Gene Transfer Clinical Trials Using Retroviral Vectors

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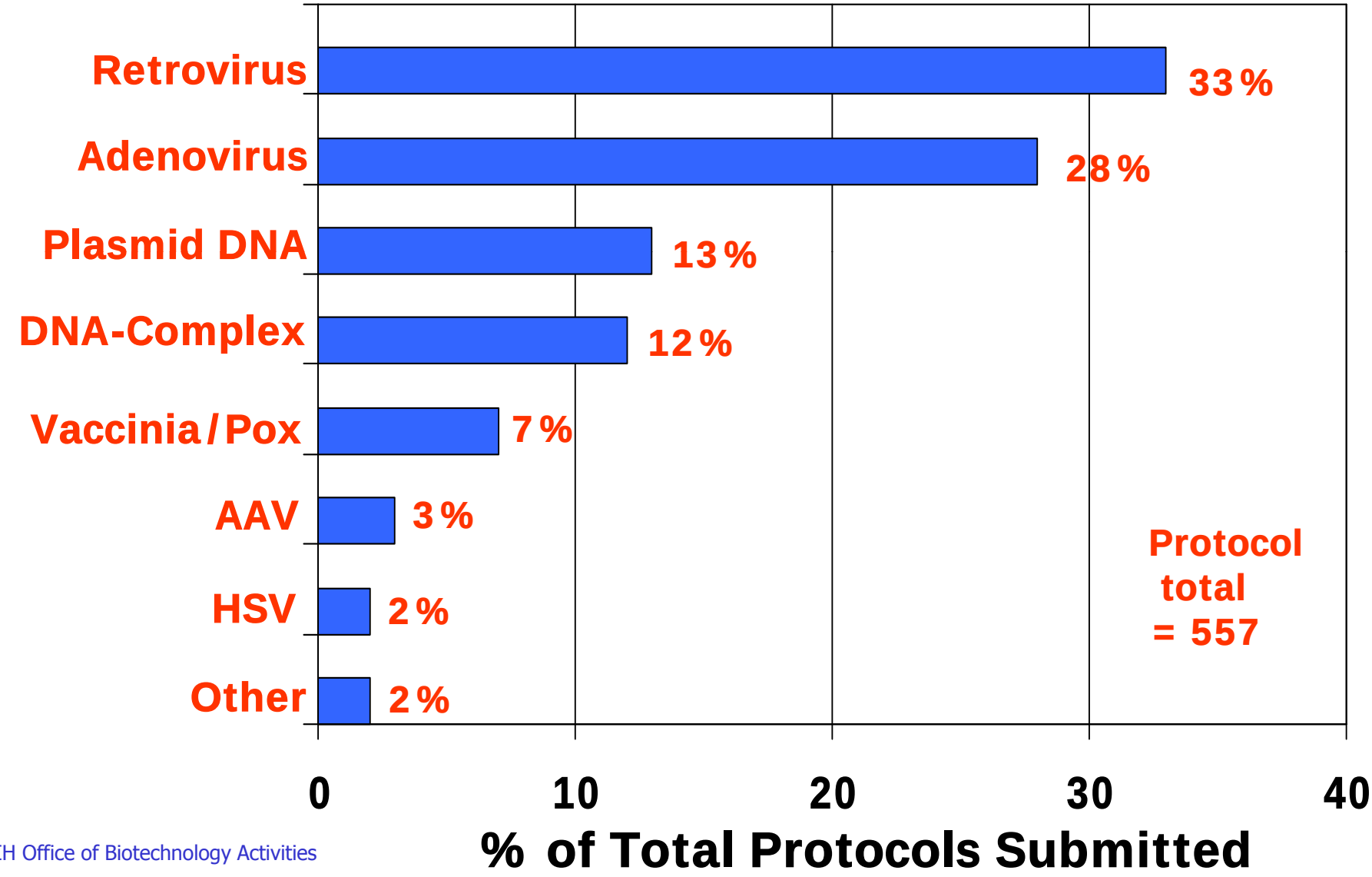
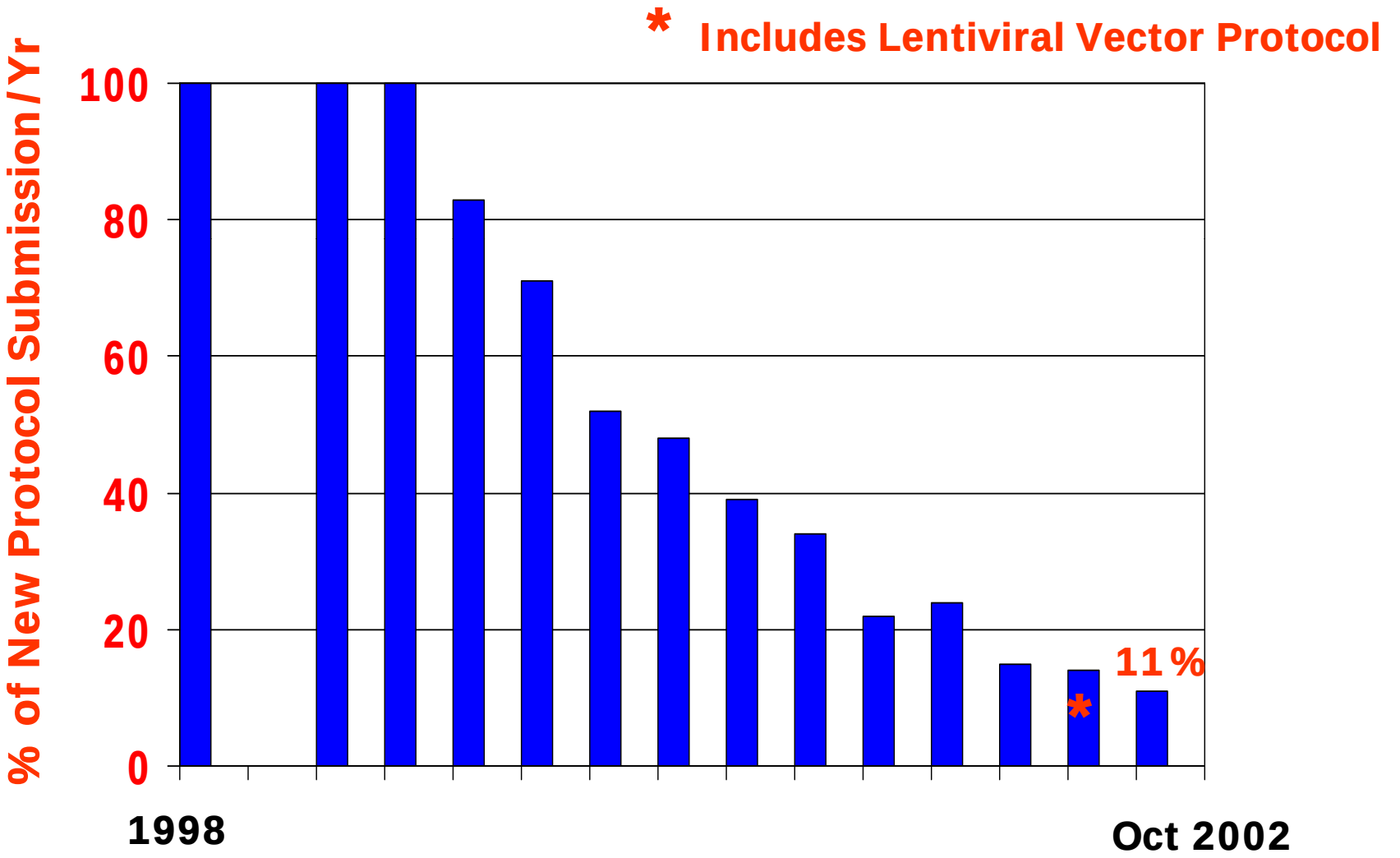
Retroviral vectors have been the most frequently used vector system in clinical gene transfer trials, having been used in 181 of 557 total protocols. They were used in

- **First clinical gene transfer protocol and were the only system used for the first three years.**
- **First marking protocol**
- **First cancer protocol**
- **First monogenic disease protocol (ADA-SCID)**
- **First infectious disease protocol (HIV-1)**

Gene Transfer Protocols by Delivery System

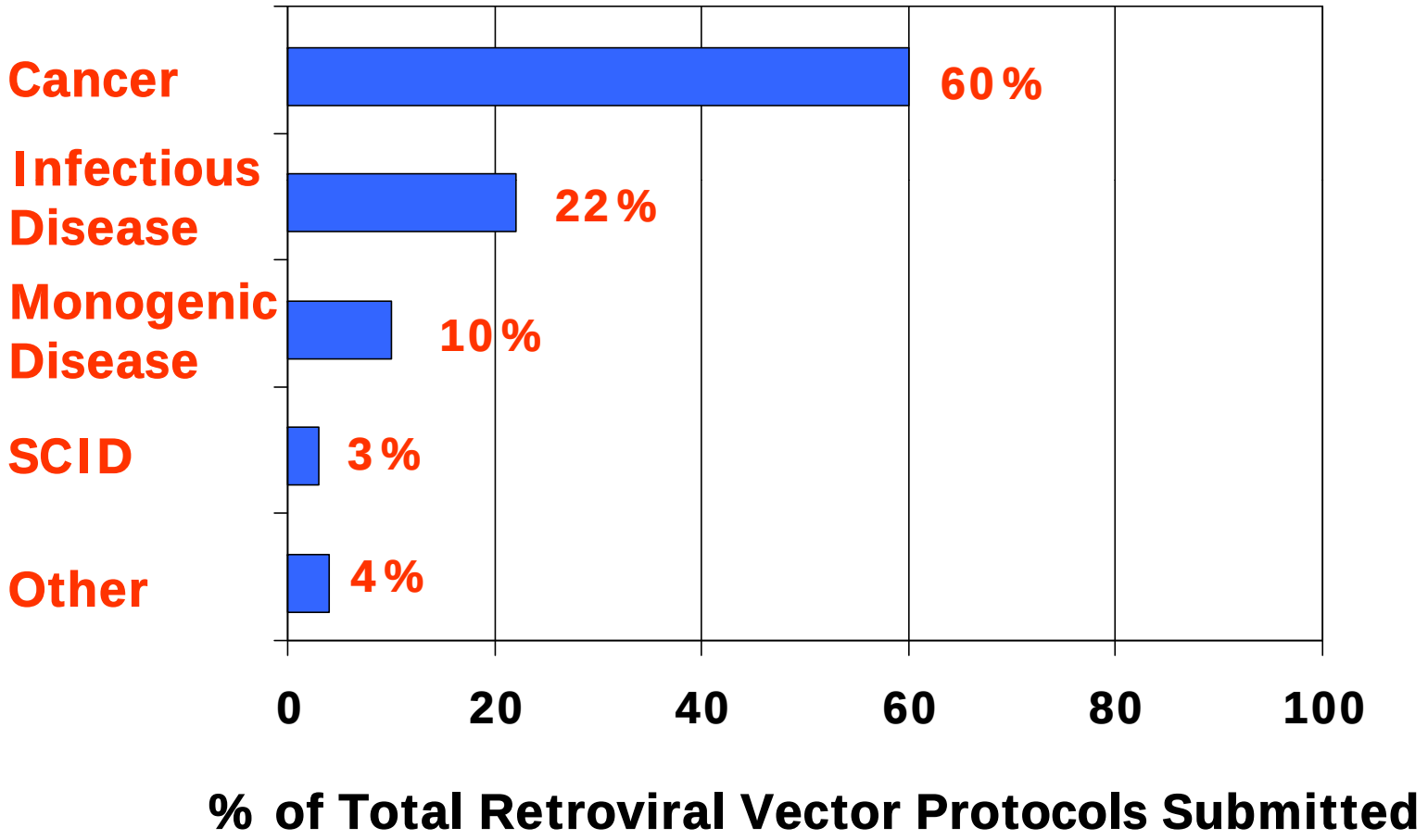


Trends in Retroviral Vector Usage
Protocols Submitted for RAC Review: 1988-2002

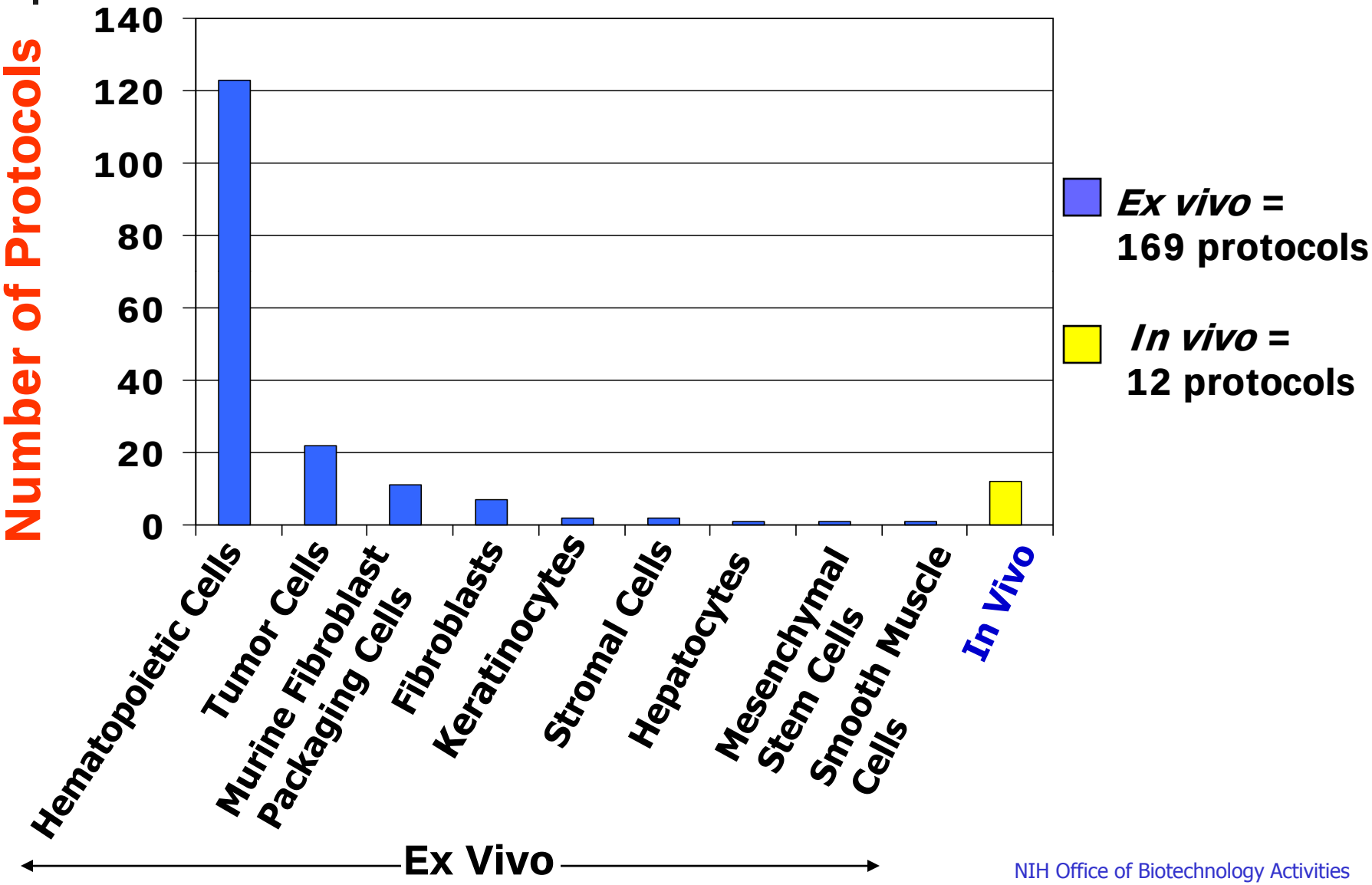


NIH Office of Biotechnology Activities

Retroviral Vector Protocols by Clinical Application



Administration of Retroviral Vectors



Summary

- Retroviral Vectors have been used for a wide range of clinical indications in 33% of the total protocols submitted to OBA.
- The majority of protocols involved *ex vivo* administration, with 73% of these targeting hematopoietic cells. However, retroviral vectors have also been used to transduce a variety of other target cell types. They were administered *in vivo* in 7% of protocols.
- For the 181 retroviral vector protocols, there have been a few reports of myelodysplastic syndrome and one report of a monoclonal lymphoproliferation. **However, no events have been reported by the Principal Investigator as related to the retroviral vector.**
- While the percentage of total protocols using retroviral vectors has been decreasing, interest in the use of lentiviral vectors is increasing and the first lentiviral vector protocol was submitted in 2001.

Overview of Gene Transfer Clinical Trials in SCID

Gene Transfer SCID Studies

- Included in this Summary
  - Studies for ADA-SCID, X-SCID and Jak3-deficient SCID
  - Total World Experience
- Not Included
  - Other primary immunodeficiency studies, such as CGD, LAD, or purine nucleoside phosphorylase deficiency

X-SCID Studies

- Five Studies
  - Dr. Fischer (1998)
    - One subject dosed in Australia
  - Dr. Thrasher (2000)
  - Dr. Weinberg (no subjects)
    - One study not initiated
    - Second study with no enrollment to date
  - Drs. Malech and Puck (no subjects)

X-SCID Studies

- **Dr. Fischer's Study**
  - PIs: Drs. Fischer, Cavazzana-Calvo, et al; Hôpital Necker-Enfants Malades, Paris.
  - Enrollment: 11 subjects (note: an additional subject received the same vector product in Australia), primarily infants/toddlers
  - Vector: MFG
  - Transgene: γc cDNA
  - Transduction Efficiency: 20-40% (in most subjects approximately 35%)

X-SCID Studies

- **Dr. Fischer's Study (cont)**
  - Clinical Course: Eleven subjects dosed with long-term (up to 4 years) favorable responses seen in 4 out of the first 5 subjects.
  - AEs: Most notable to be discussed today. Otherwise, no significant SAEs.

X-SCID Studies

- **Dr. Thrasher's Study**
  - PIs: Drs. Thrasher, Gaspar and Veys; Great Ormond Street Hospital for Children, London
  - Enrollment: 3 infants
  - Vector: MFG
  - Transgene: γc cDNA
  - Transduction Efficiency: greater than 50%

X-SCID Studies

- **Dr. Thrasher's Study (cont)**
  - Clinical Course: All 3 infants thriving and have cleared infections present at time of gene therapy. Longest follow-up time is 14 months.
  - AEs: No SAEs related to gene transfer. Transient graft vs. host-like skin rash noted in two subjects at time of T cell emergence.

X-SCID Studies

- **Dr Weinberg's Studies (OBA #152 & 494)**
  - PI: Dr. Weinberg (CHLA)
  - Enrollment: Study 152 not initiated. Study 494 open to enroll up to 12 children or infants lacking a medically eligible HLA-identical sibling donor for BMT.
  - Vector:G1γcSVNa (152) and MND-γc (494)
  - Transgene: γc cDNA. Protocol 152 also with neomycin phosphotransferase cDNA.

X-SCID Studies

- **Dr. Weinberg's Studies (cont)**
  - Transduction Efficiency: 1-10% (study 152) and 10-50% (study 494) (pre-study experiments)
  - Clinical Course/AEs: No subjects to date

X-SCID Studies

- **Drs. Malech and Puck Study (OBA #516)**
  - PIs: Drs. Malech (NIAID/NIH) and Puck (NHGRI/NIH)
  - Enrollment: Could enroll up to 6 males, 2-20 years of age, evidence of T and B cell immunodeficiency despite prior allogeneic BMT
  - Vector: MFGS-γc
  - Transgene: γc cDNA

X-SCID Studies

- **Drs. Malech and Puck's Study (cont)**
  - Transduction Efficiency: 20-50% (pre-study experiments)
  - Clinical Course and AEs: No subjects to date

ADA-SCID Studies

- Five studies
  - Drs. Blaese, Anderson, Kohn (1991, 1993)
  - Dr. Hoogerbrugge (1992)
  - Dr. Bordignon (1992/2000)
  - Dr. Onodera (1995)
  - Drs. Candotti and Kohn (2001)

Composite Experience

- ADA-SCID: 26 subjects
- X-SCID: 15 subjects
- JAK3-Deficient SCID: 1 subject
- All phase 1 studies
- All utilized retroviral vector, though minor variations in vector/transduction techniques

Composite Experience

- Variations amongst protocols:
  - Different ages: infants/toddlers/older
  - Different cells: T-cells vs. purified CD 34^{+} cells Peripheral vs. bone marrow vs. cord blood
  - Conditioning
  - Continued use vs. discontinuation of PEG-ADA