MedImmune

A member of the AstraZeneca Group

CBA, LBA or NA - Regulatory Sense or Non-Sense

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Varying Perspectives on ADAs

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Content

What is Immunogenicity?

- Ability to cause an immune response
  - **Wanted: Vaccines**
  - **Unwanted: Anti-Drug Antibodies (ADA)**

- Has only become an issue over the last decade
  - Case Study: **Erythropoietin (EPO)**

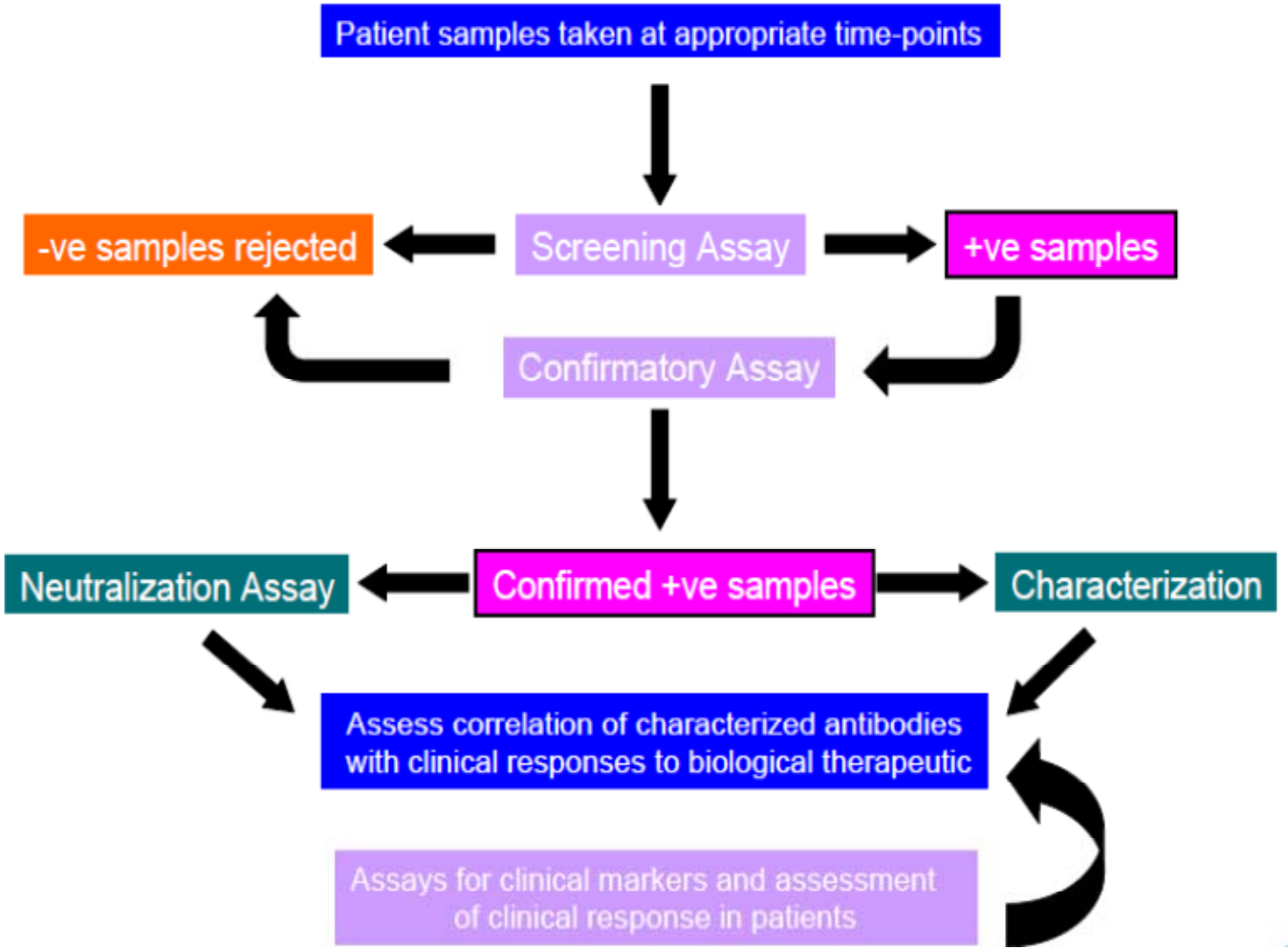
- Casadevall et al. NEJM (Feb 2002)
  - From 2000-2002 13 individuals were referred to their lab due to sudden resistance to the hormone and **pure red-cell aplasia (PRCA)** that required blood transfusions

Regulatory Concerns of ADA on Biotherapeutics

Concern	Outcome
1). Safety	ADA causes hypersensitivity reactions ADA neutralise activity of an endogenous equivalent resulting in deficiency syndrome
2). PK	Altered PK by ADA causing a change in dose level Changes in clearance
3). Efficacy (PD)	Changes in drug effects Biotherapeutic no longer affects target
4). None!	Despite presence of ADA, there are no clinical effects

ADA effects may be persistent or transient – Clinical Consequence is key

Clinical Strategy for Immunogenicity Determination: 'Tiered Approach'



Neutralising Concerns

- NAbs **block** the **biological activity** of the therapeutic molecule
  - Bind **Directly** to the Epitopes of the Active Site
  - Block the Active Site via **Steric Hindrance**

- NAb characterisation is conducted on a risk-based approach
  - **Harm to patients** characterised and evaluated should NAbs occur
  - Traditional MAbs not until **Phase 3**
  - Peptides maybe sooner
  - Generally characterisation based on **risk mitigation plan**

Bioanalytical Strategies to Support NAb Assessments in Phase 3 Programme

Option 1: Cell-Based Assay (CBA)

Option 2: Ligand Binding Assay (LBA)

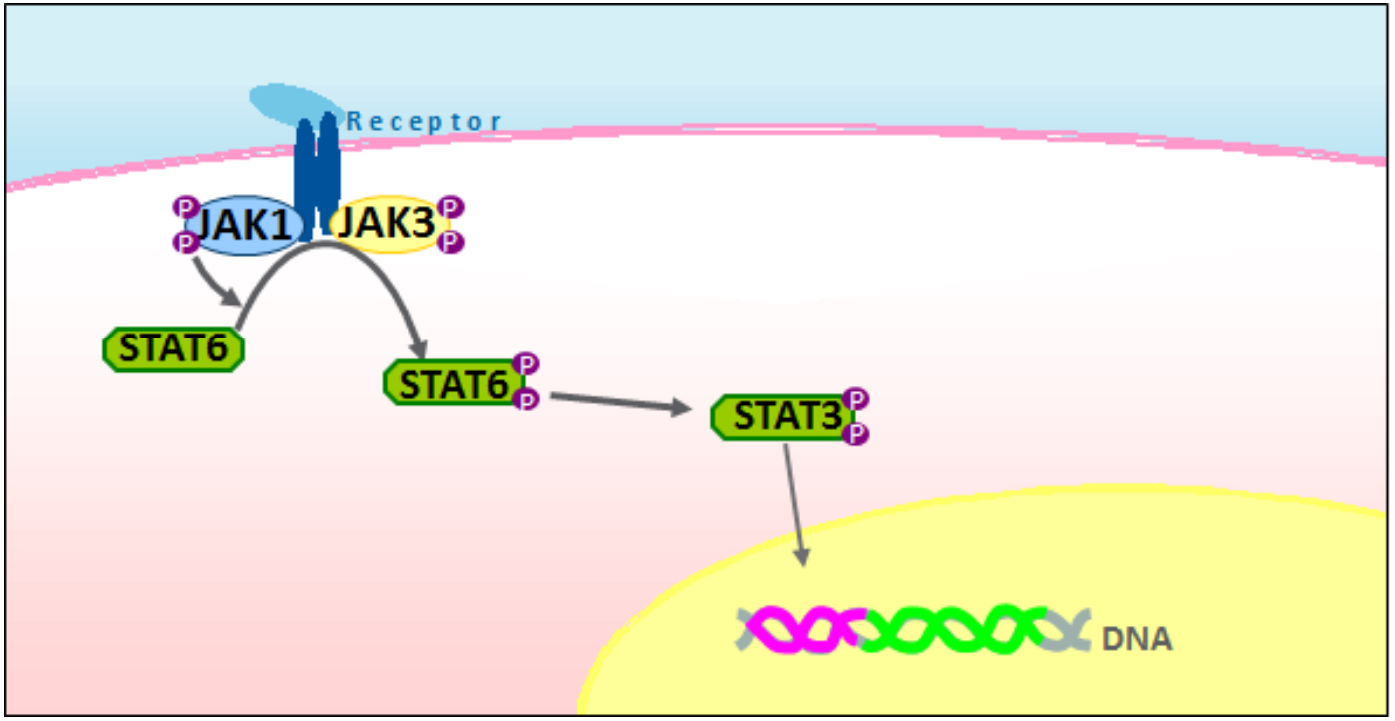
FDA Prefers a Cell Based Assays (CBA) Approach

- 'The **FDA** considers that **bioassays** are more reflective of the '*in vivo* situation' and are **recommended**'
- These **bioassays** are generally based on a cell's ability to **respond** to the **product** in question
- The **bioassay** should be related to **product mechanism of action**, otherwise the assay will not be **informative** as to the effect of **NAb** on clinical results

Ligand Binding Assays (LBA) are a Viable Alternative

- **EMA**
  - If neutralising cell-based assays are not feasible/available, **competitive ligand binding assays may be suitable**
  - When used it **must** be demonstrated that they **reflect neutralising capacity/potential** in an appropriate manner
- **FDA**
  - LBAs may only be used as an **alternative in some situations**…

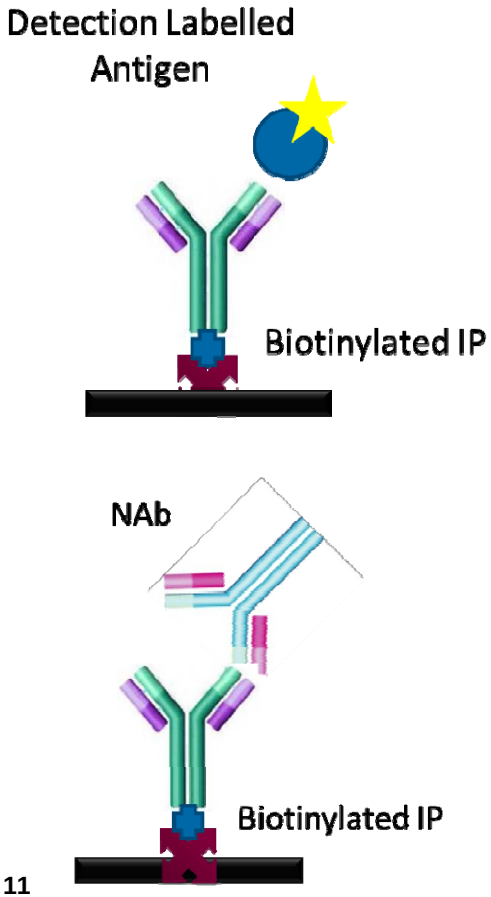
CBA – Therapeutic MoA Inhibition Demonstrated



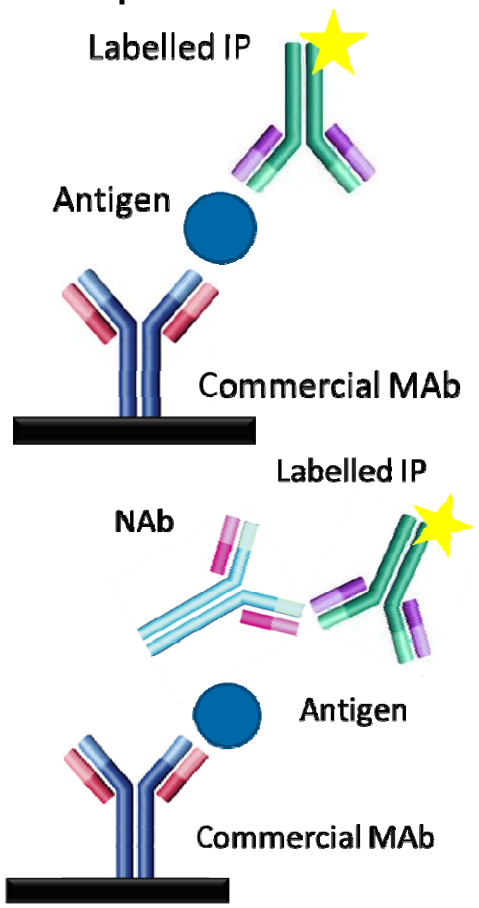
- Suspension cell-line endogenously expresses cellular receptor
- Engineered to express STAT6 response element and luciferase reporter

LBA – Various Potential Experimental Paradigms Exist

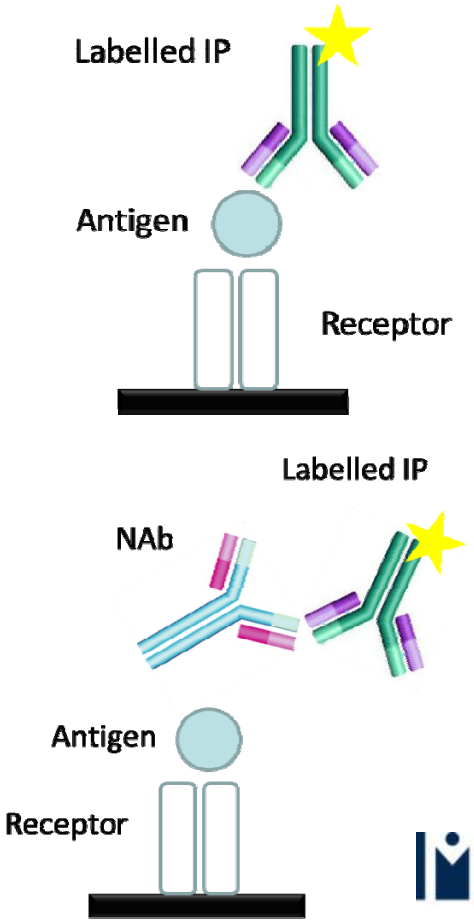
- Option 1



Option 2



Option 3



Key Assessment Criteria

- Suitable Neutralising Positive Control
- Assessment of Platform Sensitivity
- Passage Number
- Assessment of Assay Range
- Assessment of Drug Tolerance
- Assessment of Assay Variability
  - Inter-assay variability
  - Intra-assay variability
  - Inter-analyst variability

LBA Out Performs CBA in Predefined Criteria

Parameter	LBA	CBA
Estimated Sensitivity	390.6 ng/mL	20 µg/mL
Dynamic Range	0.1 to 100 µg/mL	4 to 120 µg/mL
Drug Tolerance	Detect 2500 ng/mL NAb in the presence of 1.25 µg/mL IP	TBD
Precision (%CV)	≤ 25%	≤ 25%

Or Maybe NA? Can WE Challenge the Regulators?

- Link **ADA** data to **SAE** and **TEAEs**
- What is the **ADA Incidence Rate** of the Molecule?
- Is **PK effected**?
- Is **PD effected**?
- **Concomitant Medications can reduce potential of NAbs…**

Summary and Conclusions

- **Immunogenicity** is **specific** to and can occur in **any biotherapeutic molecule**
- **Tiered** testing strategy is **well defined** and documented
  - **NAb Characterisation required** once proof of concept achieved
- Regulators **differing** in their **NAb testing paradigms**
  - **FDA**: Strong in their opinion that **CBAs** are used
  - **EMA**: **LBA** can be a **viable alternative**
- **Bioanalytical Community should challenge the regulators if the molecule allows!**

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