

Serious Adverse Events in Retroviral Trials- Revisited

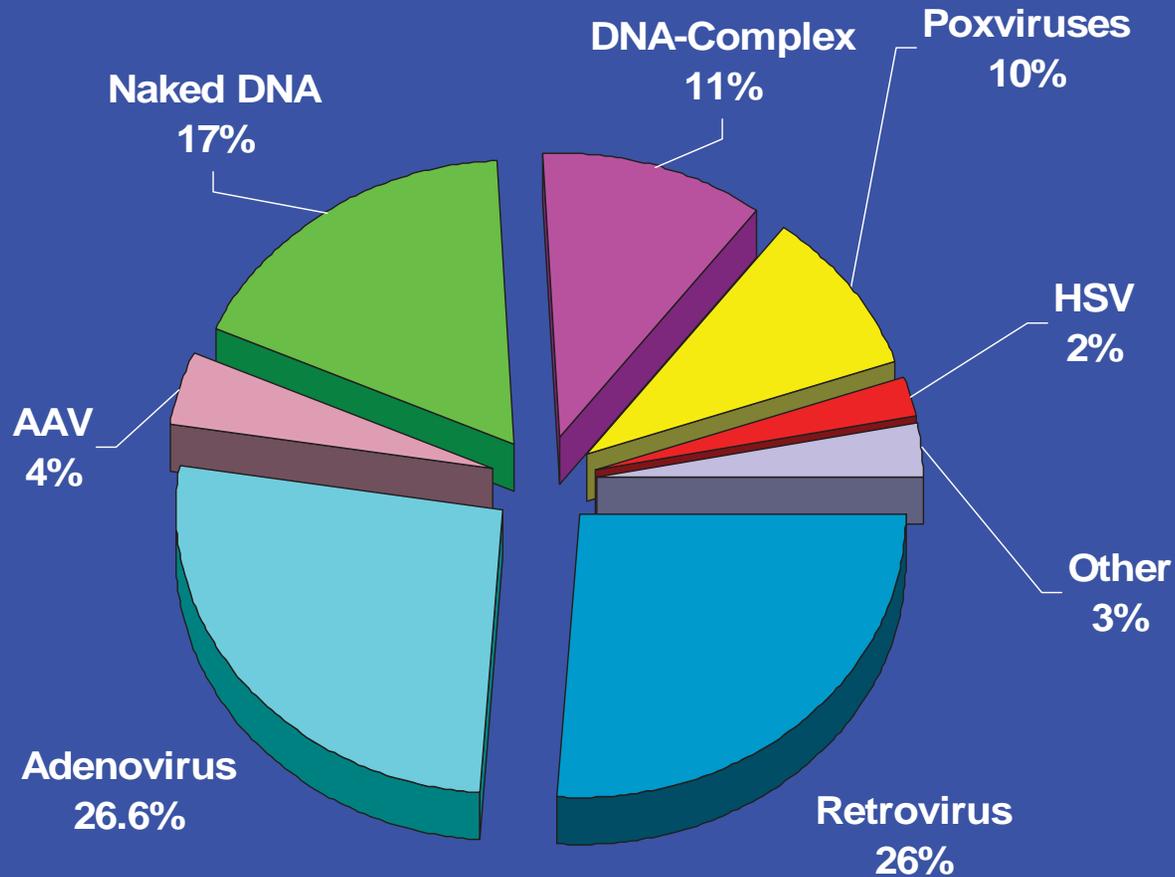
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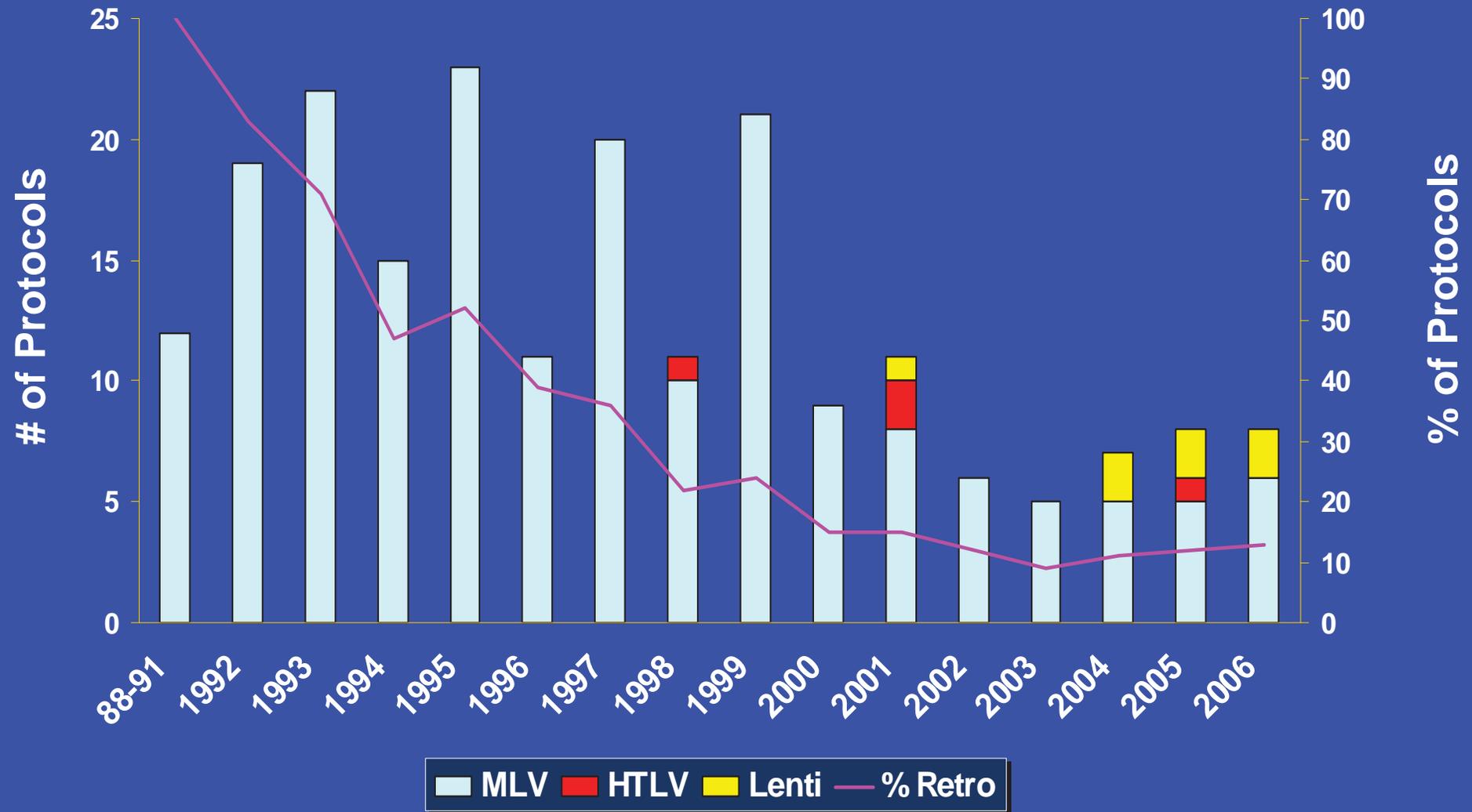
Office of Biotechnology Activities



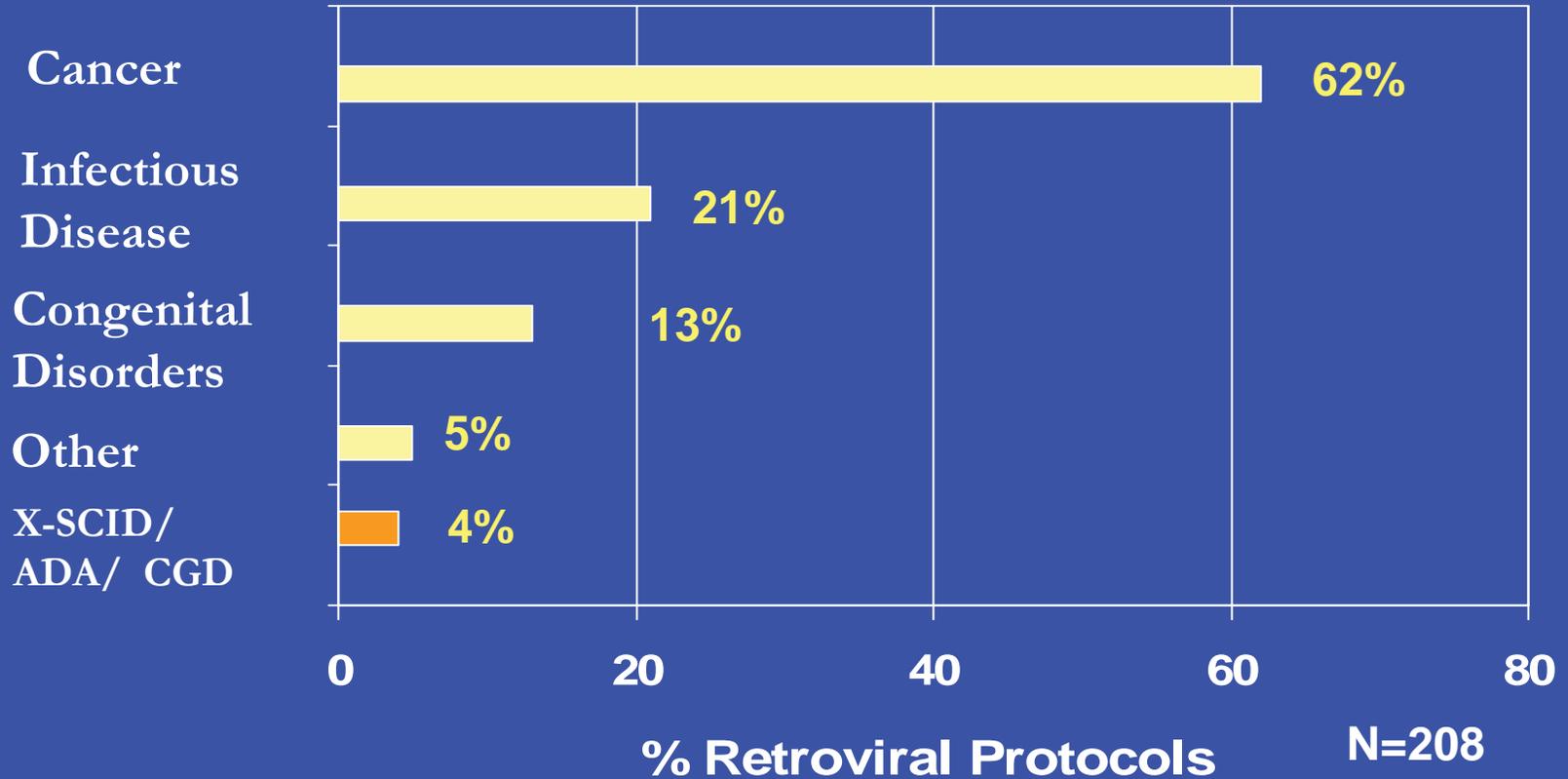
Gene Transfer Trials By Delivery System



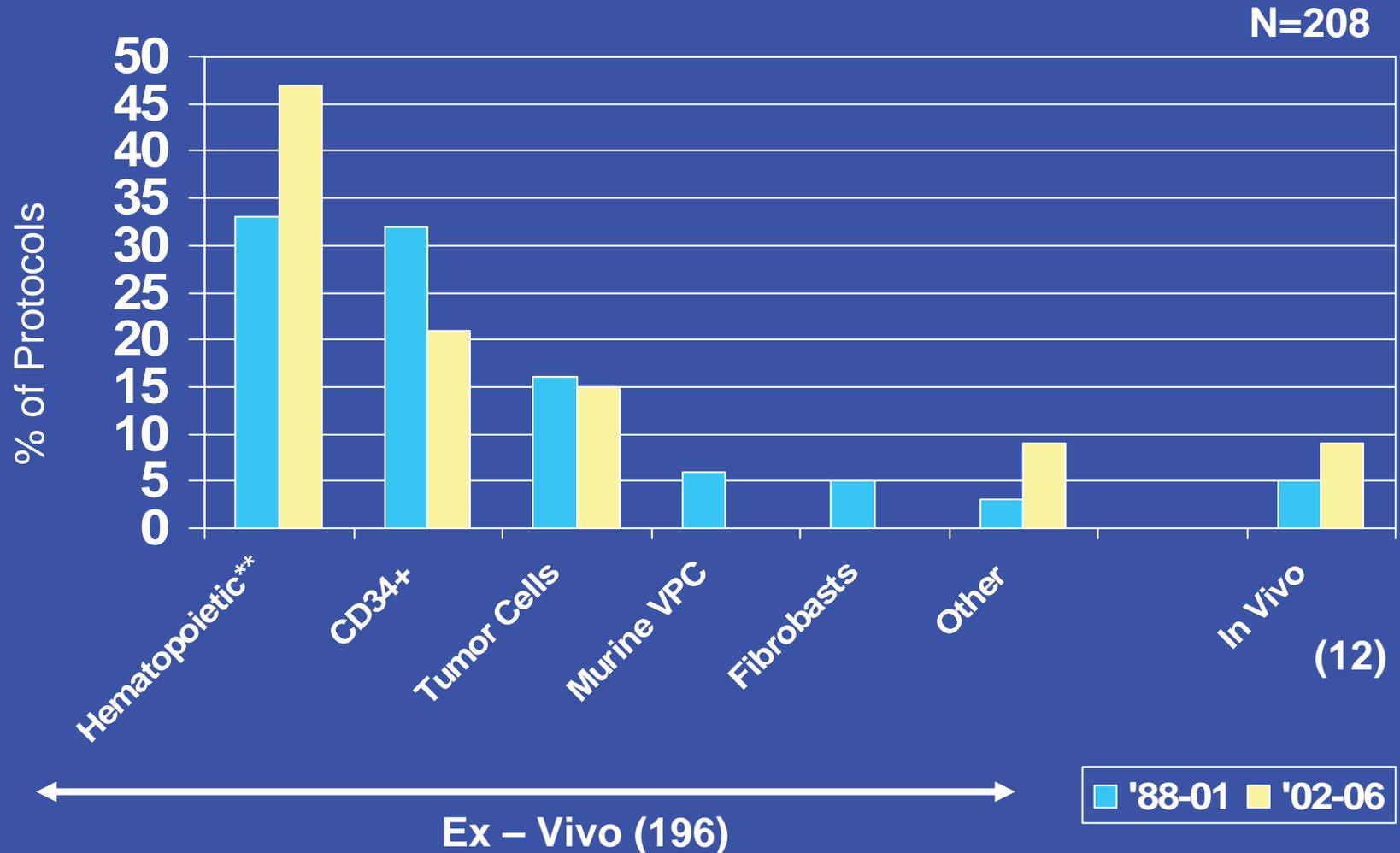
Trends in Retroviral Vector Usage 1988-2006



Retroviral Vector Protocols by Clinical Application



Administration of Retroviral Vectors



Previous Adverse Event Review

December 2002 Meeting: Presentation on
Adverse Events in Clinical Trials Using
Retrovirals

http://www.webconferences.com/nihoba/4-6_december_02.html

Summary of 2002 Review

- Searched for any malignancies, leukemias, lymphoma, myelodysplastic syndromes or monoclonal proliferations in retroviral trials
- Examined but did not further elaborate on cases that were either consistent with the disease process (e.g. Kaposi's sarcoma in patients with AIDS) or local skin tumors in studies where fibroblasts were not transduced/involved
- Data collected before complete implementation of adverse event module of Genetic Modification Clinical Research Information System (GeMCRIS)

Summary of Cases Reviewed

- Eight Cases reviewed:
 - 4 lymphomas
 - 2 myelodysplastic syndromes
 - 1 case of monoclonal lymphoproliferation
 - 1 malignant glioma

Re-analysis using GeMCRIS

- All trials using retroviral vectors screened
- Screening on lymphoproliferative, monoclonal proliferation, lymphoma, leukemia, myelodysplasia, carcinoma, cancer, neoplasm and sarcoma
- Exclusion of local skin cancers in trials not transducing fibroblasts

Results

- Query captured 8 cases discussed previously
- 4 additional cases reviewed
 - Peripheral nerve sheath tumor
 - Rectal cancer
 - Development of monosomy 7
 - Adenocarcinoma
- None of these additional serious adverse events (SAEs) were submitted since 2004

Case 1

- Murine leukemia retrovirus
- EBV specific cytotoxic T lymphocytes marked with Neomycin resistance gene
- Recipients of mismatched-related or phenotypically similar unrelated donor marrow grafts
- Subject with neurofibromatosis and acute myeloblastic leukemia

Case 1 Continued

- 8 years after receiving gene transfer develops peripheral nerve sheath tumor that is attributed to neurofibromatosis
- PCR to detect retroviral vector integrants in genomic DNA was negative

Case 2

- Murine leukemia virus with HTLV-2 envelope
- CD34+ cells transduced with vector encoding antisense constructs against HIV
- Subject diagnosed with rectal cancer 3 months after receiving transduced cells
- No data provided on PCR for vector in tumor
- Subject lost to follow-up per annual update 2001

Case 3

- Murine Leukemia Virus
- Hematopoietic progenitor cells transduced with vector containing complementation group C gene for Fanconi Anemia
- Subject with history of genital warts diagnosed with squamous cell carcinoma of vulva approximately 2 months after gene transfer and undergoes pelvic radiation
- Initial peripheral blood sample collected prior to and immediately after radiation did not show evidence of gene marked cells

Case 3 continued

- Following recovery from radiation-induced bone marrow suppression, peripheral blood and marrow mononuclear cells collected 220+ days after infusion were positive for gene marked cells
- Routine cytogenetics done 1 1/2 years after gene transfer showed 7/20 metaphase cells with loss of chromosome 7
- Per Investigator, monosomy 7 is “common” in Fanconi anemia and the radiation treatment was felt as possible contributing factor. In addition, the PCR signal for the transgene from bone marrow and blood was declining at the same time monosomy clone developed. Therefore it was felt the development of monosomy 7 was unrelated to gene transfer

Case 4

- Murine Leukemia virus
- Hematopoietic progenitor cells transduced with vector containing Fanconi Anemia Group A complement cDNA
- Subject developed vaginal adenocarcinoma 2+ years after receiving transduced cells
- Given the Fanconi Anemia patients are at increased risk of developing solid gynecologic tumors and the fact analysis of bone marrow and blood failed to show detectable gene marking, the development of adenocarcinoma felt to be unrelated to gene transfer

Summary

- GeMCRIS helped augment initial queries from 2002
- GeMCRIS only covers trials registered with OBA and may not capture all serious adverse events in gene transfer trials
- Small number of cases seen across multiple trials with retroviral vectors, including those transducing hematopoietic cells
- Almost all of the cases identified have genetic/PCR or clinical evidence making it unlikely that the adverse event was related to retroviral vector

Contributors

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