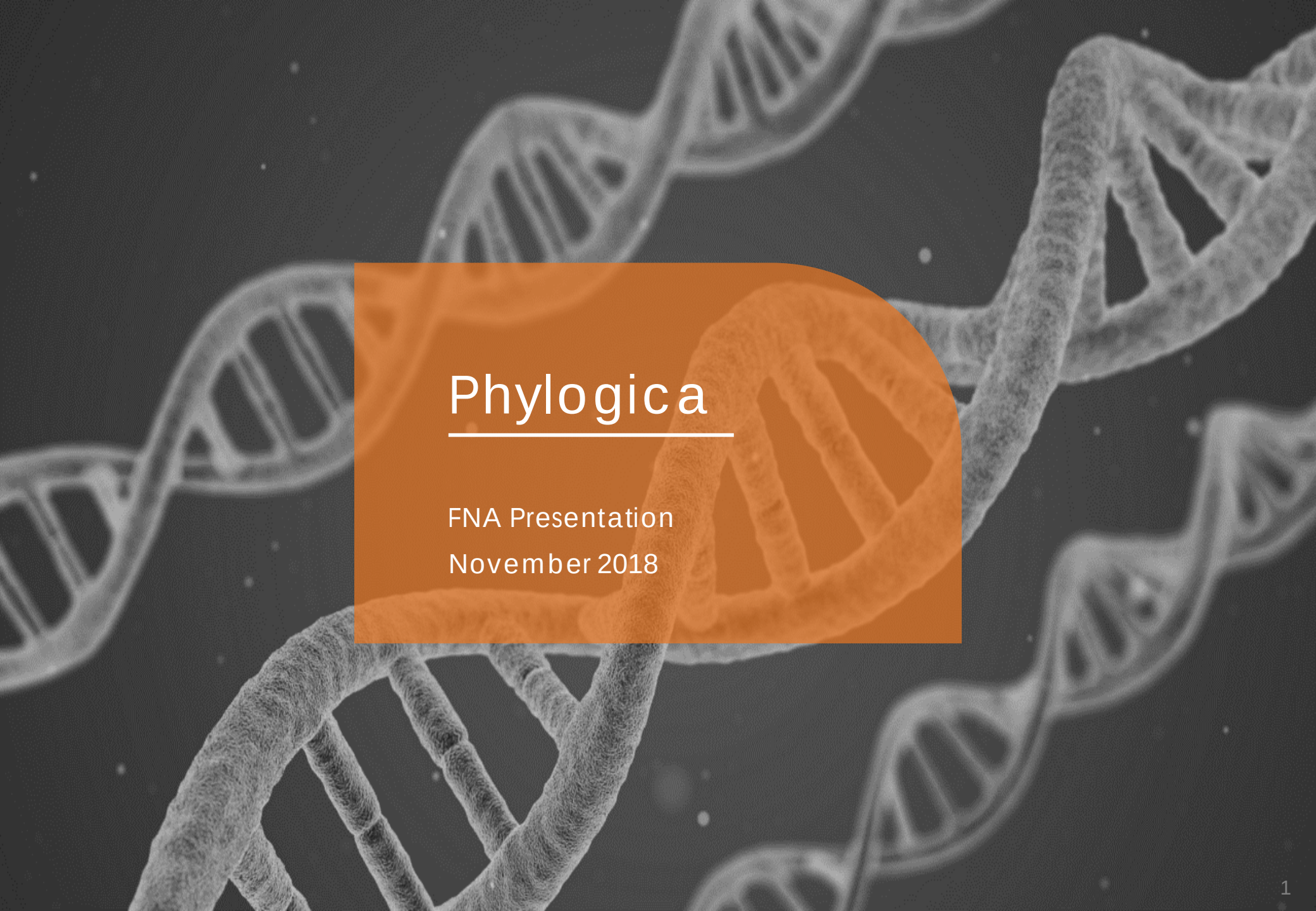


Phylogica

FNA Presentation

November 2018

Delivery is key

PHYLOGICA

- **The problem**: Delivery to target tissues is the primary obstacle impeding the clinical translation of OligoNucleotide (ON) therapeutics

- **The solution?** Cell Penetrating Peptides (CPPs) are increasingly prominent in the quest to address this delivery obstacle

- They've been around for 40 years with only incremental progress demonstrated – **what's different this time**?

    - Unimproved 'hit' sequences that are more than 10x as efficient as 'conventional CPPs'
    - Evidence of tissue tropism to target specific cell types – concentrating drug in diseased tissues
    - Developments in analytics frameworks that enable multi-variate optimisation (improving 'hit to lead' and development conversion)
    - Early transition to 'build the delivery platform' in the context of the cargo – essential in the context of cargo-specific properties
    - Indications that absolute disease correction thresholds are within reach (eg. Sarepta's pipeline of PPMO therapies)

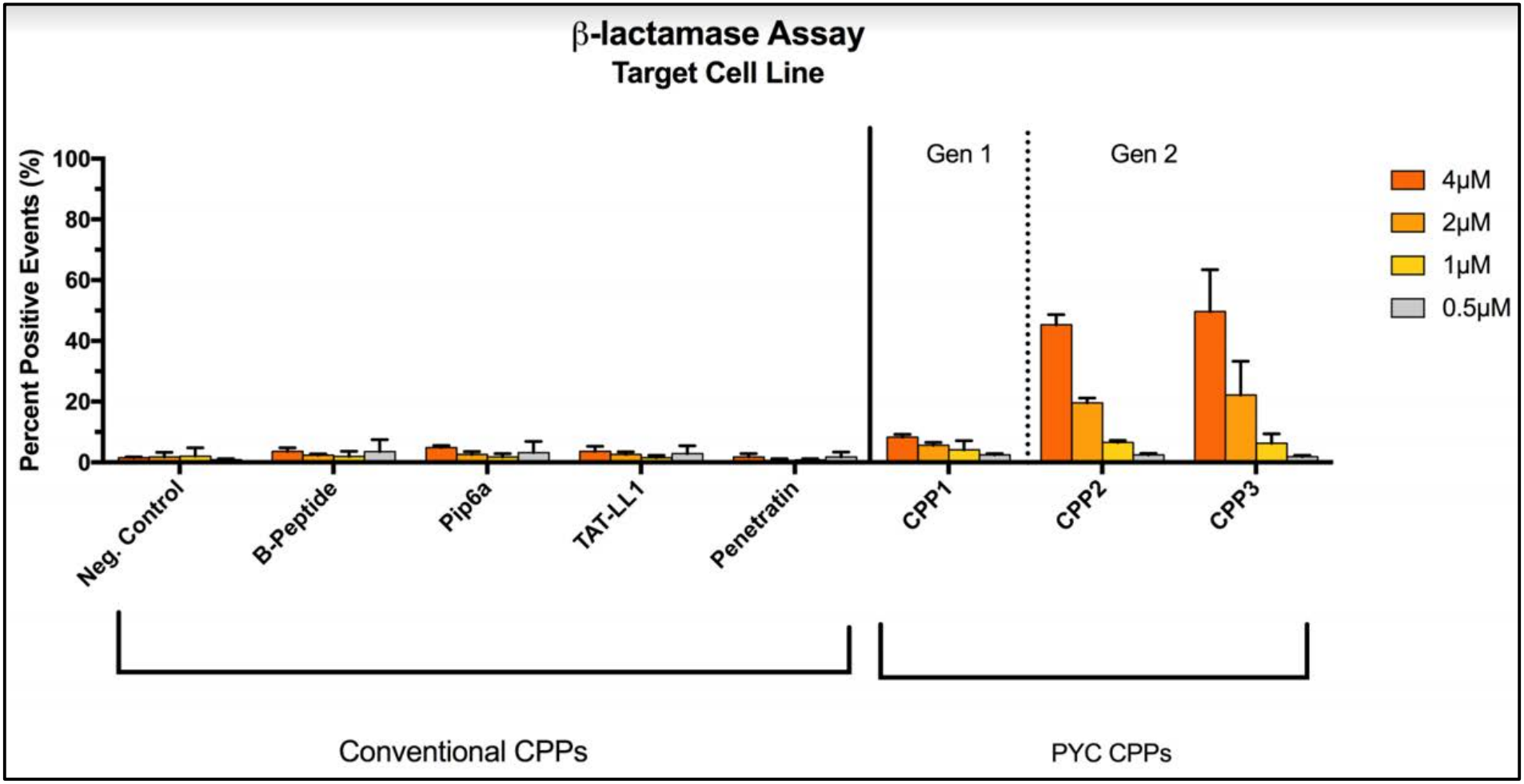
A tale of two companies...

Company	Parental CPP sequences	CPP sequences evaluated in lead selection	Development stage
SAREPTA THERAPEUTICS	1*	4	• 1 clinical PPMO • 5 IND submissions for PPMOs planned in 2019
PHYLOGICA	1,000 – 10,000	~100	Pre-clinical – therapeutic *in vivo* validation

We are balancing the need to rapidly develop the platform with the value of carefully considering the breadth of data we have

* Sarepta used the B-peptide (a modified poly-arginine CPP) as their starting sequence

Phylogica's CPPs are more efficient than 'conventional CPPs'



Our '1st generation' CPPs are effective *in vivo* - '2nd gen' results will follow soon

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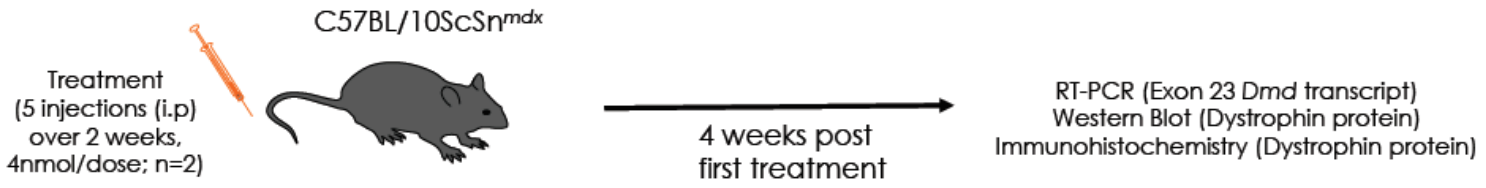
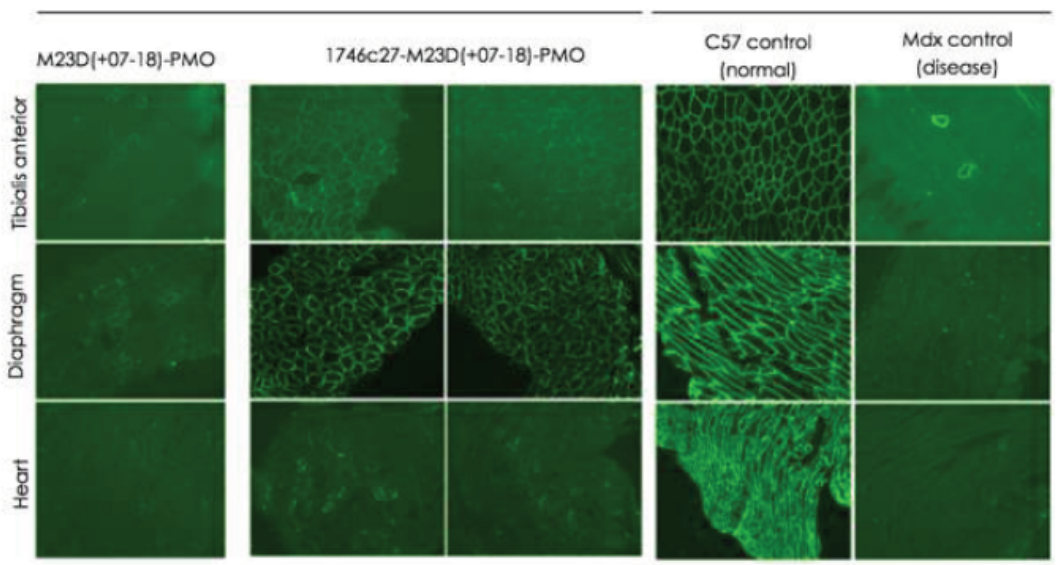
Dystrophin levels are restored by CPP-mediated delivery of DMD PMO *in vivo*

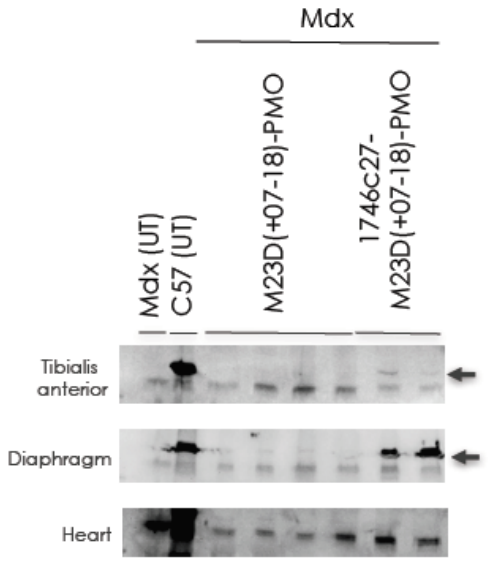
Sustained response in CPP-PMO treated mice



IHC staining



Western blot



* Mdx mice have a nonsense mutation in exon 23 of the *dystrophin* gene

Collaborator: Sue Fletcher

Indications of cell-specific CPPs suggest further concentration of cargo is possible

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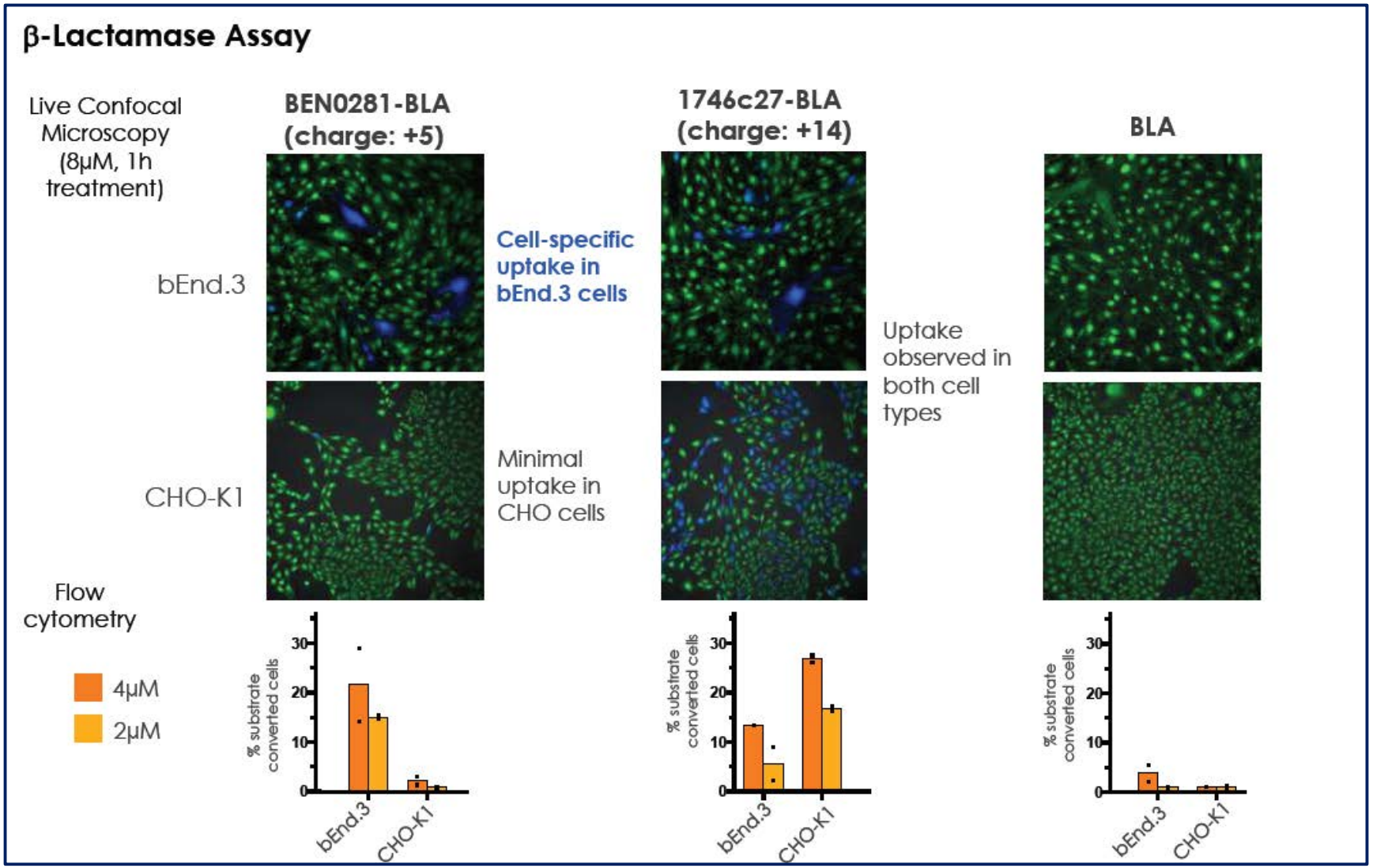

Recent developments in analytics allow us to consider many more variables

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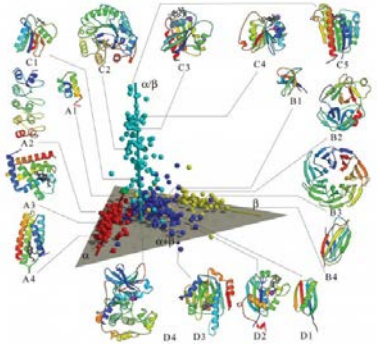
Phylogica's 'up-stream' CPP identification process

Peptide source



Screening method

- *In vitro* generic
- *In vitro* specific
- *In vivo* screen

Validation method

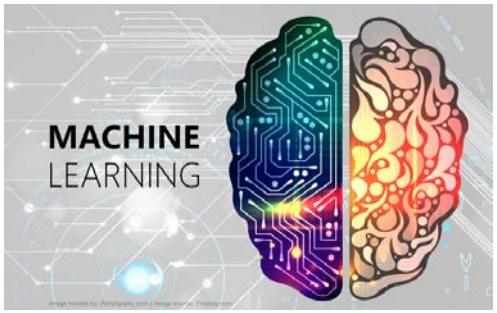
- Reporter cargo
- Therapeutic cargo

Biophysical property filter

Stop

Optimisation approaches

- Therapeutic cargo



- Observation
- Observation
- Observation

- Predicted sequences

Identifying the right CPP for a therapeutic cargo is a complex process that is specific both to the cargo and target tissue of interest

Is the juice worth the squeeze?

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- The richness of the data set that we generate from the Phylomer libraries is both a blessing and a curse:
  - A blessing in the number and quality of CPPs that we identify (Phylogica's CPPs substantially outperform the 'conventional CPP landscape'); and
  - A curse in the amount of data that we are handling – screening and validating CPPs is both expensive and time-consuming

- We have the privileged ability to see the 'macro rule' (the link between the properties of a CPP and its ability to deliver a cargo) across CPPs of divergent characteristics (raising the possibility that we can combine 'parts' of CPPs to create high performing 'chimeras')

- We can also define the 'micro' rule through creation of variants of parental sequences to 'fine tune' a CPP

- <u>BUT…</u>

- These activities must be conducted in the context of the cargo of interest (and ideally the target cell of interest too) - we are building a platform tailored for ONs

In summary…

- CPPs have the ability to open up new target tissues/cells and disease indications for ON therapeutics

- Phylogica's platform can deliver a step change in the amount of drug delivered into a target cell by:
  - Using substantially more efficient 'second generation' peptides;
  - Exploiting observed patterns of differential cellular uptake to target diseased cells; and
  - Using advanced analytics to select for drug-like properties

- We are building our platform specifically for ON therapeutics and will be moving into therapeutic *in vivo* evaluation very shortly

Thank you

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