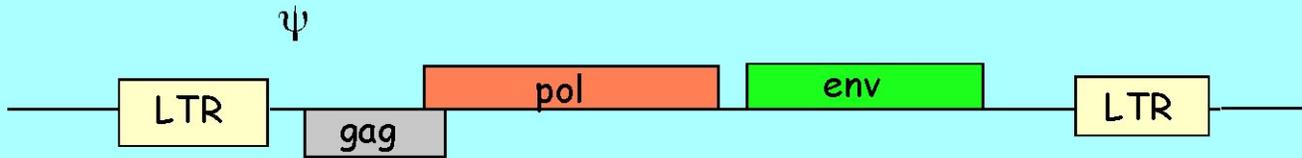


New Developments in X-SCID Gene Transfer

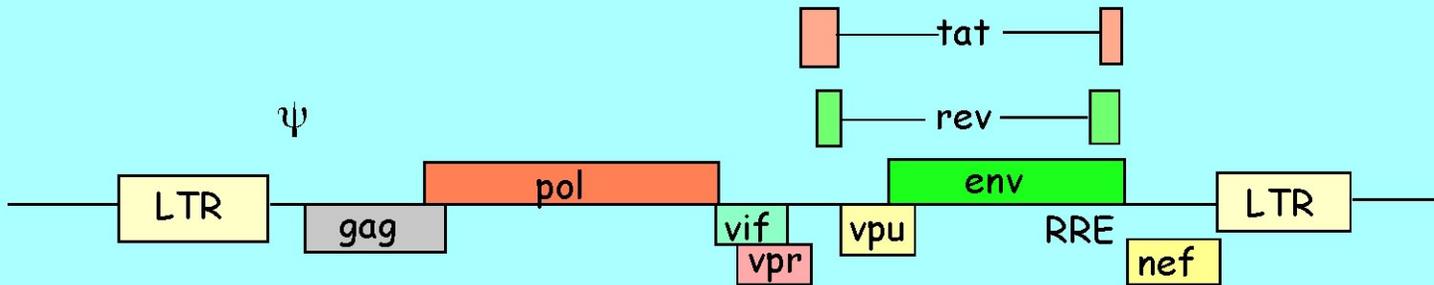
March 11, 2008

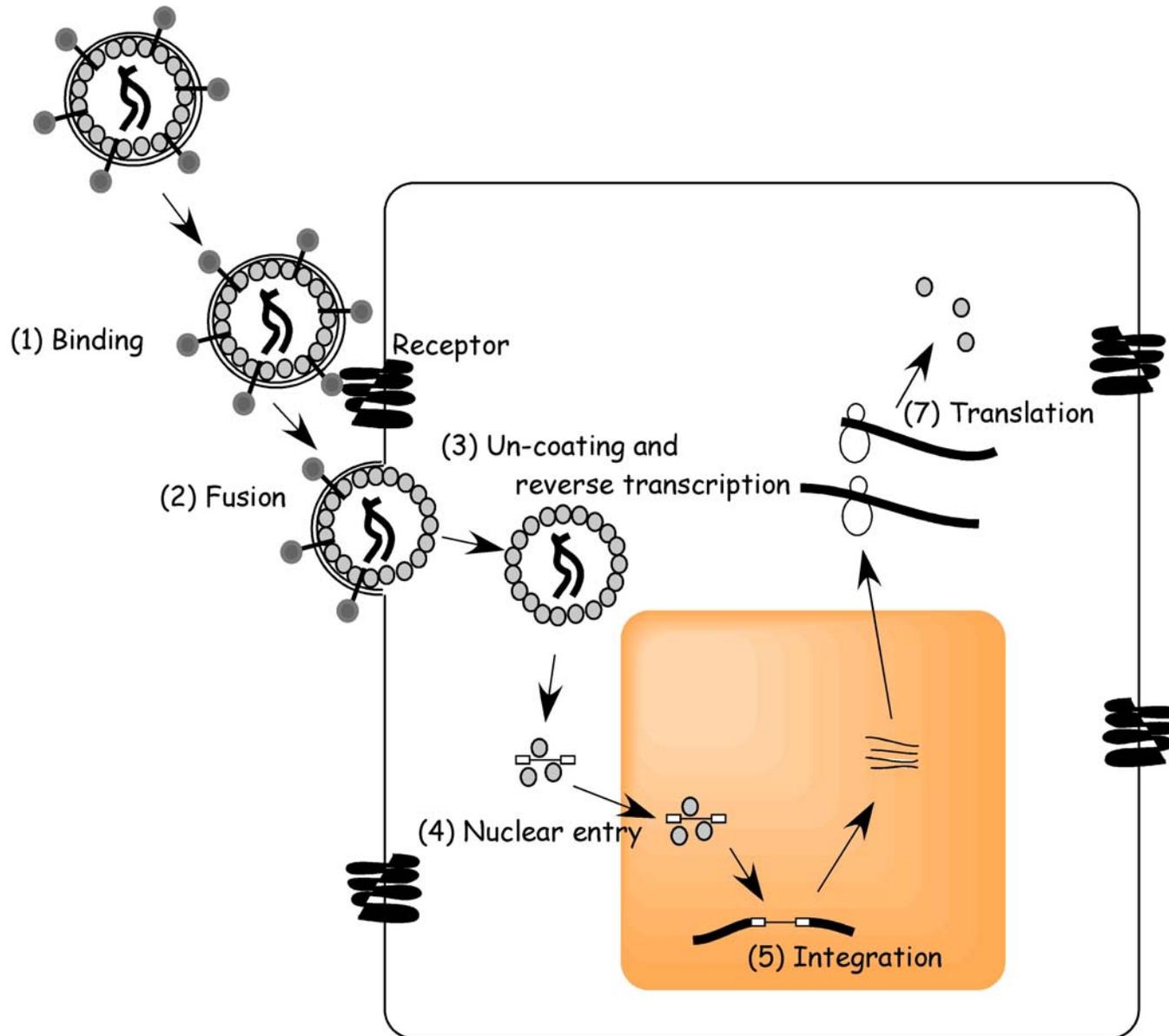


MLV - an oncoretrovirus

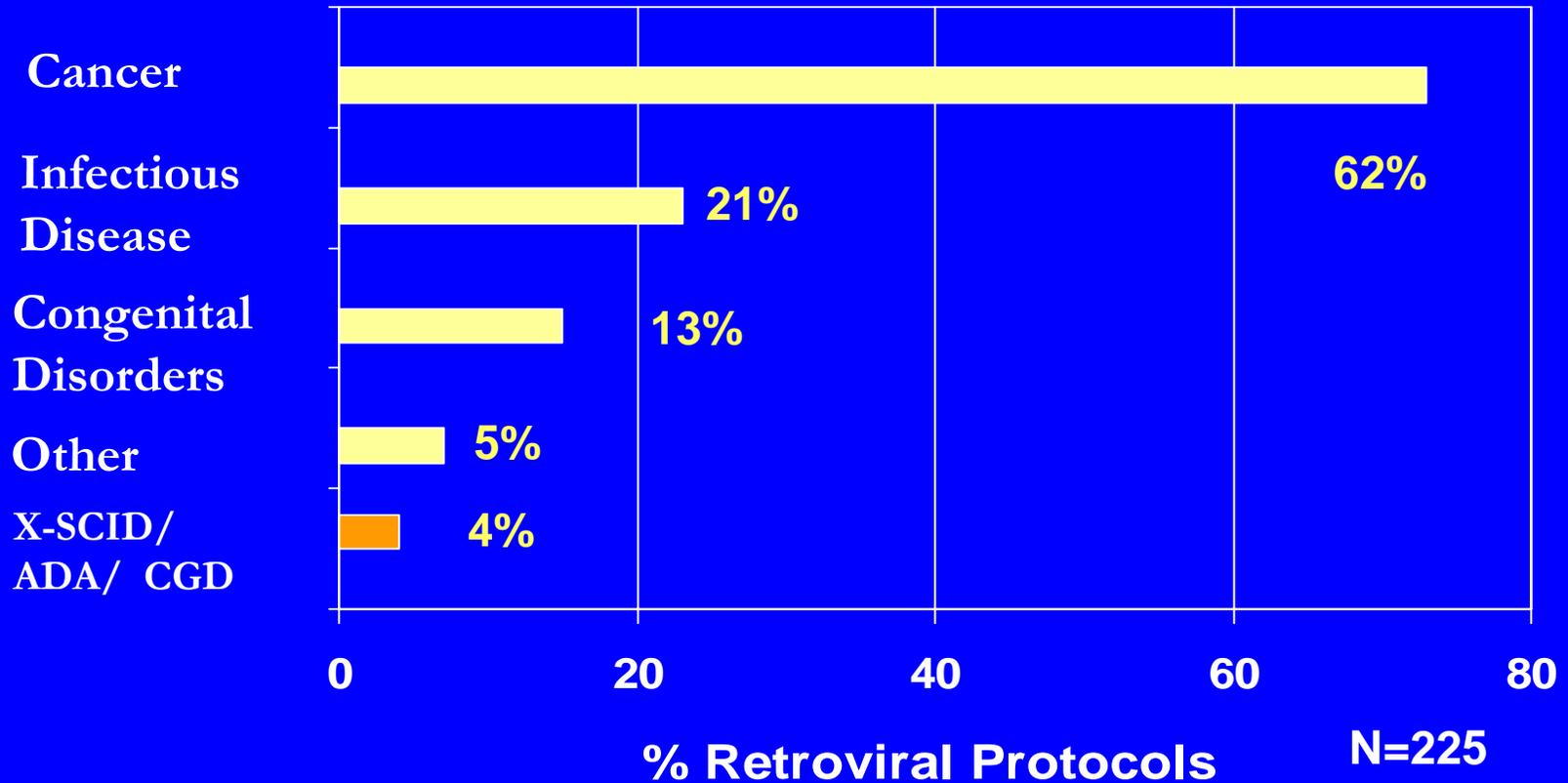


HIV - a lentivirus





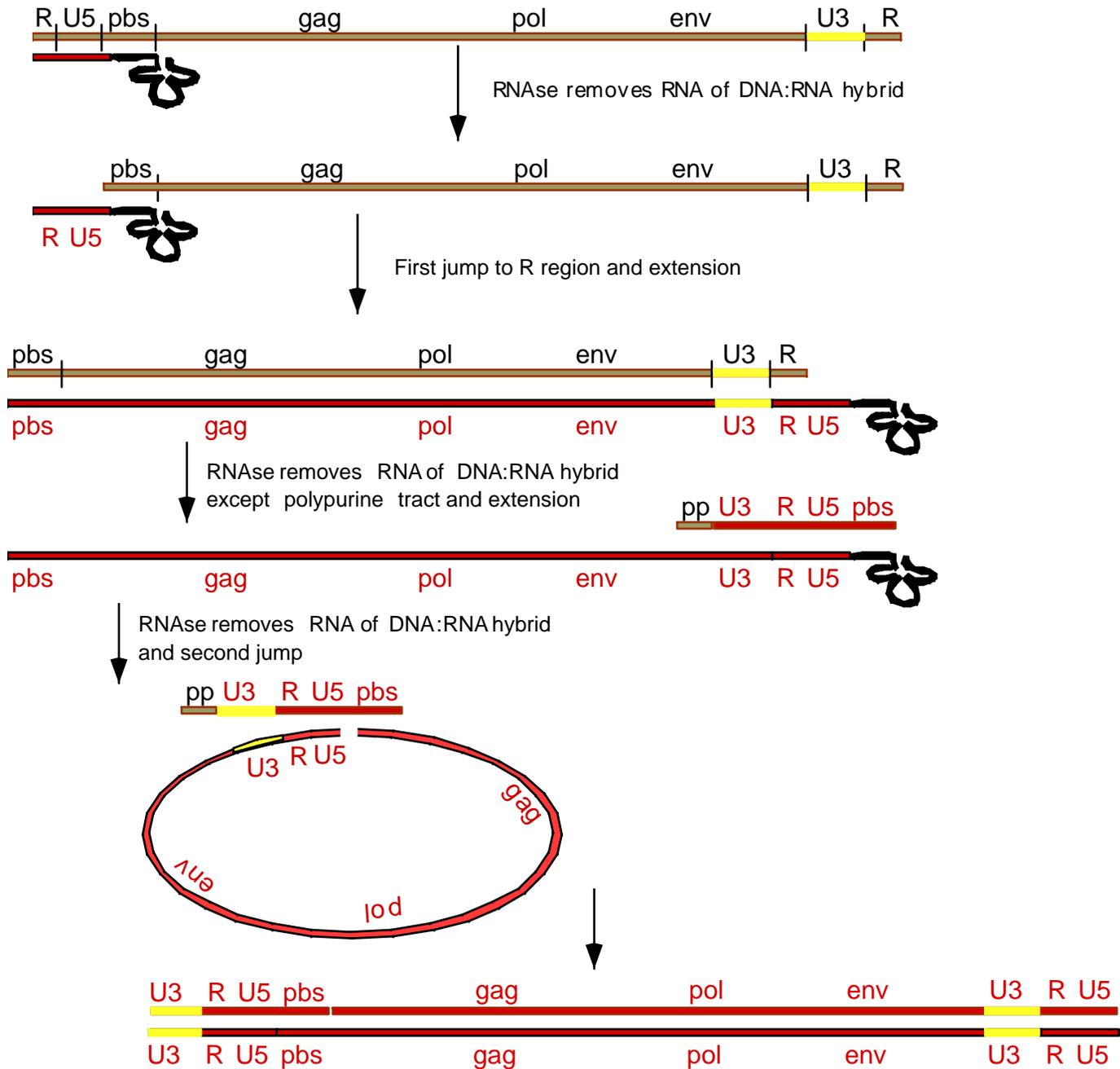
Retroviral Vector Protocols by Clinical Application





Gene X = LMO2

Gene X = BmiI
(repressor of Arf)



~~Gene Y~~ (**MONOSOMY**)



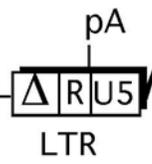
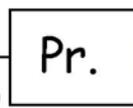
Gene X

Gene X = LMO2

Gene X = BmiI
(repressor of Arf)

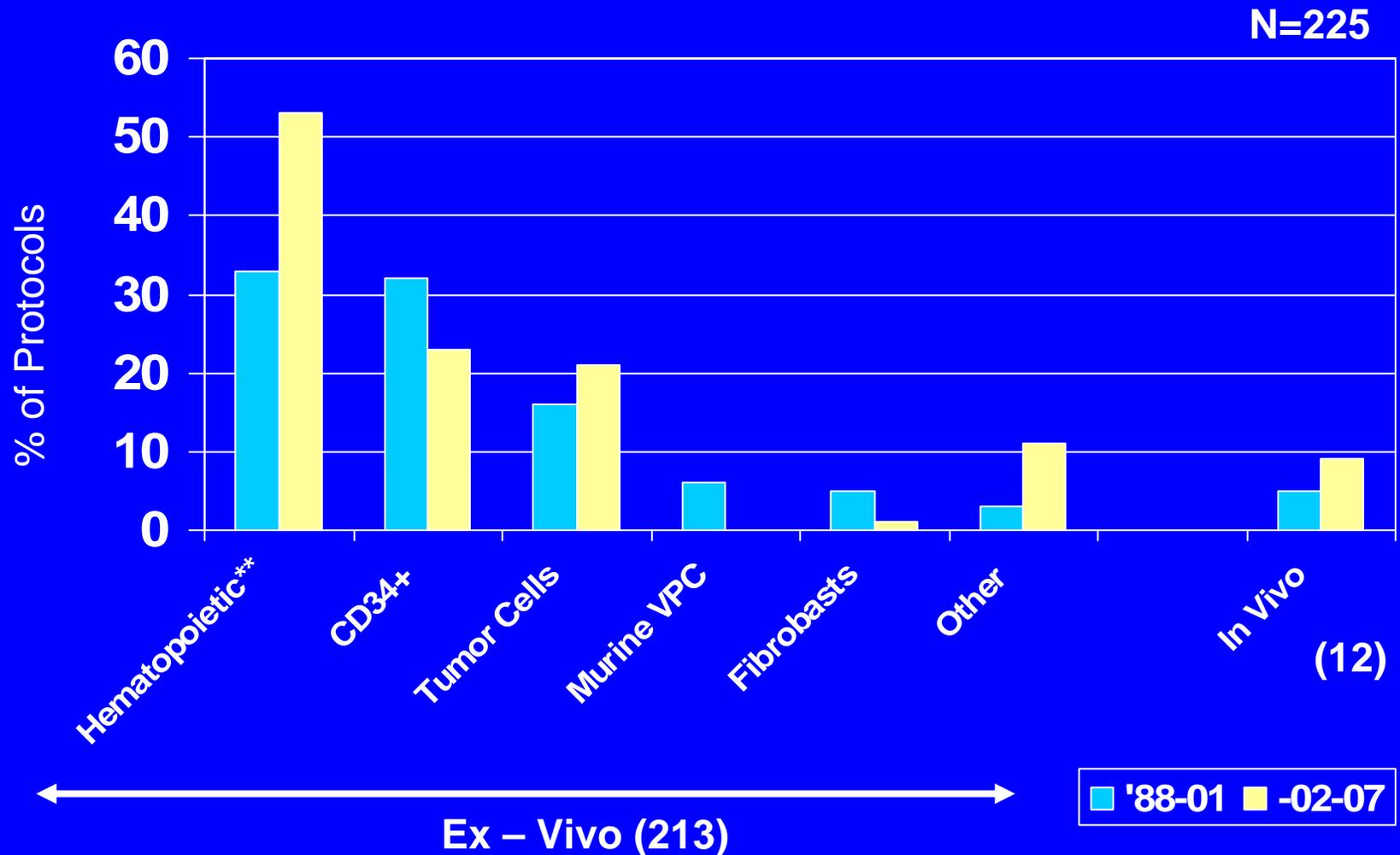
SIN VECTORS

~~Gene Y~~

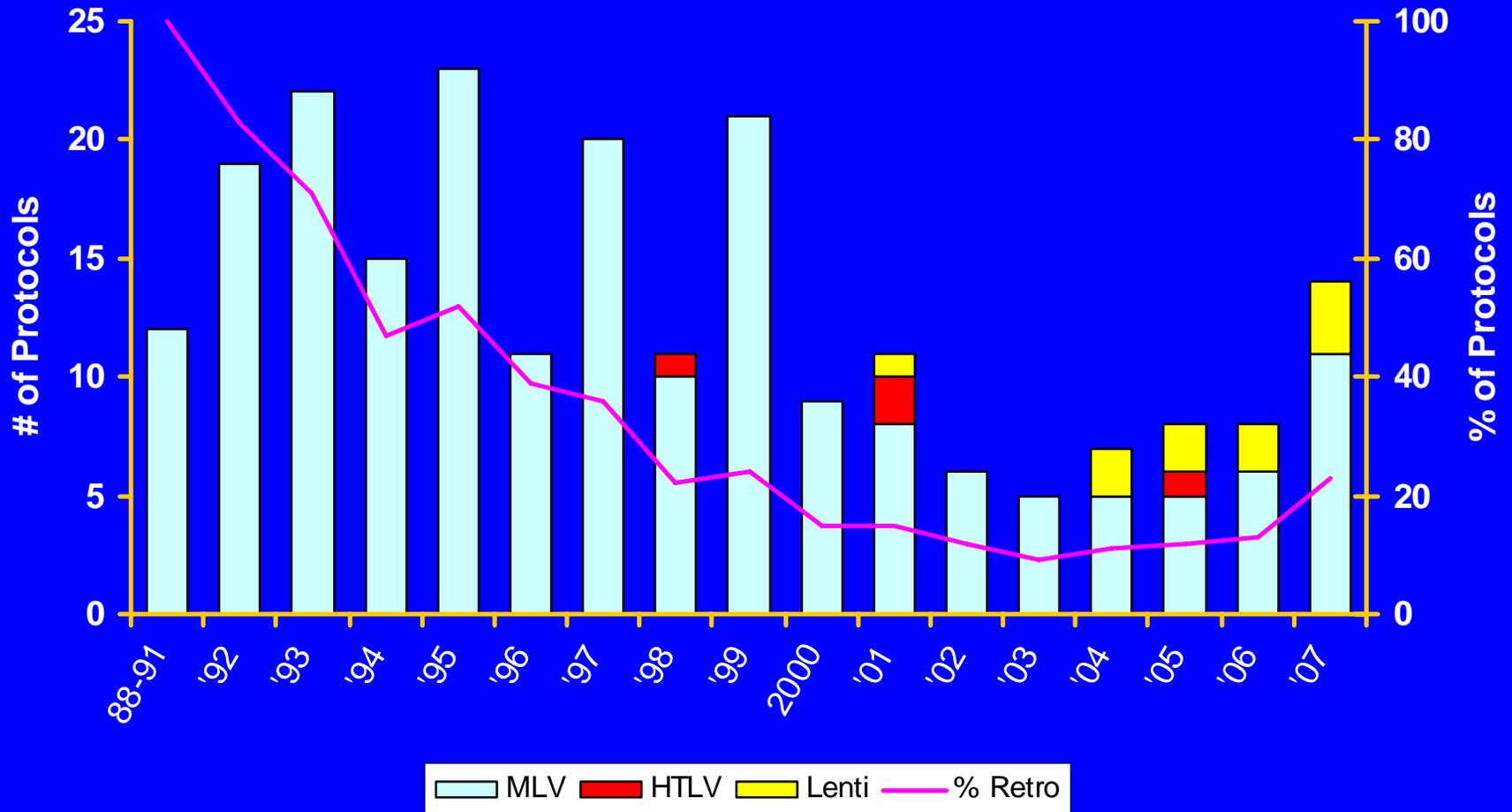


Gene X

Administration of Retroviral Vectors



Trends in Retroviral Vector Usage 1988-2007



Previous RAC Meetings on Gene Transfer for X-SCID

NIH RAC has reviewed the clinical and molecular data concerning the four previous serious adverse events that occurred in a human gene transfer study conducted in France to correct X-linked SCID.

- December 5, 2002
- February 10, 2003
- March 15, 2005
- March 14, 2007

RAC Recommendations Regarding Retroviral vectors and X-SCID

- Pending further data or extenuating circumstances, reviewed on a case-by-case basis, retroviral gene transfer studies for X-linked SCID should be limited to patients who have failed identical or haploidentical stem-cell transplantation or for whom no suitable stem cell donor can be identified. Case-by-case review would include appropriate risk: benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

RAC Recommendation regarding Gene Transfer with Retroviral Vectors

- There are not sufficient data or reports of adverse events directly attributable to the use of retroviral vectors at this time to warrant cessation of other retroviral human gene transfer studies, including studies for non-X-linked SCID. Such studies may be justified contingent upon appropriate risk: benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

RESEARCH ETHICS:

- RISK-to the subject
- BENEFIT* may include:
 - a. benefits to the subject
 - b. benefits to society (i.e., knowledge)
 - c. benefits to the investigator/ sponsor
- ALTERNATIVES

*Subpart D requires that the benefit consideration in pediatric research focus on a. rather than b/c

SEQUENCE MATTERS

Risk:Benefit assessment by investigator and IRB must precede informed consent/surrogate permission/assent of incompetent subject.

If the risk:benefit ratio is not acceptable, the research should not proceed.

CLINICAL EQUIPOISE

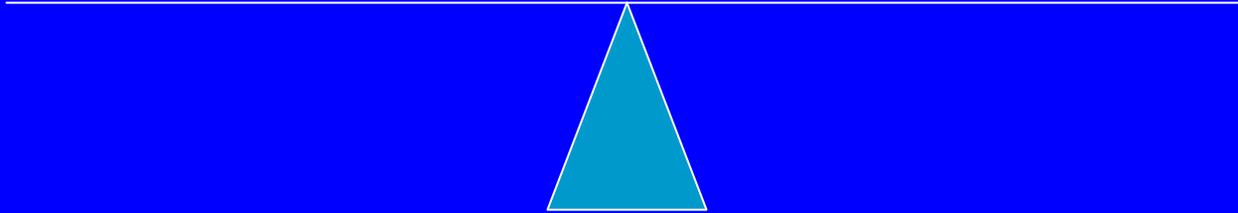
- THE ABSENCE OF CONSENSUS (“GENUINE UNCERTAINTY WITHIN THE EXPERT MEDICAL COMMUNITY”) REGARDING THE COMPARATIVE MERITS OF THE INTERVENTION TO BE TESTED.

B.Freedman, NEJM 317:141-145

EQUIPOISE (within a study)

ARM A

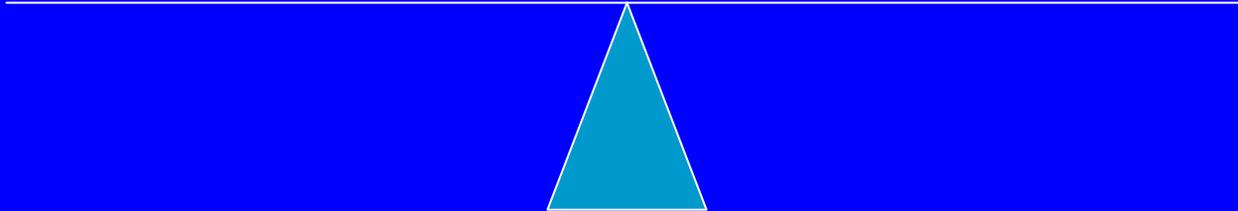
ARM B



EQUIPOISE (external)

Investigational approach

Other trials or non-research
approaches



Assent: A Research Definition

“A child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.”

-CFR 46.402 (b)