

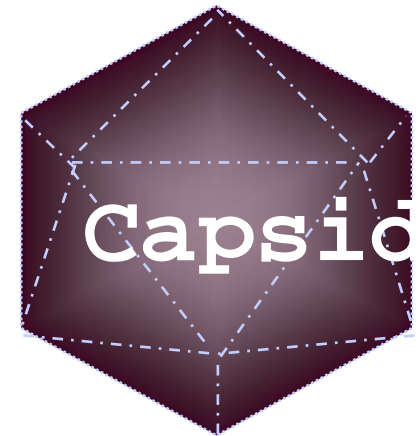
# **rAAV Vectors as Genetic Vaccines**

- 1. Biology of rAAV as  
a vaccine**
- 2. Issues with a  
clinical trial**

# rAAV Vectors Are DNA Delivery Vehicles

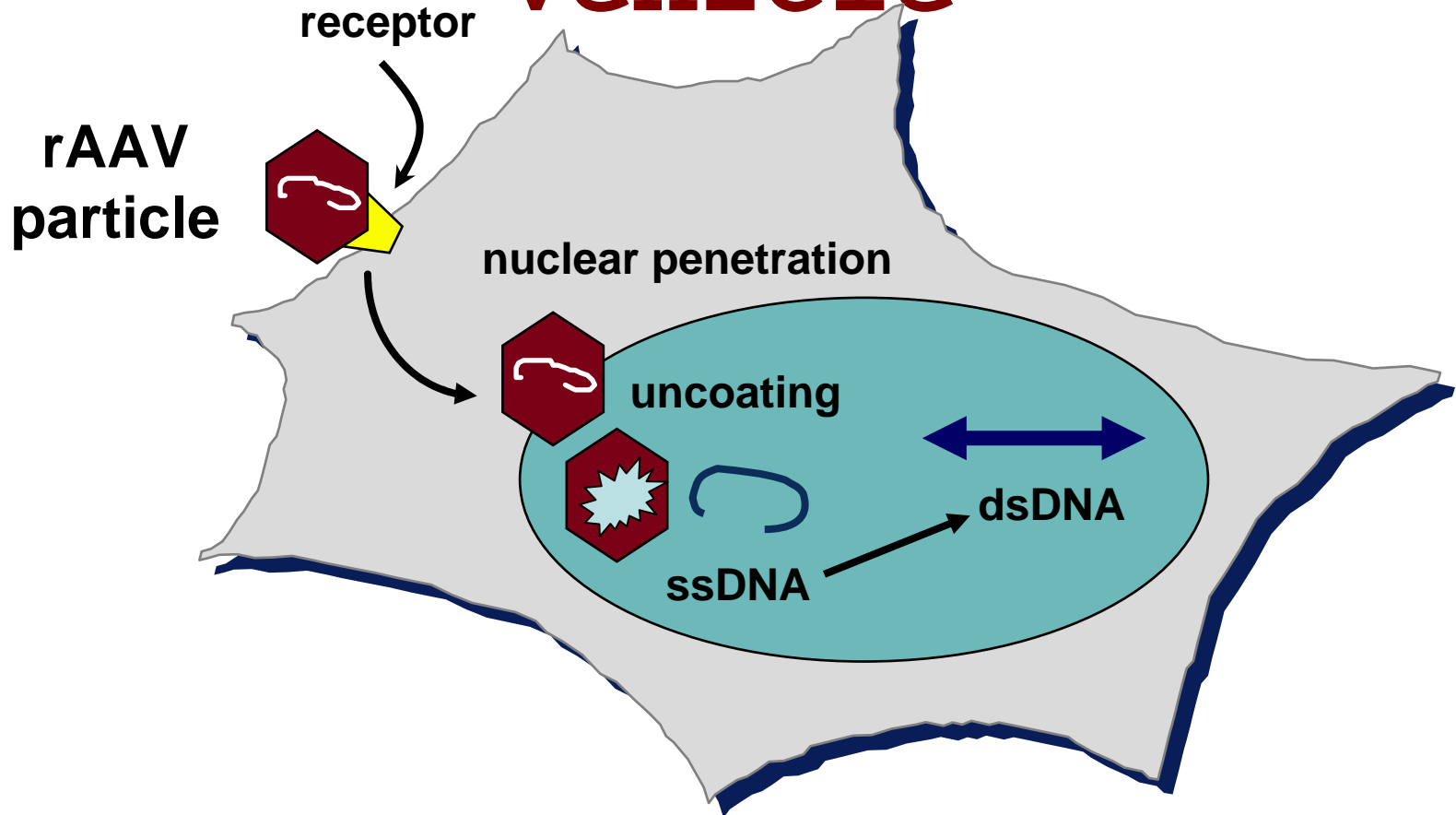


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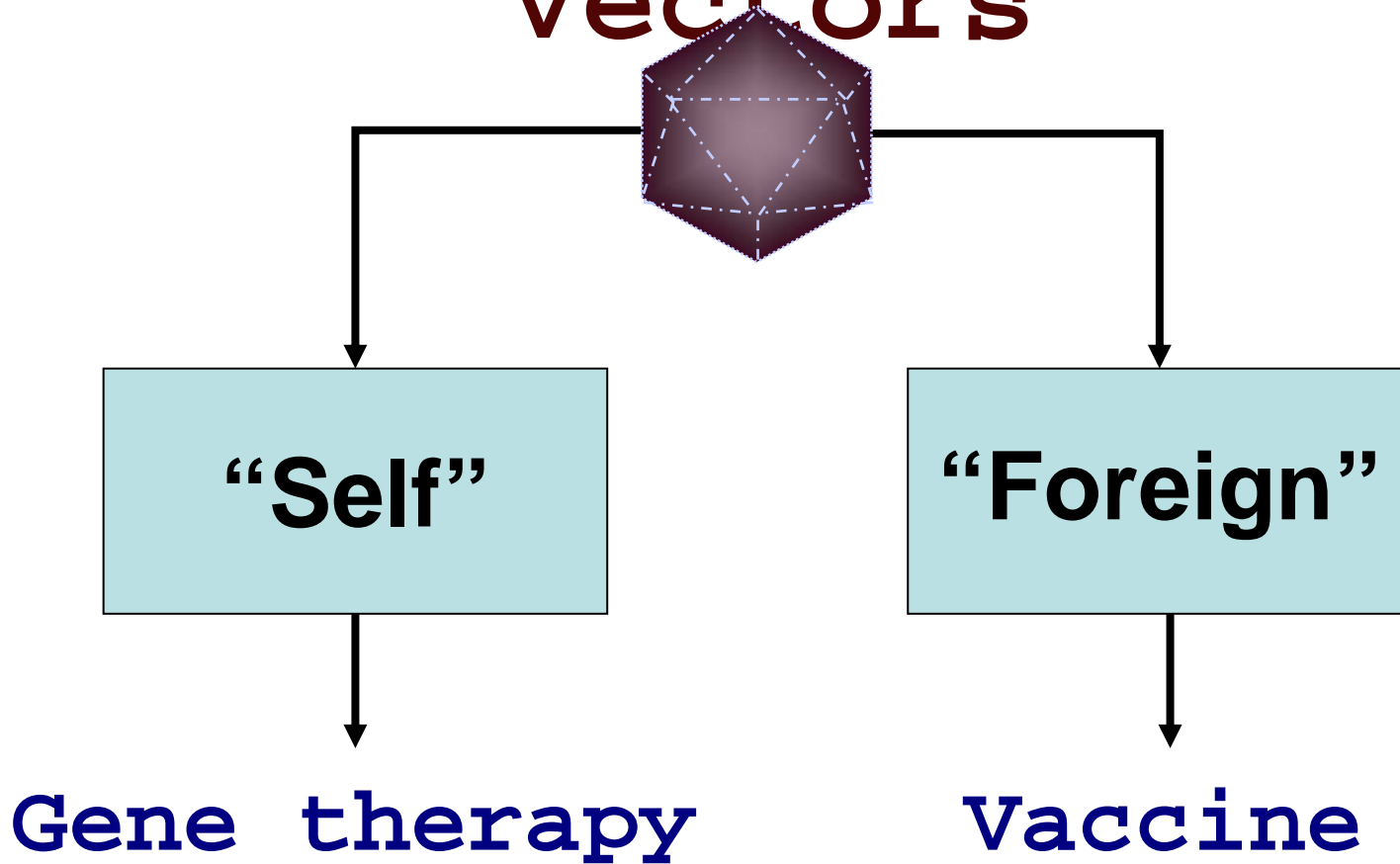
- Akin to plasmid delivery systems
- Less "extra" DNA than plasmids

# rAAV is a DNA Delivery Vehicle

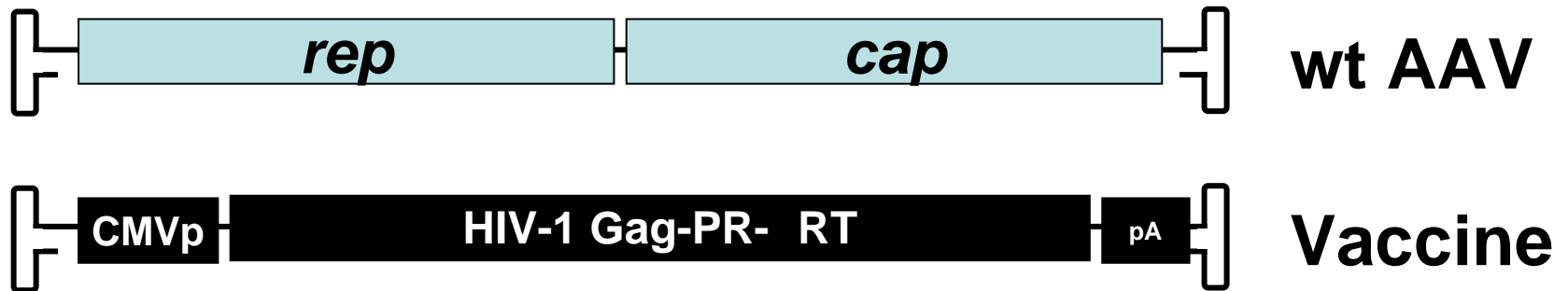


Orders of magnitude more efficient than plasmid

# The Two Faces of rAAV Vectors

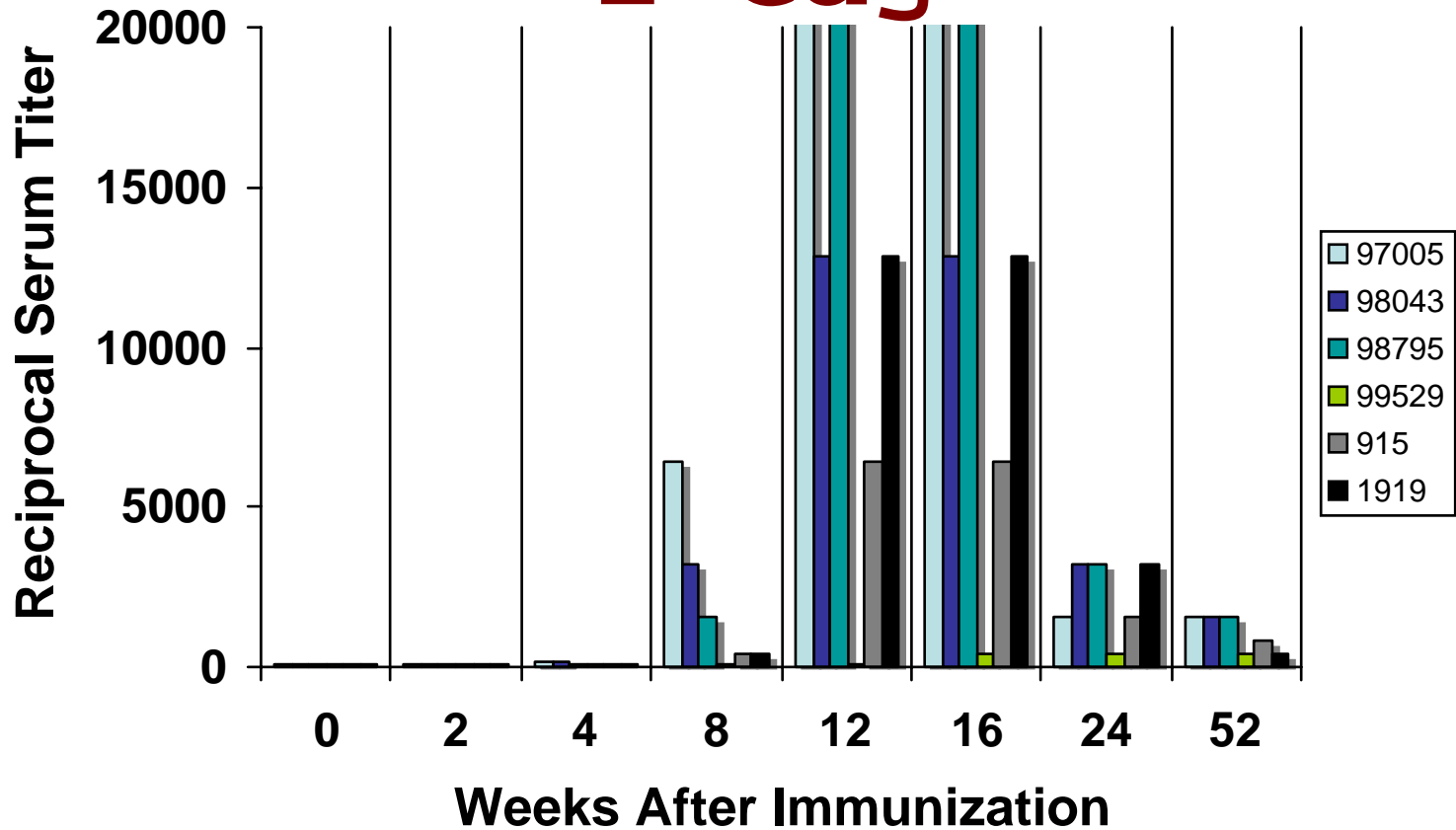


# rAAV HIV-1 Gag-PR- RT



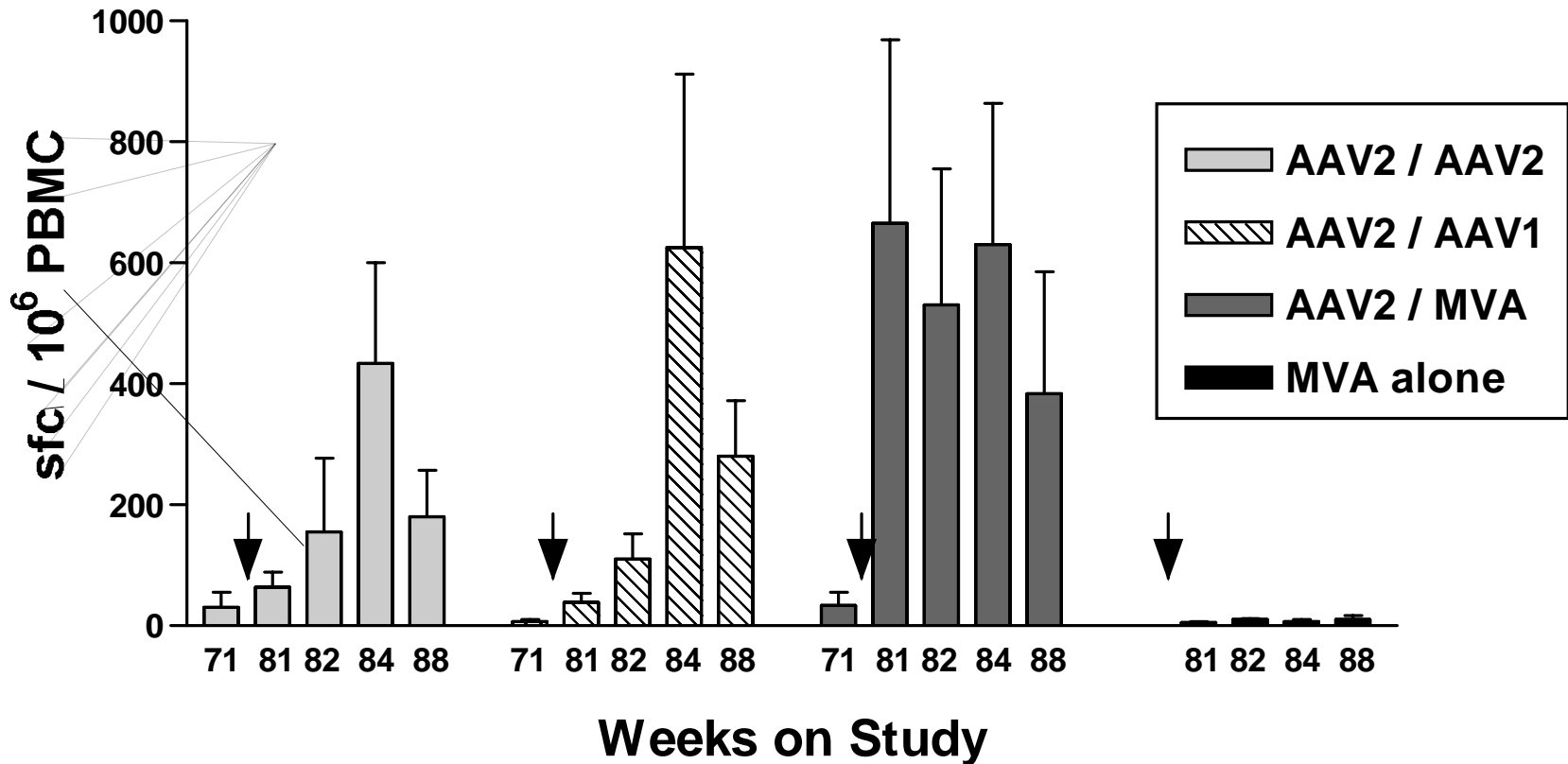
- **Single IM injection**
- **Rhesus macaques**
- **Dose range (human equivalence)**

# Antibody Responses to HIV-1 Gag



12 weeks: 6/6 responded  
52 weeks: 6/6 remain positive

# Demonstration of Memory T Cell



- Prime dose of AAV2 given at week 0, boost at week 80
- ELIspot (IFN- ) responses against a single peptide pool of HIV-1 Clade C Gag

# Question:

Why does an rAAV vaccine induce transgene specific immune responses, since rAAV does not induce a robust host inflammatory response?

resj

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## Differential Activation of Innate Immune Responses by Adenovirus and Adeno-Associated Virus Vectors

Anne-Kathrin Zaiss,<sup>1</sup> Qiang Liu,<sup>2</sup> Gloria P. Bowen,<sup>2</sup> Norman C. W. Wong,<sup>1,2</sup>  
Jeffrey S. Bartlett,<sup>3,4</sup> and Daniel A. Muruve<sup>2\*</sup>

*Department of Biochemistry and Molecular Biology<sup>1</sup> and Department of Medicine,<sup>2</sup> University of Calgary, Calgary, Alberta T2N 4N1, Canada, and Department of Pediatrics, Ohio State University,<sup>3</sup> and Children's Research Institute, Children's Hospital,<sup>4</sup> Columbus, Ohio*

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Adenovirus vectors induce acute inflammation of infected tissues due to activation of the innate immune system and expression of numerous chemokines and cytokines in transduced target cells. In contrast, adeno-associated virus (AAV) vectors are not associated with significant inflammation experimentally or clinically. We tested the ability of AAV vectors to induce the expression of chemokines *in vitro* and to activate the innate immune system *in vivo*. In human HeLa cells and murine renal epithelium-derived cells (REC cells) the

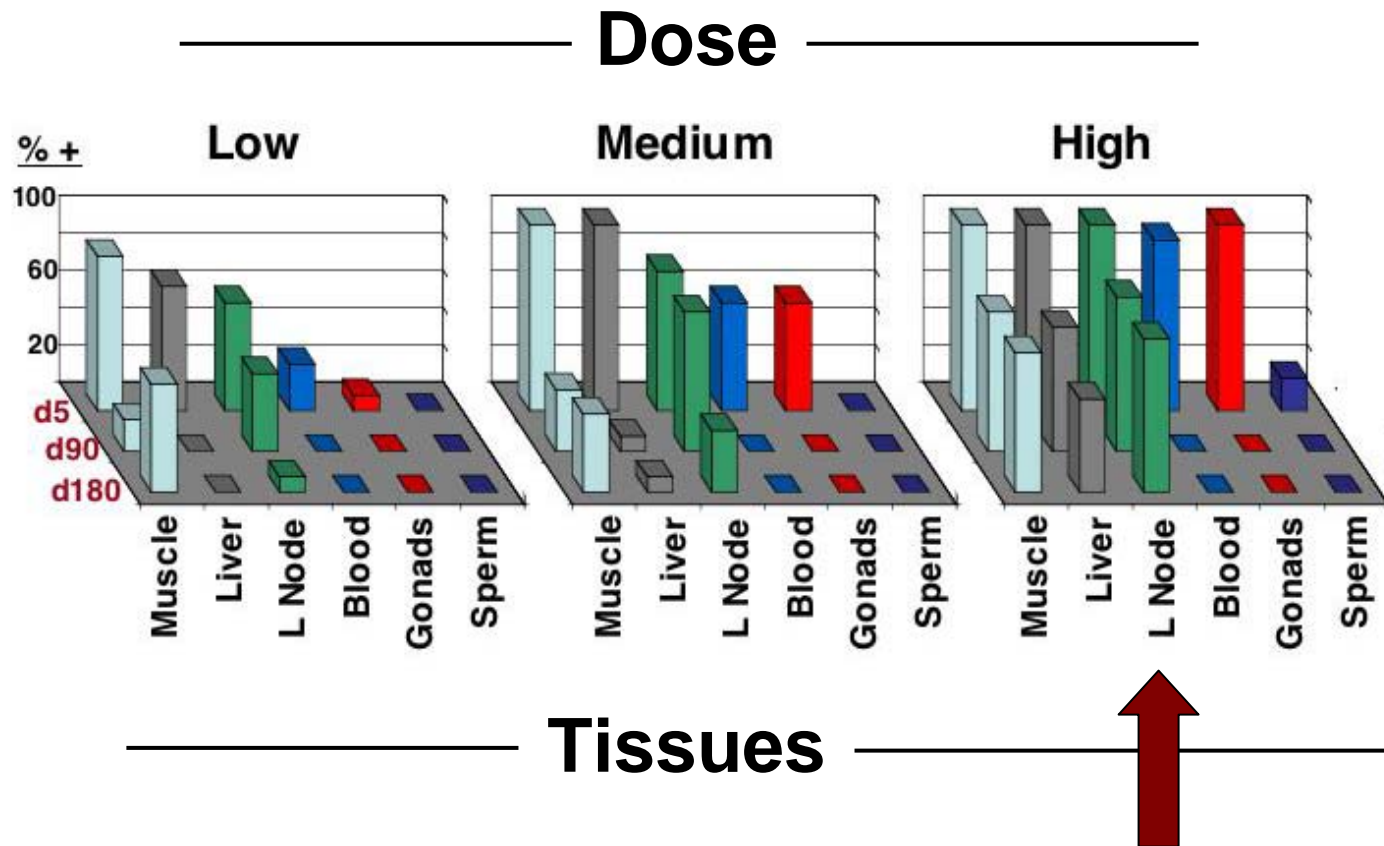
## Answer :

1. There is *some* early inflammation
2. Direct *vs* cross presentation
3. Location, location, location

# Direct vs cross presentation

- Muscle loaded with antigen
- rAAV vectors transduce DCs

# Location, location, location



Question:

Can you explain the delay in such responses?

Answer:

Yes.

## Question:

What are the issues for a vaccine trial for HIV - scientific, clinical, regulatory?

## Answer:

1. Results in pre-clinical models
2. Normal human subjects
3. Safety

## Question:

Why should it work and is this unique to HIV or can it be advanced to other infectious diseases?

## Answer:

1. Results in pre-clinical models
2. Absolutely not unique to HIV
3. HCV, anthrax, RSV

## Question:

What are the outcome variables for vaccine evaluation?

## Answer:

1. Safety

2. Safety

3. Immunogenicity, efficacy

## Question:

What are the safety issues in this population?

## Answer:

1. Normal human subjects
2. Phase III
3. General safety profile of rAAV

## Question:

What were the factors you considered in deciding to launch the clinical study in Europe as opposed to the US?

## Answer:

1. Sponsor
2. Speed

## Question:

What results can be shared now?

## Answer:

1. Short-term safety demonstrated
2. Immunologic assessments incomplete
3. Boosting doses underway

## Question:

What were the biggest hurdles in getting the trial launched? In bringing it to completion?

## Answer:

1. Pre-clinical safety assessments
  - cell substrate, biology of the vector
2. Funding

# Acknowledgements

- Johnson Laboratory
- NIAID/DAIDS
- Targeted Genetics Corporation
- International AIDS Vaccine Initiative