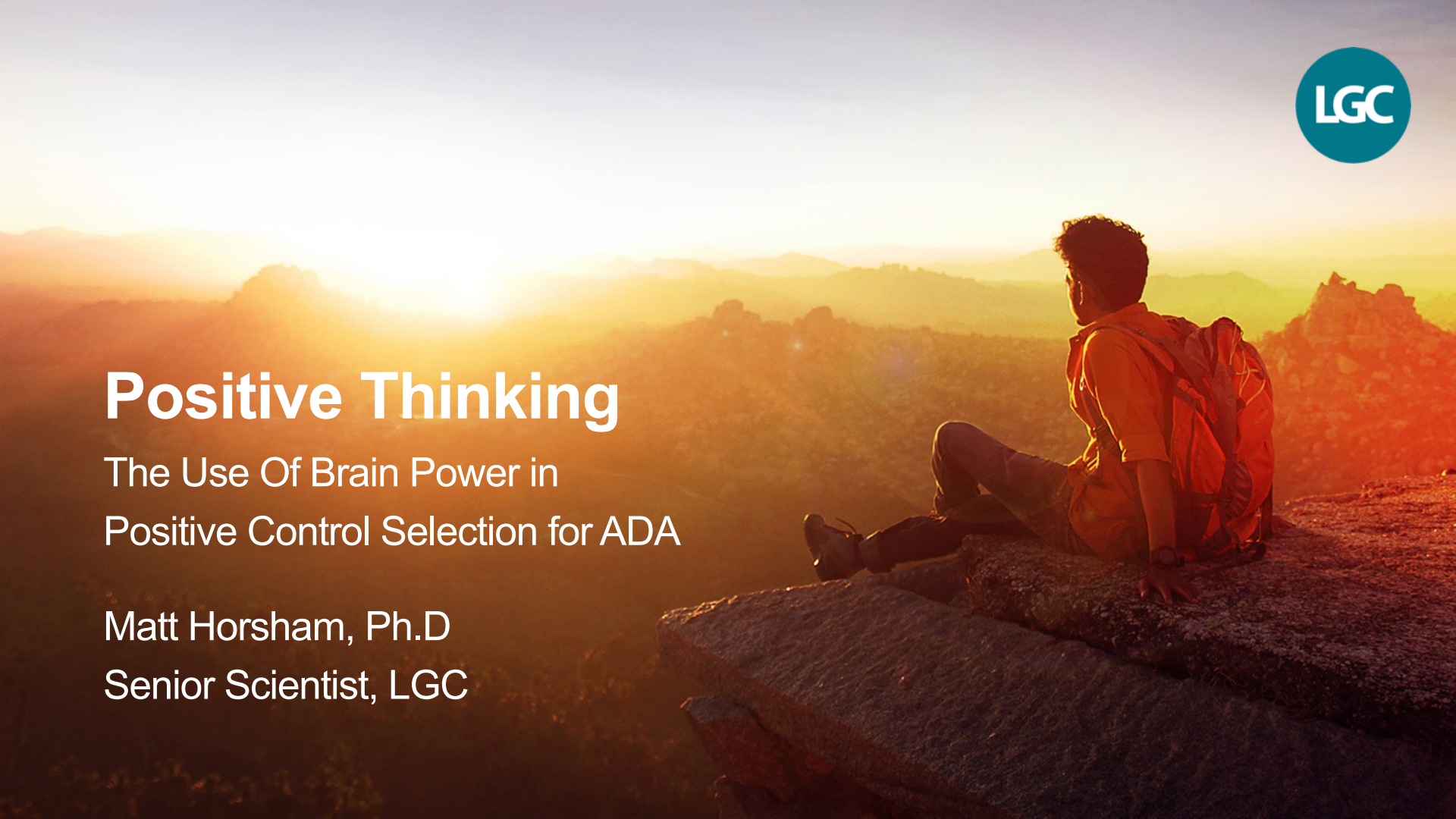

Positive Thinking

The Use Of Brain Power in Positive Control Selection for ADA

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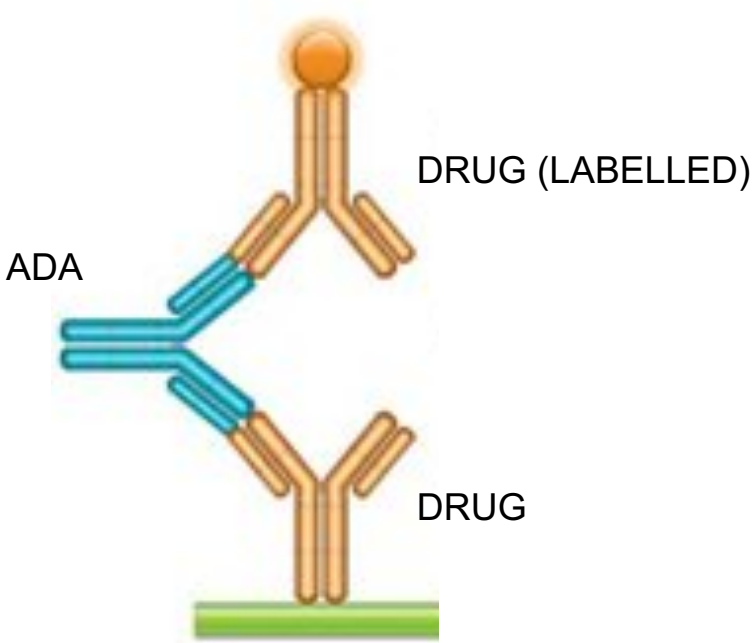
Intro

Anti Drug Antibodies (ADA):
***unwanted* immune response to an administered drug**

This talk will focus on

- Types of positive control (PC)
- Considerations
- Theoretical examples
- When, why and downstream impact

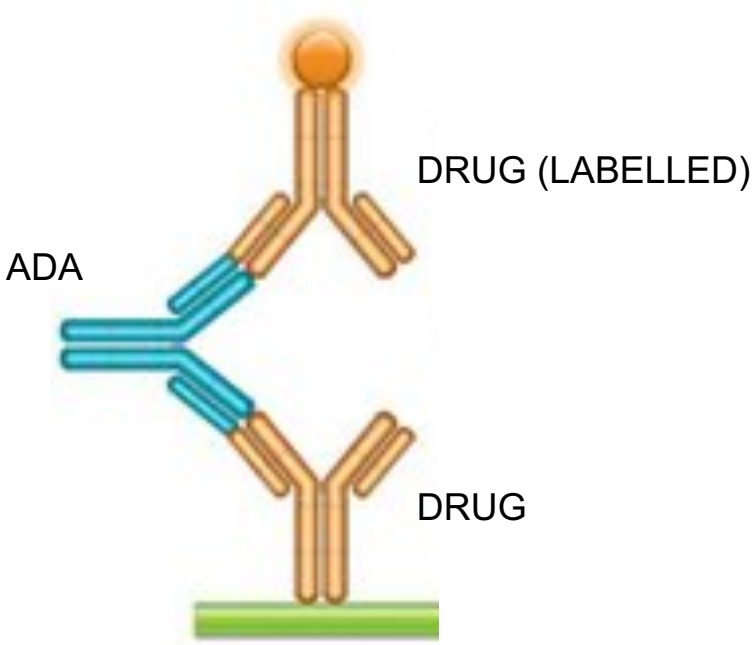


Bridging Assay Format

Image Credit: Bio-Rad.com

What are PCs and why do we need them?

- PCs play the role of ADA in development & control of our assays
- They are the most Critical Reagent in our ADA assays
- They are there to show that an immune response can be raised against our drug
- PCs give us confidence in our assay performance



Bridging Assay Format

Image Credit: Bio-Rad.com

The world we live in

- **In reality there is no IDEAL positive control**
  - Gold Std: a human pAb against whole drug
  - pAbs contain all subtypes, but every person is unique
- **Whatever we choose it is a SURROGATE for true ADA response**
  - Monitors assay performance
  - Regulatory requirement

"Considering the scope of this guideline is wide, the recommendations will have to be adapted on a case-by-case basis to fit into an individual development program."

-EMA Guidance on Immunogenicity 2017

Considerations

- **What is the current field of play?**
  - Changes in latest guidance
- **What do we know about our drug?**
  - Multi-domain?
  - How complex: Fusion protein?
  - Modifications?
- **What knowledge do we need to gain from our data?**
  - Preclinincal vs clinical study?

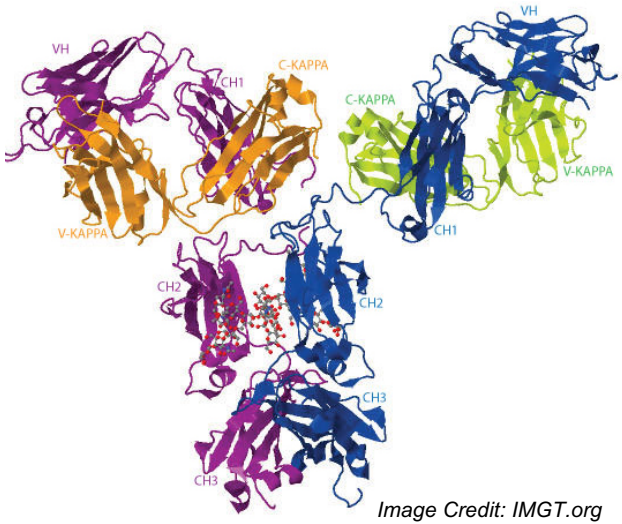
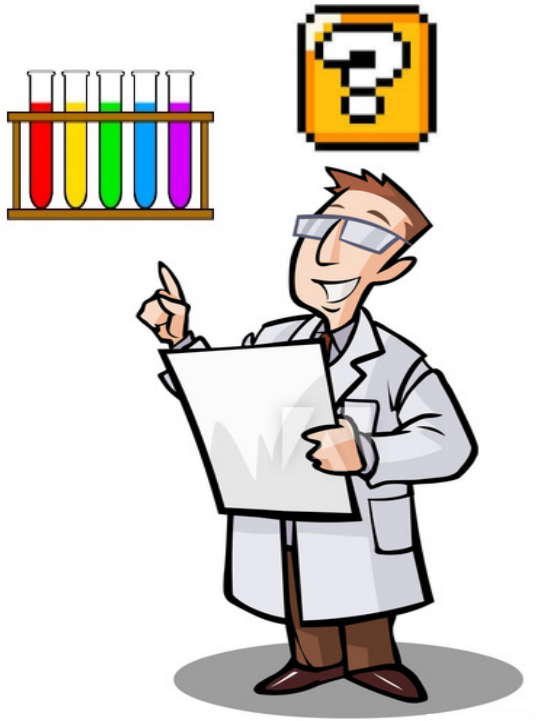


Image Credit: IMGT.org
http://www.imgt.org/IMGTeducation/IMGTlexique/G/Glycosylation.html

Whichever PC we choose, it is a SURROGATE for a true ADA response

PC options - lets go shopping

- Polyclonal Antibody (pAb)
- Pre-exisiting Abs from Samples
- Monoclonal antibody (mAb)
- Anti-idiotypes



PC options - lets go shopping

	GOOD	BAD	UGLY
pAb	Closest to true ADA Contains multiple subtypes Can bind to multiple epitopes	Lower specificity	Critical Reagent Control = DIFFICULT
Pre-existing Abs		Whole matrix - impurities	Uncharacterised
mAb	High Specificity Critical Reagent Control = GOOD	Single Sub-type	Can miss the full immunogenicity picture
			FDA states mAb should bind to the variable region
Anti-Id		Needs to be at least F(ab')2 to work in bridging assay	Sometimes the subtype is unknown

More shopping…….

Off The Peg

V

Bespoke

Lets look at some hypothetical examples of why we might make different choices…..

1. We choose a pAb

- **Why?**
  - The closest we can get to REAL ADA response
  - We were able to elicit a response in our assay & achieve the required critical parameters
- **What if I can't get purified pAb - what do I do?**
- **Does it provoke a response in your assay?**
  - Use the unpurified pAb in matrix
  - Assess target interference to evaluate if there are any issues arising from using the matrix

1. We choose a pAb

- **We have had experiences with complex molecules:**
  - Bispecific drugs
- **A pAb has proved ideal for this situation**
  - Able to bind both parent molecules and the drug product
- **Allows us to employ a multi-arm approach for screening and confirmatory analysis.**

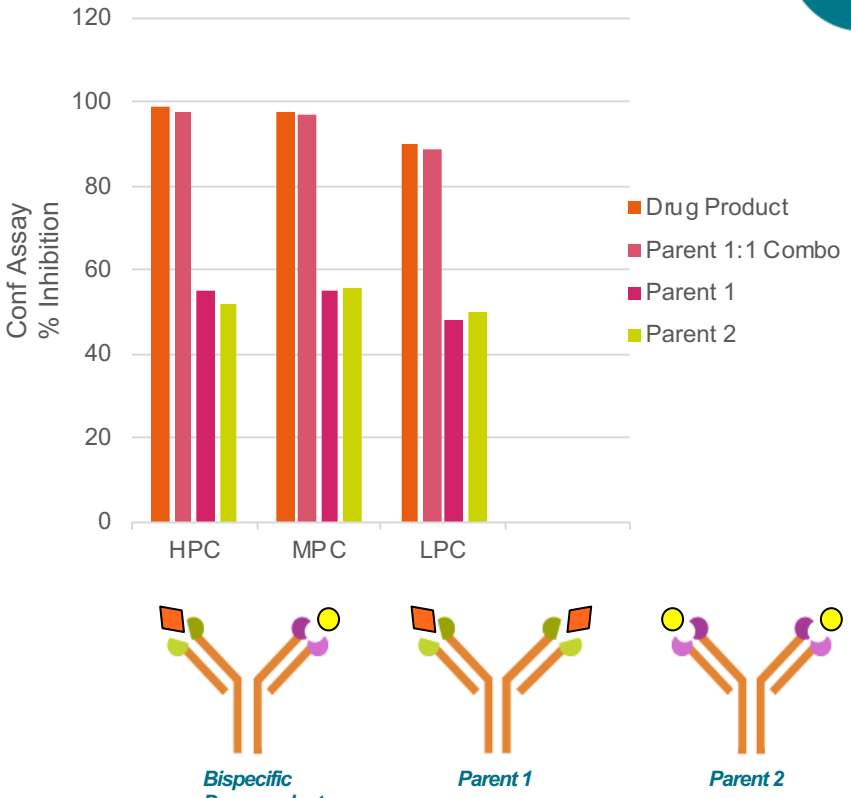


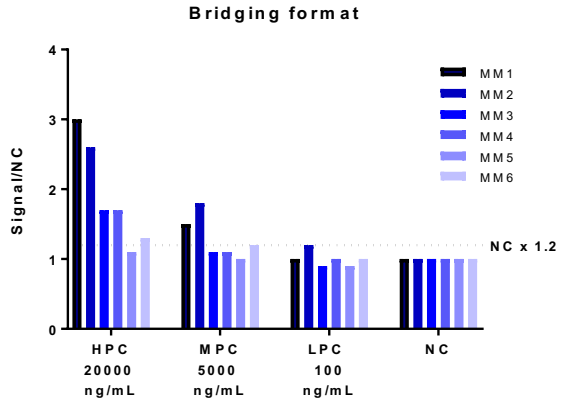
Image credit: Abbvie Oncology

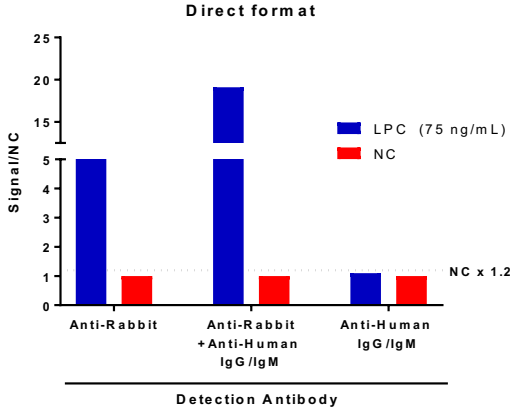
Data on presented on this slide are mock data intended for illustration only

1. We choose a pAb

- **We have had experiences where factors have been limiting:**
  - Budget
  - Time
- **And drug molecules challenging:**
  - Smaller drug molecules
  - Advised to boost immunogenicity by conjugation to a carrier protein
  - Resulting assays have provided challenges in meeting sensitivity
- **A mAb with higher specificity would have been easier to work with and provided the information needed**

1. We choose a pAb





	Bridging	Direct
Sensitivity at 100 ng/mL	✗	✓
Drug Tolerance	✓	✓
Species reactivity	✓	✗
IgG/IgM reactivity	✓	✗

Data on presented on this slide are mock data intended for illustration only

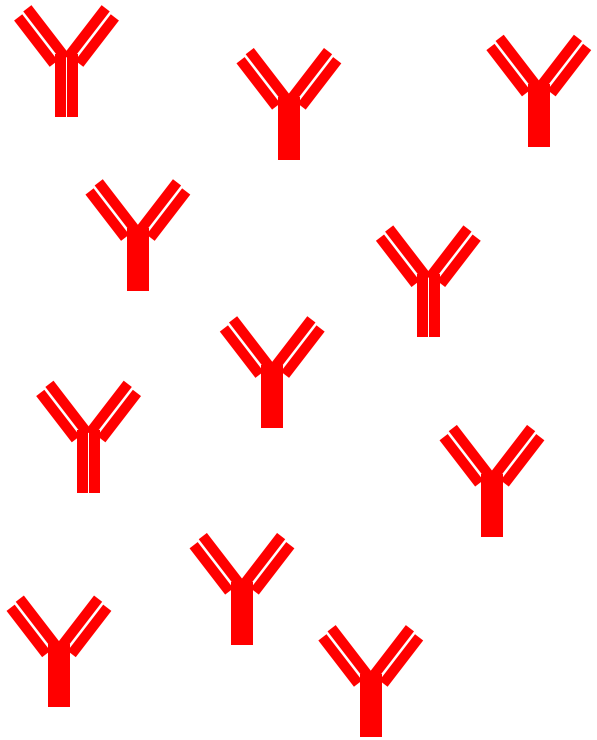
2. we choose a mAb

Why?

- Suitable pAb not available
- We were able to get an adequate method with a stock mAb

For Consideration:

- Are we capturing the complete immunogenicity picture?

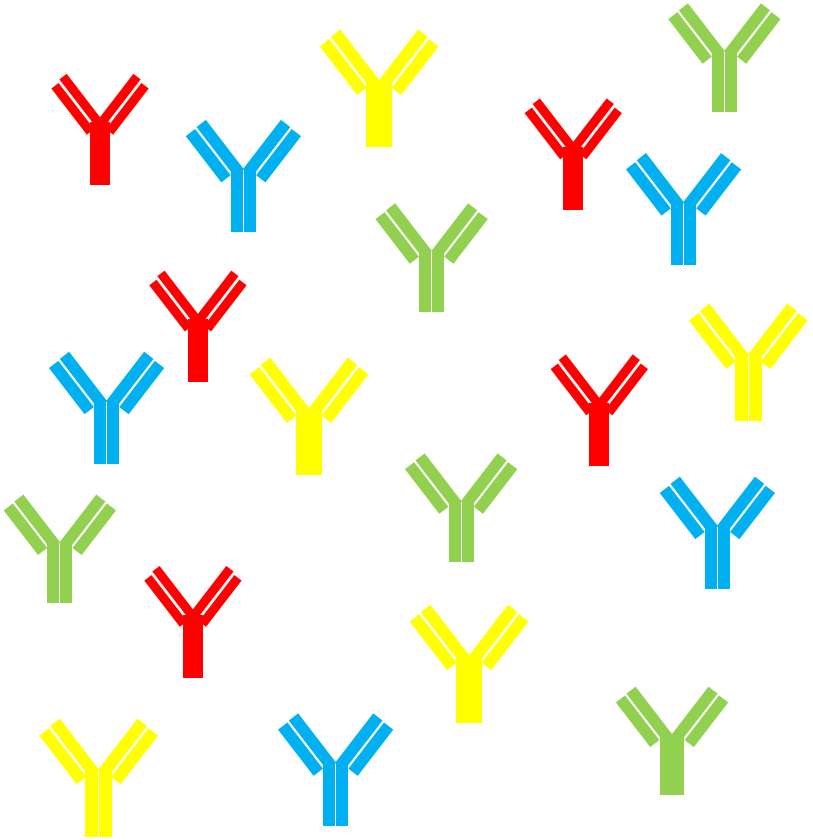


2. we choose a mAb

For Consideration:

Would a mAb *mixture* have been a better option?

- Cost
- Complexity
- Critical Reagent impact



2. we choose a mAb

- **We have had experience where factors have been limiting:**
  - PC availability
  - Time
  - Legacy methods

- **Generally historic assays which were needing brought in line with current guidelines**

- **Employing pAb PCs in assays originally developed with mAb PCs has generally led to different drug tolerance and sensitivity levels for the two PCs**

3. We choose a mAb / pAb dual approach

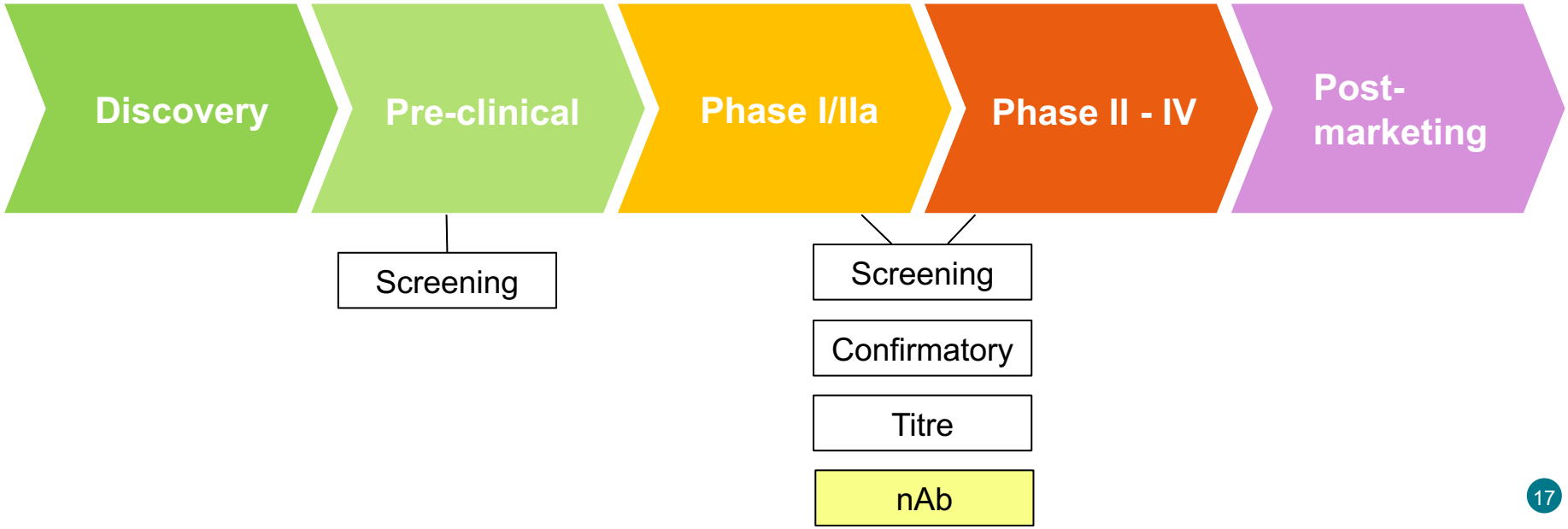
- **Why?**
  - mAbs give us
    - Higher sensitivity
    - Greater critical reagent control
  - pAbs give us
    - Lower sensitivity
    - Greater physiological relevance
  - Use the pAb for critical assessments
  - Use the mAb to control the assay during sample analysis

For Consideration:

- Takes time and extensive planning to set up
- Costly to implement

Choice and downstream impact

- We adopt a tiered approach as we progress through the drug development timeline



From tick box to brain power

- We know there is a general preference for PC choice
- Case by case basis
- Strike a balance between interpretation of the guidelines, physiological relevance and the assay requirements
- Show that it is scientifically justifiable and fit for purpose

The most exciting phrase to hear in science, the One that heralds new discoveries, is not 'Eureka!' but 'That's funny...'

Isaac Asimov

Acknowledgements

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