Cytokine Assessment from a FDA Pharmacology/Toxicology Reviewer's Perspective

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Disclaimer

- The views disseminated in this talk are my own views and do not necessarily represent the views of the FDA

Cytokine Assessment Assays

- When do we see them?
- When do we ask for them?
- What do we expect from them?
- How do we use them?

When do we see them?

- Frequently submitted when the therapeutic target is characterized as being involved in immune activation
- Often submitted for antibodies with targets that aren't known as immune activators if they are expressed on immune cells
- Often for products disrupting immune inhibitory signals

When do we ask for them?

- When a candidate targets immune cells (with suspected agonist or antagonist activity) and it hasn't been done already
- When there are questions of species relevance for a target with potential immune activity
- When there are changes made to a candidate with known potential for cytokine release
- When 2 candidates with limited clinical experience are being used together, even if the individual antibodies haven't demonstrated cytokine release potential

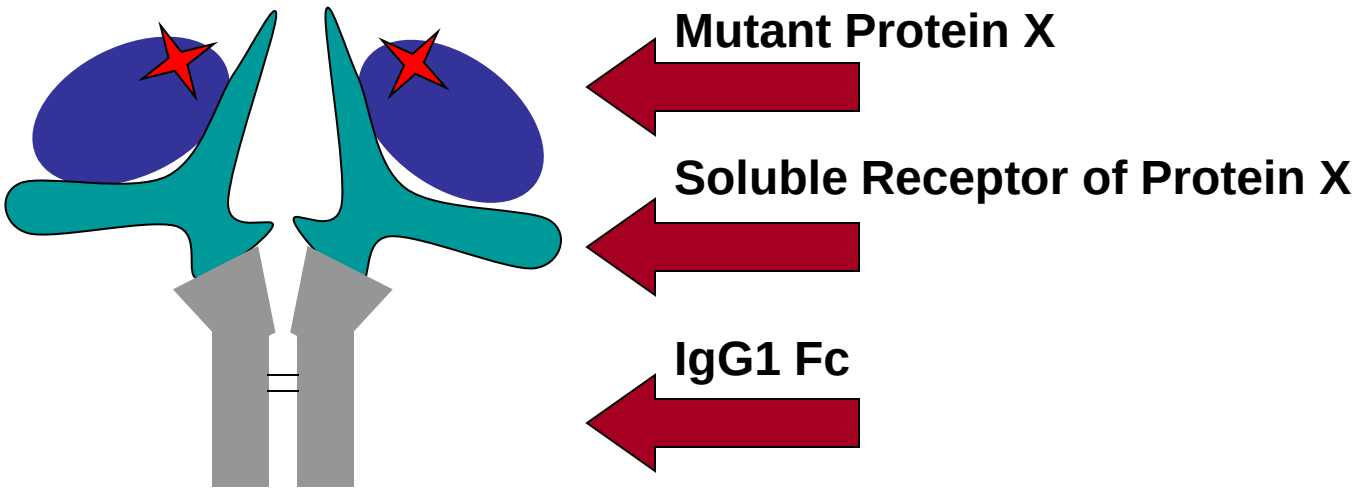
What do we expect from them?

- We have not required that they be conducted under GLP
- Show validation by positive and negative controls
- At least triplicate samples

How Do We Use Them?
Case 1

- Protein X binds to a receptor on T cells and initiates cell signaling
- Endogenous Protein X is reported to be involved in maintenance and homeostatic proliferation
- The Sponsor's product, Deceptikine Fusion, incorporates a modified Protein X designed to increase the potency of signaling in human cells, but not in animal models
- Endogenous Protein X exists as a monomer

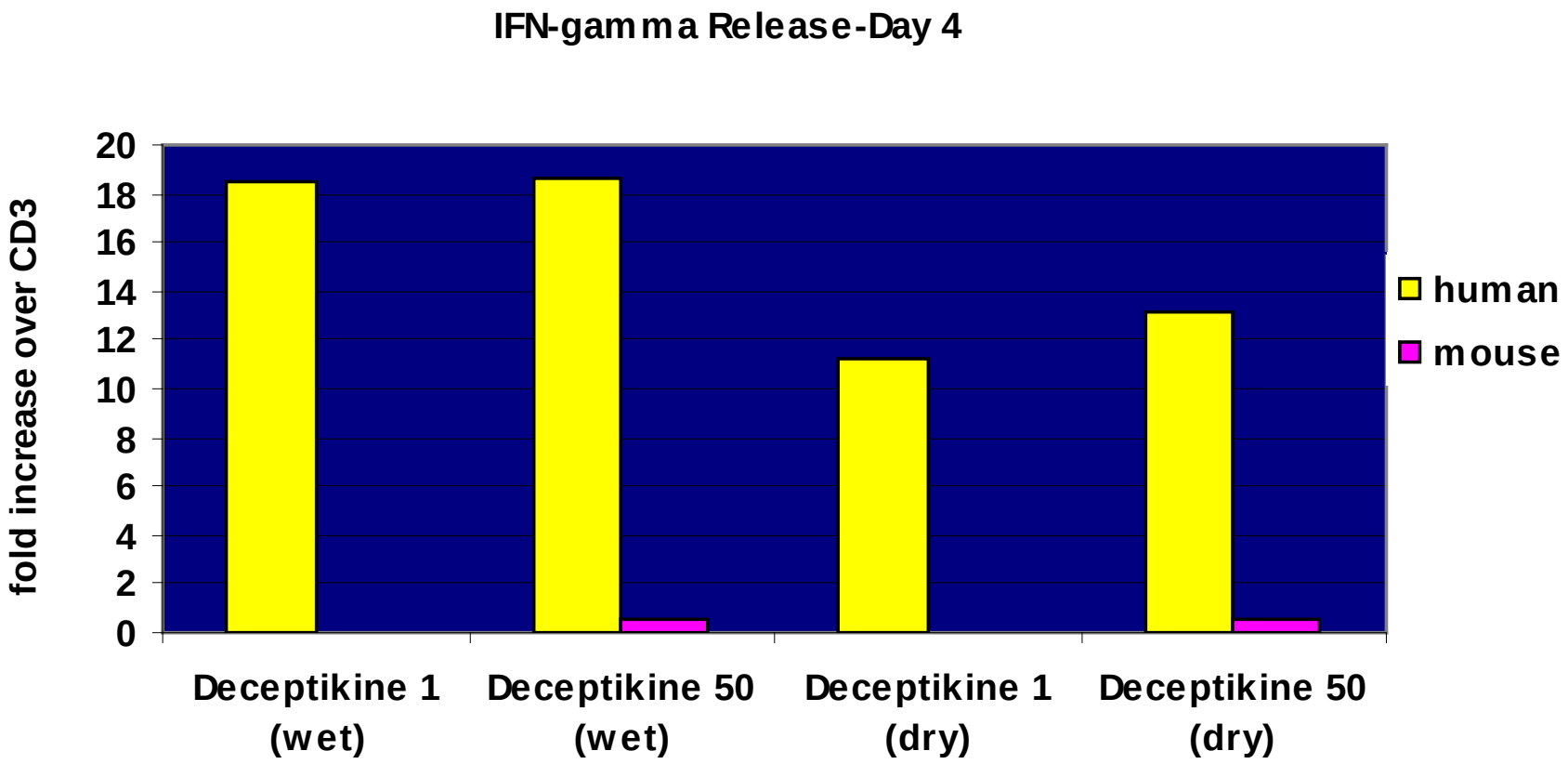
Deceptikine Fusion



- Would you ask for cytokine release data?

Increased IFNγ

At 24 hours, levels of IFNγ seen after incubating human PBMCs with high concentrations of Deceptikine Fusion were comparable to those of anti-CD3; at Day 4 they were higher



Other Considerations

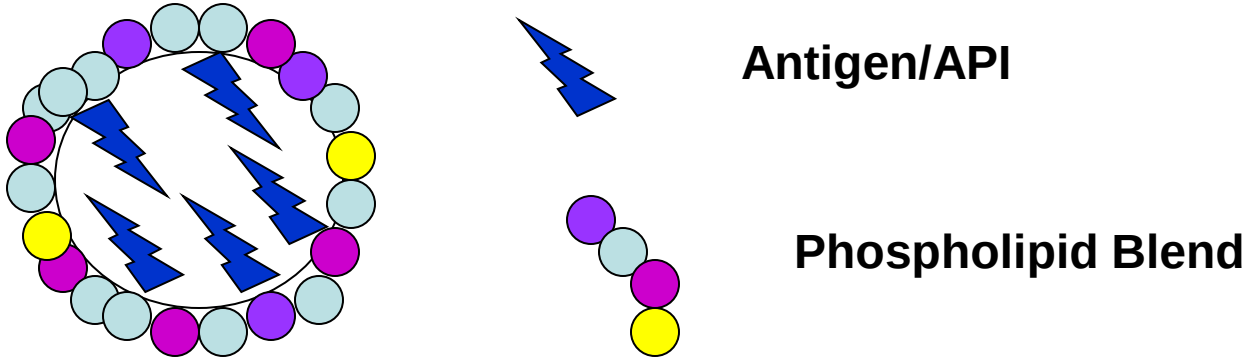
- There were increases in other cytokines as well
- Responses were not always clearly concentration dependent between the Deceptikine Fusion1x (theoretical concentration at the proposed FIH dose) and 50x dose levels
- Human cells were more responsive than mouse

Outcome

- Lower the starting dose 3x
- Wait at least 72 hours before treating the next patient in each cohort

Case 2

- FoxpFree Inc. has a product that has been previously tested as a vaccine adjuvant
- The company has placed the product in a liposome and wants to use it *now* to induce immune tolerance for allogenic proteins for the prevention of GVHD

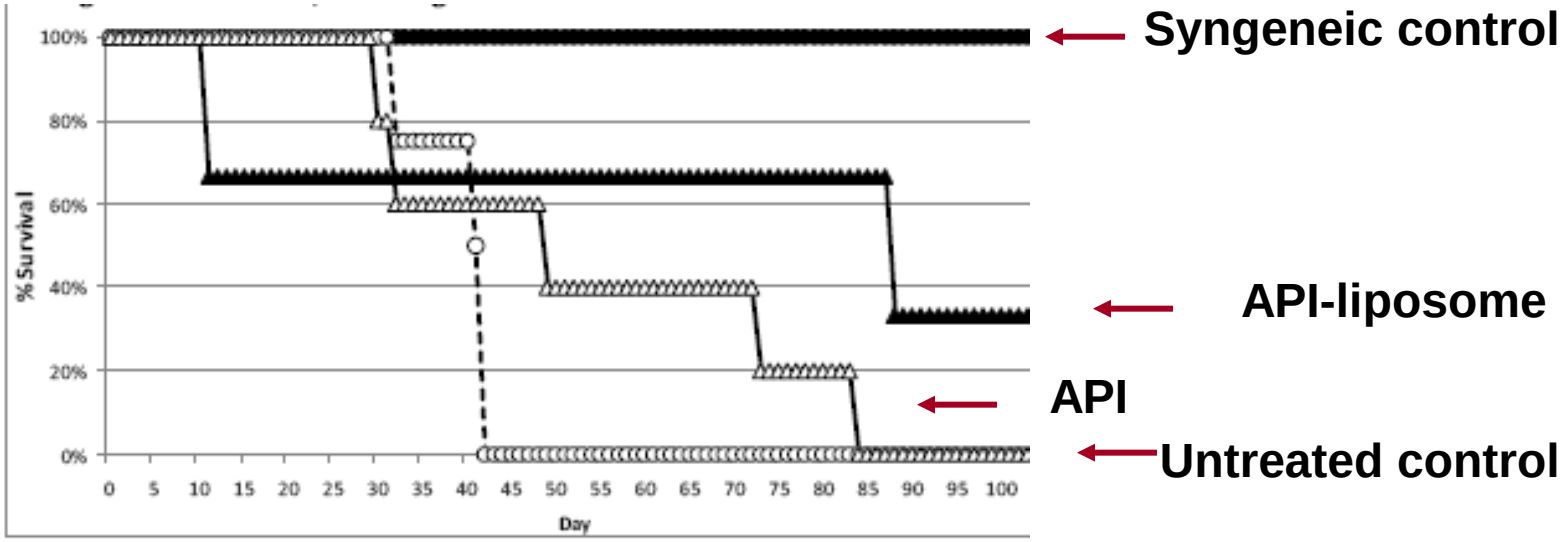


- Original proposal was a healthy volunteer study
- A NOEL was not determined in tox studies due to large increases in spleen weight at all dose levels in both species
- Proposed indication: GVHD

Additional Factors

•Unclear pharmacology contributed to concern, GVHD models showed inconsistent or marginal results

•Major concern that in the GvHD population that there is potential for causing an inappropriate inflammatory response that will enhance rather than inhibit the syndrome heightened by the previous clinical pursuit of the API as an immunostimulator



- Would you ask for a cytokine study?

Outcome

- We did ask for a cytokine study
- Cytokine responses observed were far below PHA control
- Responses to the API-liposome were similar to those for the API alone
- No clear increase in “regulatory” cytokines compared to “inflammatory” cytokines
- Sponsor was asked to lower the starting dose and submit clinical data for review before moving to next cohort

Case 3
Combination Problems?

- Combination study using 2 antibodies to targets involved in maintenance of immune tolerance, one FIH and one with some clinical development.
- Neither antibody showed direct agonistic effects on PBMCs alone. Would you ask for a combination PBMC study?

Outcome

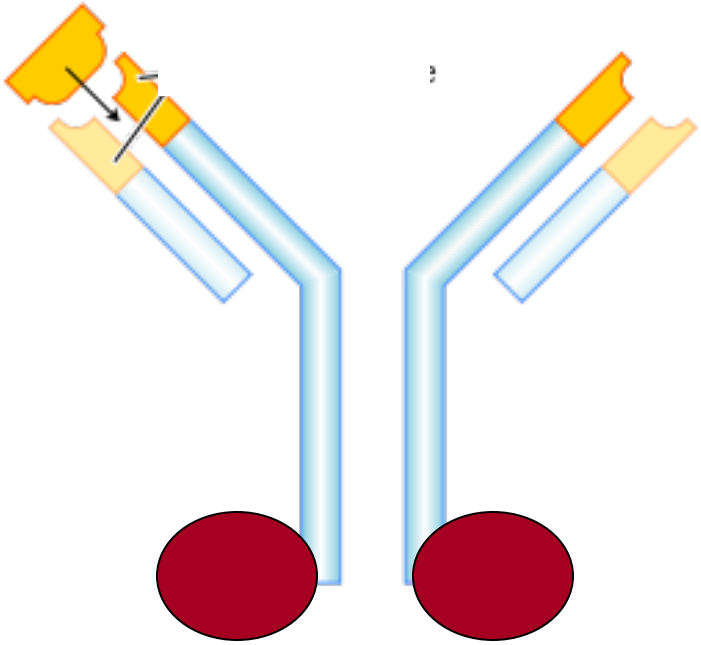
- Data suggested that cytokine release was not major concern for this combination
- While a nonclinical comment was sent suggesting that a PBMC study with the combo be considered before initiation of Part 2, it was a non-hold comment
- Study was allowed to proceed

Case 4

Immediate Cytokine Release on the 2nd Dose?

- **Active Protein alone was shown to cause schedule dependent toxicity in previous clinical studies**
- **New studies in animals with the clinical candidate suggested an inflammatory reaction, but they were not conducted according to the proposed clinical schedule**

Non-species Specific Ag



Active Protein

Cytokines in Real Time

- Cytokines were assessed in the repeat dose animal study
- Animals developed ADA that significantly reduced the PK and possibly the PD effects of the product.
- Sponsor proposed to monitor the cytokine profile in patients and ensure that levels were at baseline before administration of the 2nd dose

Would you require an in vitro restimulation assessment before allowing a second dose?

Outcome

- **Sponsor produced cytokine release data from single administration patient studies**
- **Restimulation of PBMCs from patients that had received single dose administration was not conducted**
- **Because levels of cytokine induction seen at the single dose administration were low at the early doses studied, the Sponsor was allowed to proceed with increased time between patients at the 2nd administration, real time cytokine monitoring, and a lower dose than they had reached in the single dose administration phase of the study**

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Questions/Discussion