Overview of 3 R's Research at the Center of Biologics Evaluation and Research

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Overview

- Introduction to CBER
  - Mission
  - Regulatory Portfolio
  - Research Approach
- Selected Research
  - Established Product Areas
  - Emerging Product Areas

CBER's Mission

To ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, blood and blood products, and cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions or injury.

ICCVAM Mission

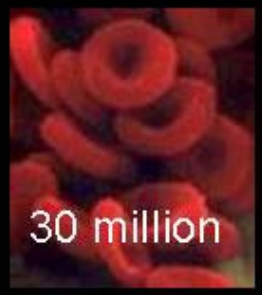
ICCVAM's mission is to facilitate development, validation and regulatory acceptance of new and revised regulatory test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment.

Complementary Missions

- CBER and ICCVAM missions are complementary
  - Promote public health
  - Promote prudent regulation
  - Stress scientific validity of data
  - Allow flexibility with respect to methods to achieve missions

GENERAL REGULATORY PRACTICES

CBER REGULATED PRODUCTS



Blood Derivatives

Vaccines

Blood Components

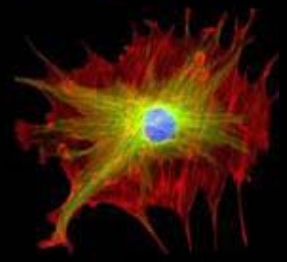
Allergenics

Whole Blood

Somatic Cell &
Gene Therapy

Tissues

Devices



Xenotransplantation

Human Biologics Regulations in the United States

- Human biologics regulations are typically focused on endpoints not specific tests
  - Requirements compel provision of data to support safety and effectiveness of product administration in humans
  - Most biologic regulations are not proscriptive as to specifics of methods used to produce data

SELECTED RESEARCH ACTIVITIES

Multitasking at the FDA: Research Supports Regulatory Mission

CBER researchers fully integrated into the regulatory process (~50% average time)= “Researcher-Regulator”

- Development of Policy and Guidance Documents
- Meeting with Sponsors and Advisory Committees
- Participation in Pre-license and Biennial Inspections
- Review INDs, BLAs, 510ks, PMAs, IDEs, HDEs
- Evaluation of Adverse Drug Reactions and Risk Assessment
- Performing research relevant to product evaluation of safety, efficacy, manufacturing: Developing/evaluating scientific tools & knowledge
- Outreach, communication with stakeholders

Relevant CBER FY08 Research Priorities*

- Improve or develop new methods to measure and augment biological product safety and efficacy.
- Evaluate, develop, integrate novel scientific technologies to improve biologics product regulatory pathways, availability, quality.
- Facilitate the development of new biological products for high priority public health threats, including pandemic influenza, emerging infectious diseases, and agents of bioterrorism.

**Developed by CBER's Research Leadership Council*

CBER Research

In vitro assessment of adjuvant safety and activity

Development of “Detector cell lines “ for rapid evaluation of activity and safety of novel adjuvants

NEW ADJUVANTS: SAFETY CONSIDERATIONS

- Excessive amounts of pro-inflammatory & pyrogenic mediators (systemic effects)=>unaccepted safety profiles
- Organ specific toxicity
- Severe local reactogenicity
- Break-down of self tolerance => autoimmunity
- Combined toxicity (of different vaccine and adjuvant components)
- Progressive toxicity (after repeat vaccinations)

ADJUVANT TOXICITY: POTENTIAL BENEFITS OF NON-ANIMAL TESTING

- Reduction in animal use for acute and chronic toxicity studies
- Refinement (pain and distress reduction)
- Cost (Potentially)
- Control for species specific adjuvant effects:
  - cytokines, immune-modulators
  - TLR cellular distribution
  - Expression/distribution of other cellular targets
  - Differences in skin and mucosal sites

RAPID IN VITRO ADJUVANT-SCREENING ASSAYS COULD HELP IN PREDICTING IN VIVO TOXICITIES AND REDUCE THE NEED FOR ANIMAL USE

Adjuvant evaluation: CBER Approach

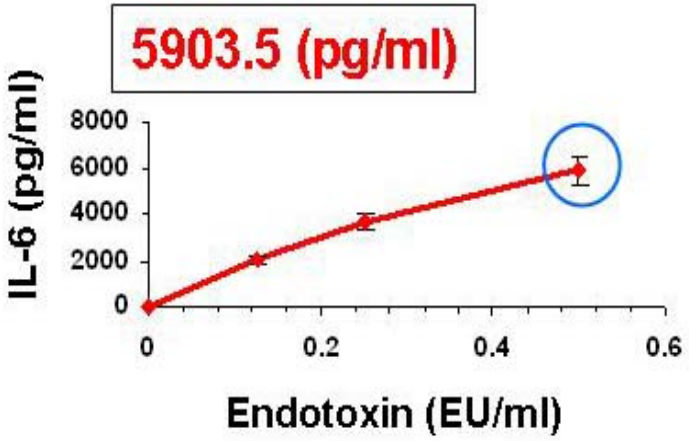
- **Rationale: Most common reactions induced by adjuvants in clinical trials are related to pain, tenderness, erythema, and granuloma at the injection site. There are also rare cases of systemic reactions such as chills, fever, and headaches.**
- **Early data from studies in animals have shown that fever is associated with an increase in the levels of pro-inflammatory cytokines, IL-1β, TNFα, and IL-6 in periphery and in the brain*.**
- **Goal of the study: To develop an *in vitro* assay that could be used to predict *in vivo* toxicity of adjuvants**
- **Approach I: Human promonocytic cell line, MM6, with known spectrum of TLRs was used to determine the levels of pro-inflammatory cytokines released in presence of adjuvants.**

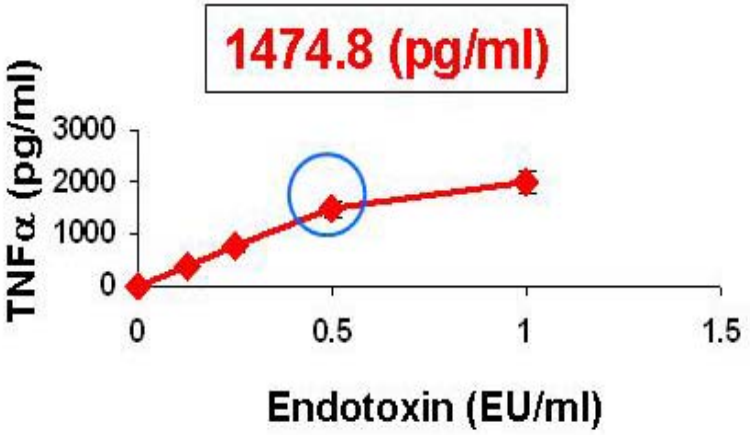
**Zetterstrom et al., Ann NY Acad Sci 1998, 856:48; Luheshi et al Acad Sci 1998, 856:83; Wakabayashi et al, Am J Physiol 1994, 267:R329*

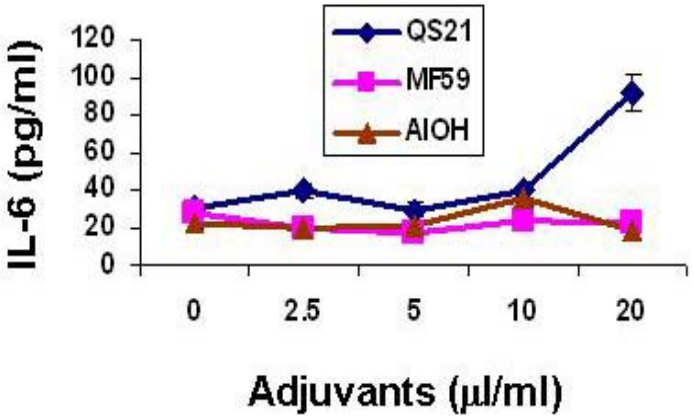
Stage I: Evaluate Adjuvants that are licensed or tested in clinical trials with known safety record

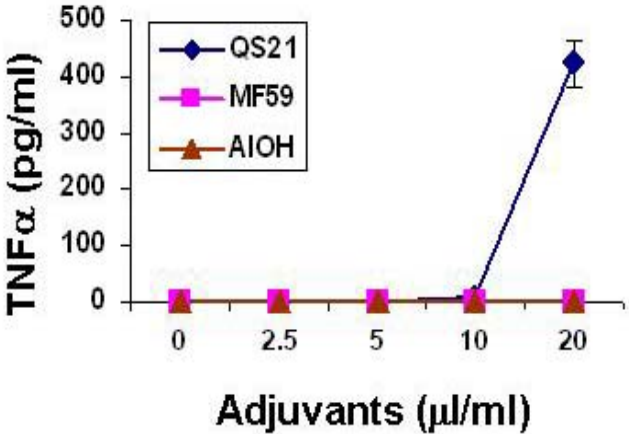
- **Aluminun adjuvants (licensed in US and Europe). Extensive record of safety (billions of doses). Mechanism: antigen deposit at injection site, Neutrophil recruitment.**
- **MF59 water-in-oil emulsion (licensed in Europe only). Mechanism: may promote up-take of antigen by APC. Good safety record.**
- **Saponin, QS21, in trials. *Quillaja saponoria* is widely used in animal vaccines. QS21 is Currently in human trials with mixed safety record.**

Induction of IL-6 & TNFα in MM6 cells cultured with QS21, ALOH, or MF59









Summary: Differential pro-inflammatory cytokine responses in MM6 cells treated with various adjuvants and delivery systems

	IL-1β	IL-8	IL-6	TNFα
Alum	-	-	-	-
Water-in-oil emulsions (MF59)	-	-	-	-
TLR agonists (FSL1, Pam3, Flagellin)	++	++	++	-
Delivery (Archaeosomes, PLG)	-	+ (Arch)	-	-
Emulsifiers (CAP)	++	++	+/-	+/-
QS21	+	++	-	+/-
Adeno vectors (Ad35, Ad5)	++	+	+/-	-

Conclusion and future plans

- **Current data demonstrated good correlation between in vitro results with in vivo safety records for several adjuvants and delivery systems.**

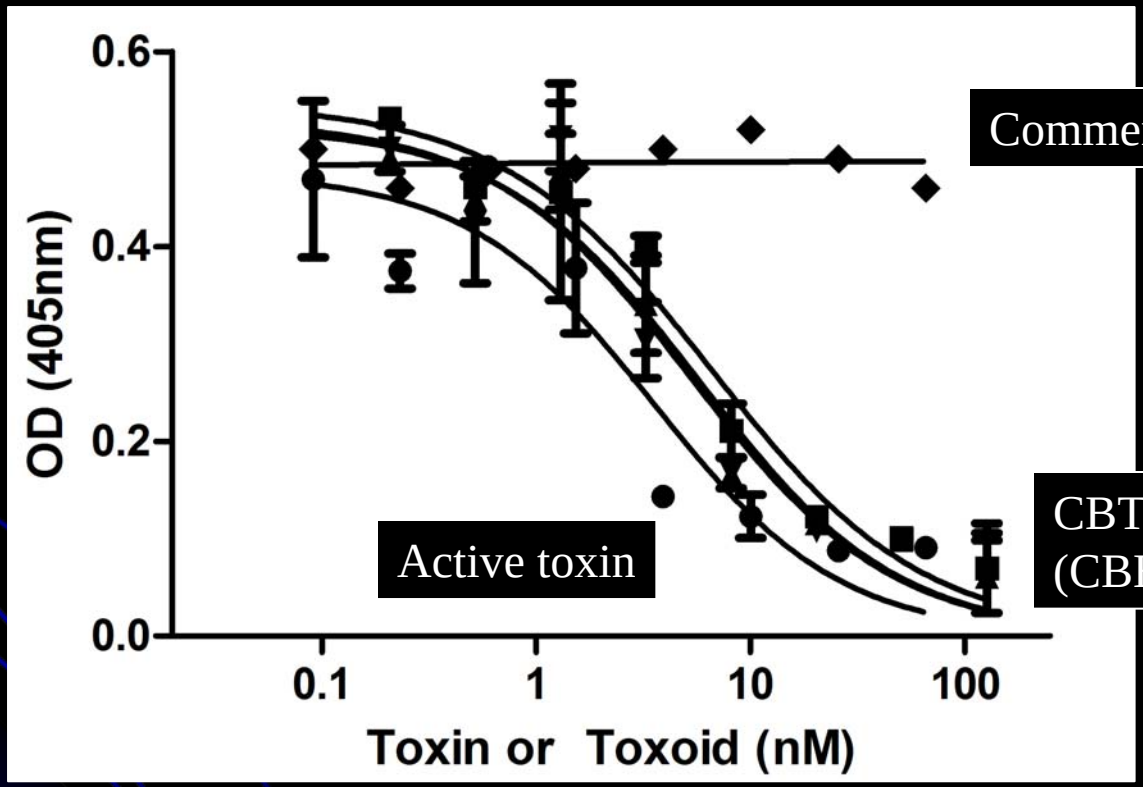
- **Testing of multiple pro-inflammatory cytokines released by pro-monocytic human cells such as MM6 could be used as a first screen of novel adjuvants. Other Detector Cell Lines are under development to evaluate potential neurotoxicity and hepatotoxicity.**

CBER Research

In Vitro Measurement of Vaccine Potency

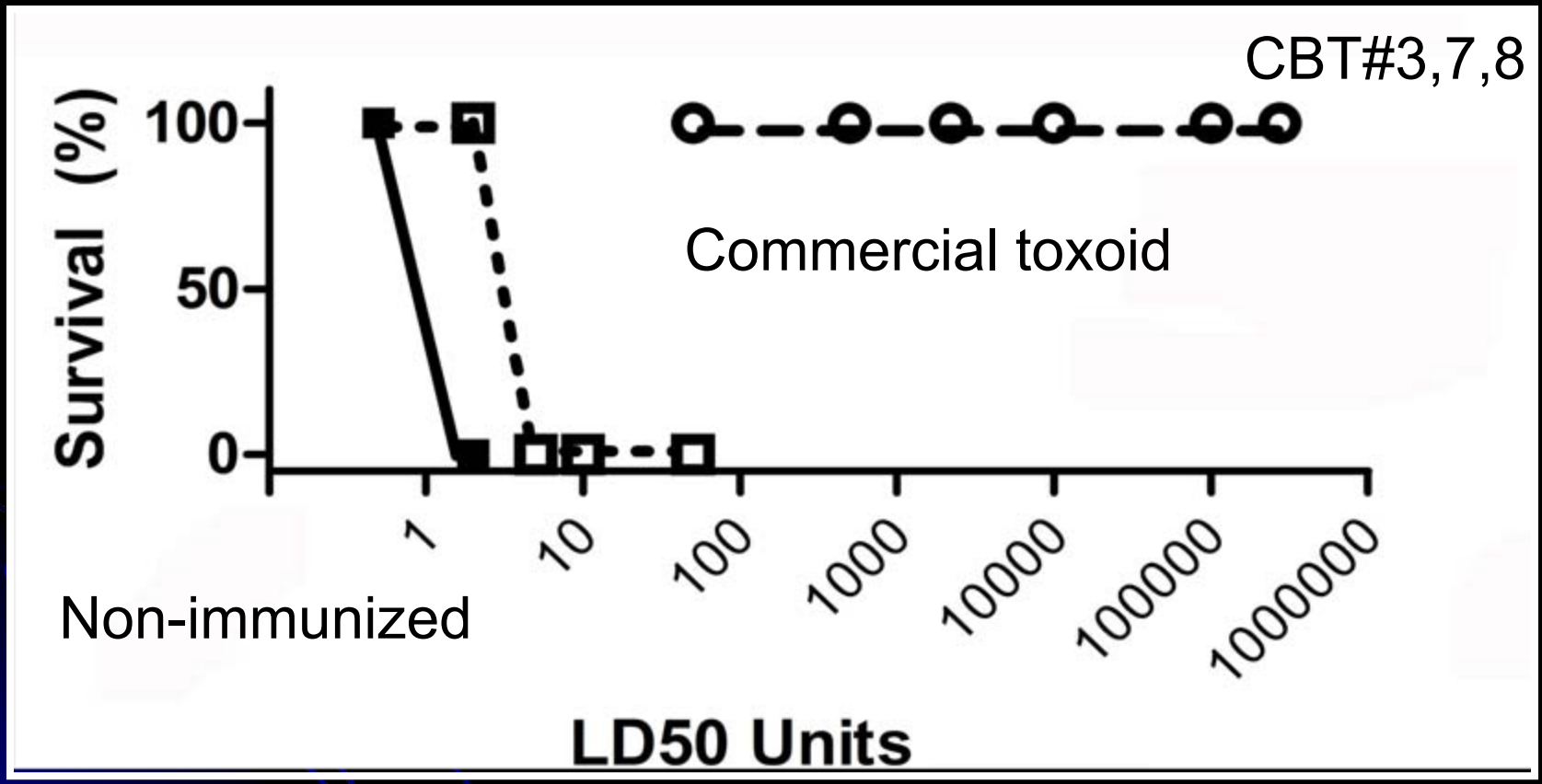
Development of ELISA to quantify vaccine antigenicity relative to the native neurotoxin.

New Antigenicity ELISA

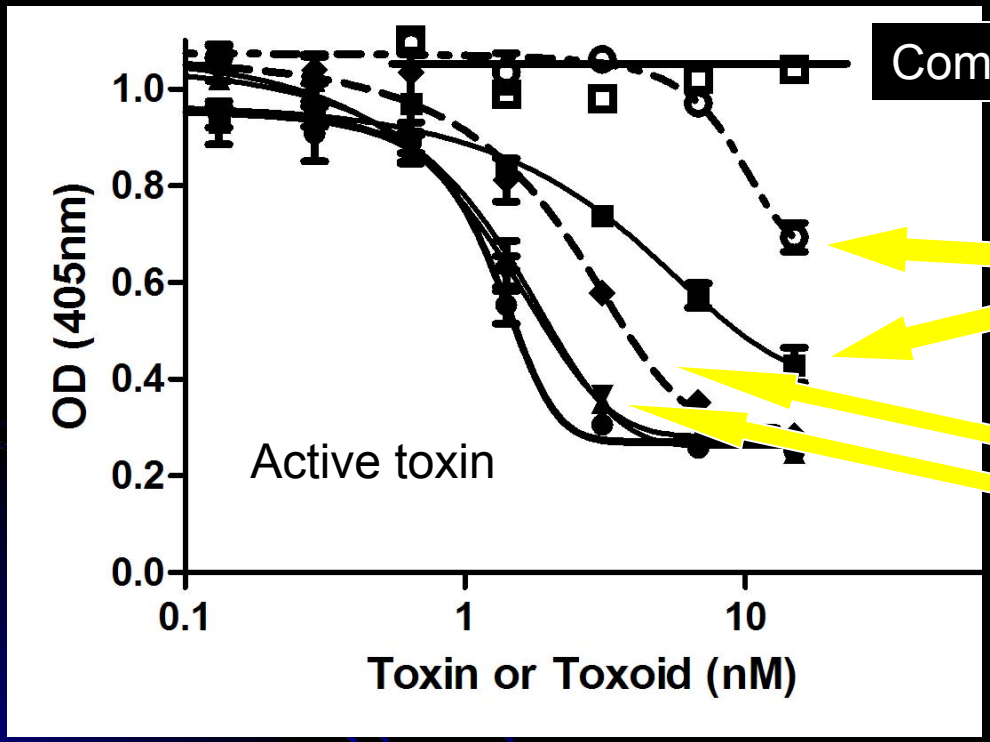


Assessment of in vitro assay to in vivo response

Protective Immunity *in vivo*



New Antigenicity ELISA



Commercial toxoid

5 CBT Variants with incrementally reduced antigenicities relative to the native toxin

Conclusion and Future Directions

- Generated several toxin variants (CBTs) with differing antigenicities from native toxin
- Currently in the process of characterizing vaccine potencies
- If the potency values correlate with the reduced antigenicities
  - THEN the *in vitro* assay will help to reduce or replace animal potency testing of the CBTs.
  - MAY serve as a basis to develop similar ELISAs for other vaccine candidates.

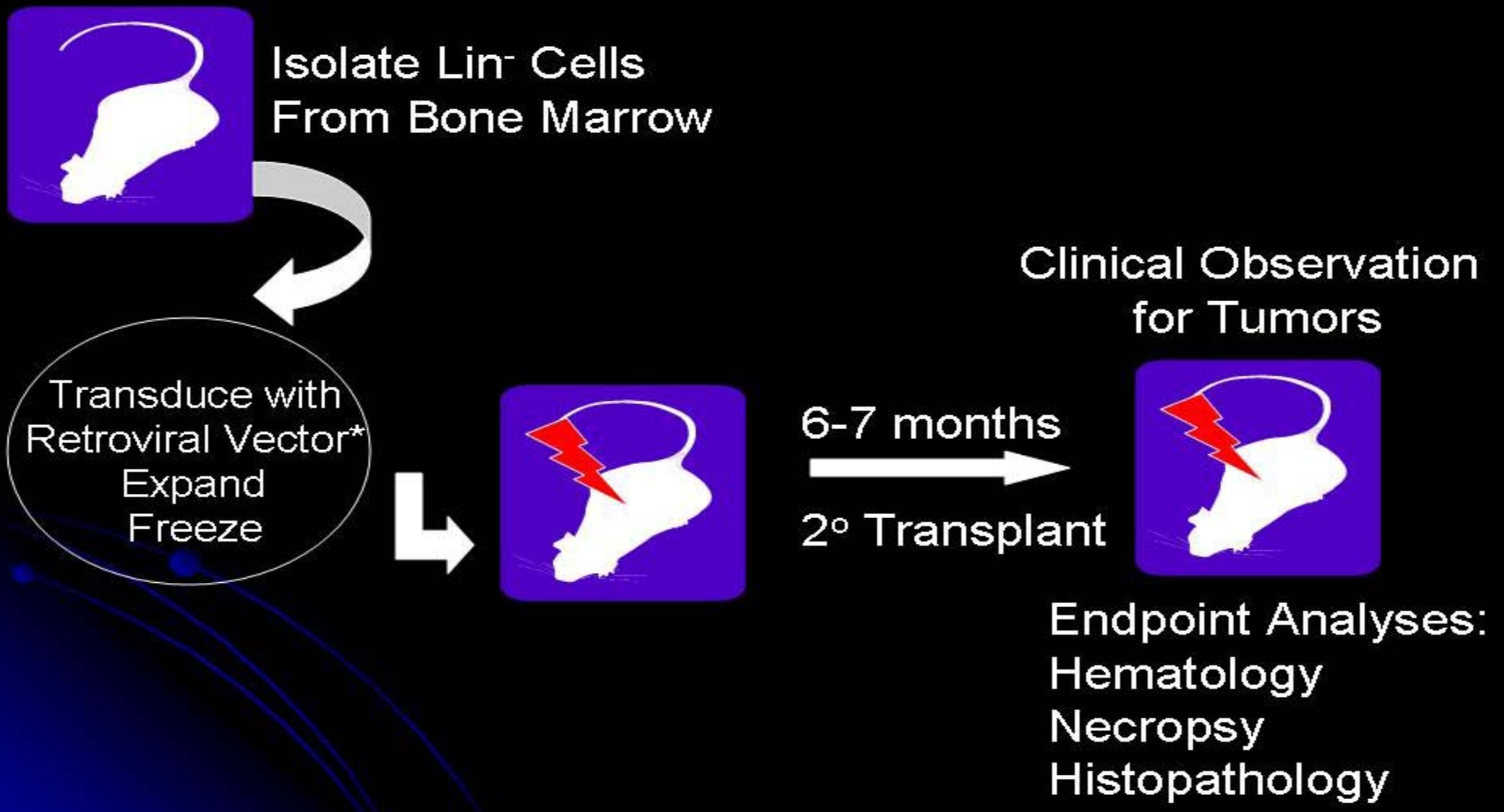
CBER Research*

In Vitro Methods of Assessing Safety of Gene Therapy

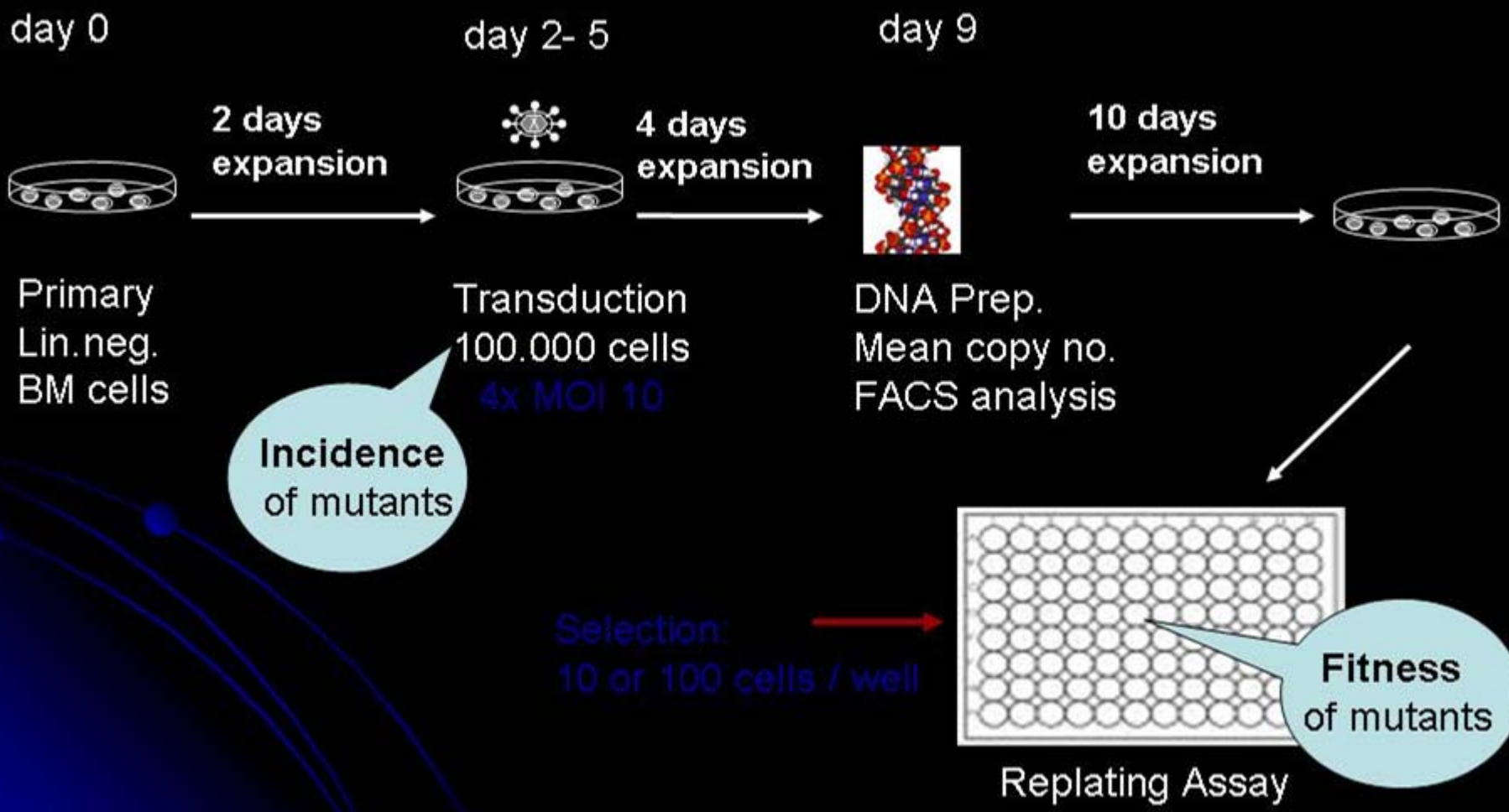
FDA (CBER, NCTR) and NTP Collaboration

Development of pre-clinical assays to evaluate of cancer risk of new and existing gene therapy products

Overview of Proposed Study



Genotoxicity Assessment in the Replating Assay: In vitro tool to screen for tumorigenic risk



Modlich et al., 2006
Zychlinski et al., 2008

Conclusion and Future Steps

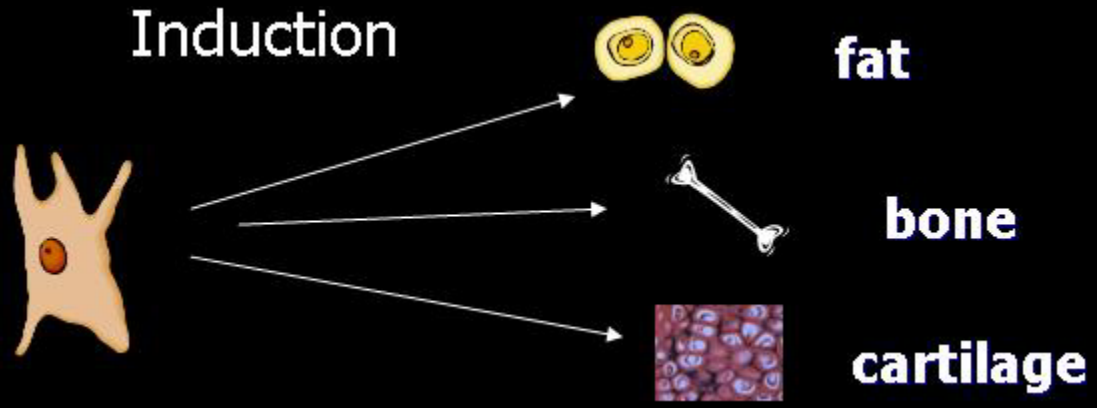
- NTP study will include side-by-side assessment of vectors using the in vivo and in vitro assays to determine the sensitivities and reproducibilities of both methods.
- Critical Path Initiative is funding work to develop cell lines to use for the in vitro assay to assess immortalization – to increase throughput and reproducibility of the assay.

CBER Research

In Vitro Methods of Assessing Quality and Safety of Cellular Therapy

Development of pre-clinical assays for characterization of cellular therapy products

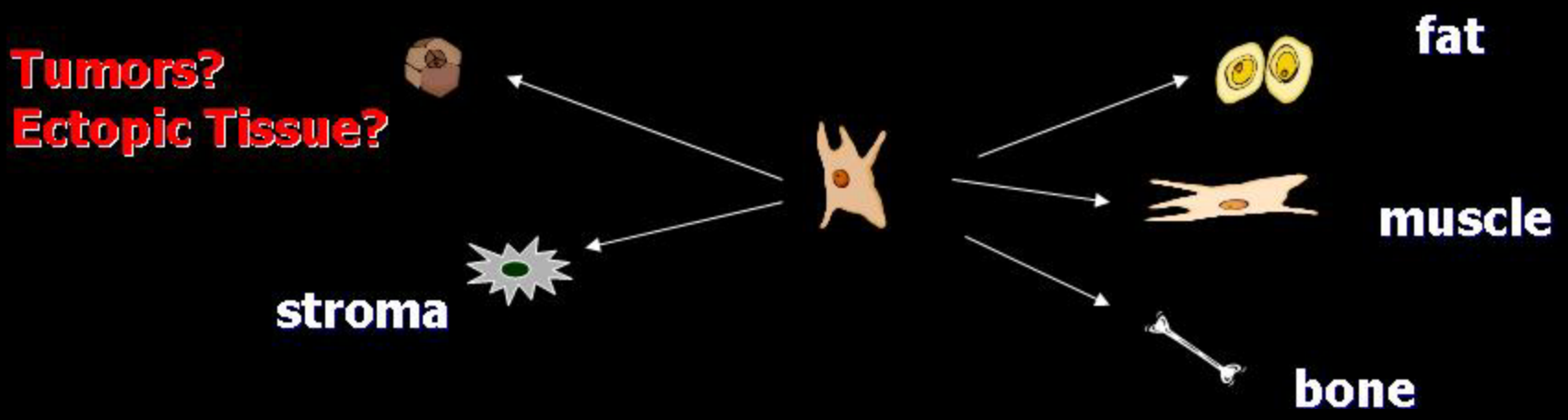
Biomarkers for MSC Quality: Tri-lineage Development



Quantitative Assessment

- **In vitro Precursor Frequency**
  limiting dilution
- **Determine biomarkers that correlate with self-renewal or with differentiation**

Mesenchymal Stem Cells



- Tumorigenicity/Ectopic Tissue
  - Current Approach
    - Administer to immunodeficient animals
    - Observe for tumors, ectopic tissue formation
  - Future Approach
    - Biomarkers for appropriate differentiation, lack of inappropriate differentiation (tumors, ectopic tissue)

Conclusions

- CBER's Research Program addresses ICCVAM's priorities
  - **BIOLOGICS**
  - Immunotoxicity
  - Chronic toxicity/carcinogenicity
- CBER's Research Program relates to all four of the NICEATM-ICCVAM Five Year Plan Central Challenges

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