



GTSAB REPORT

Recombinant DNA Advisory Committee

December 11, 2014



National Institutes
of Health

Protocols Submitted for Fourth Quarter 2014

- 16 total submissions, one was selected for public review
- ~14% of protocols selected this year

Protocols not Selected this Quarter

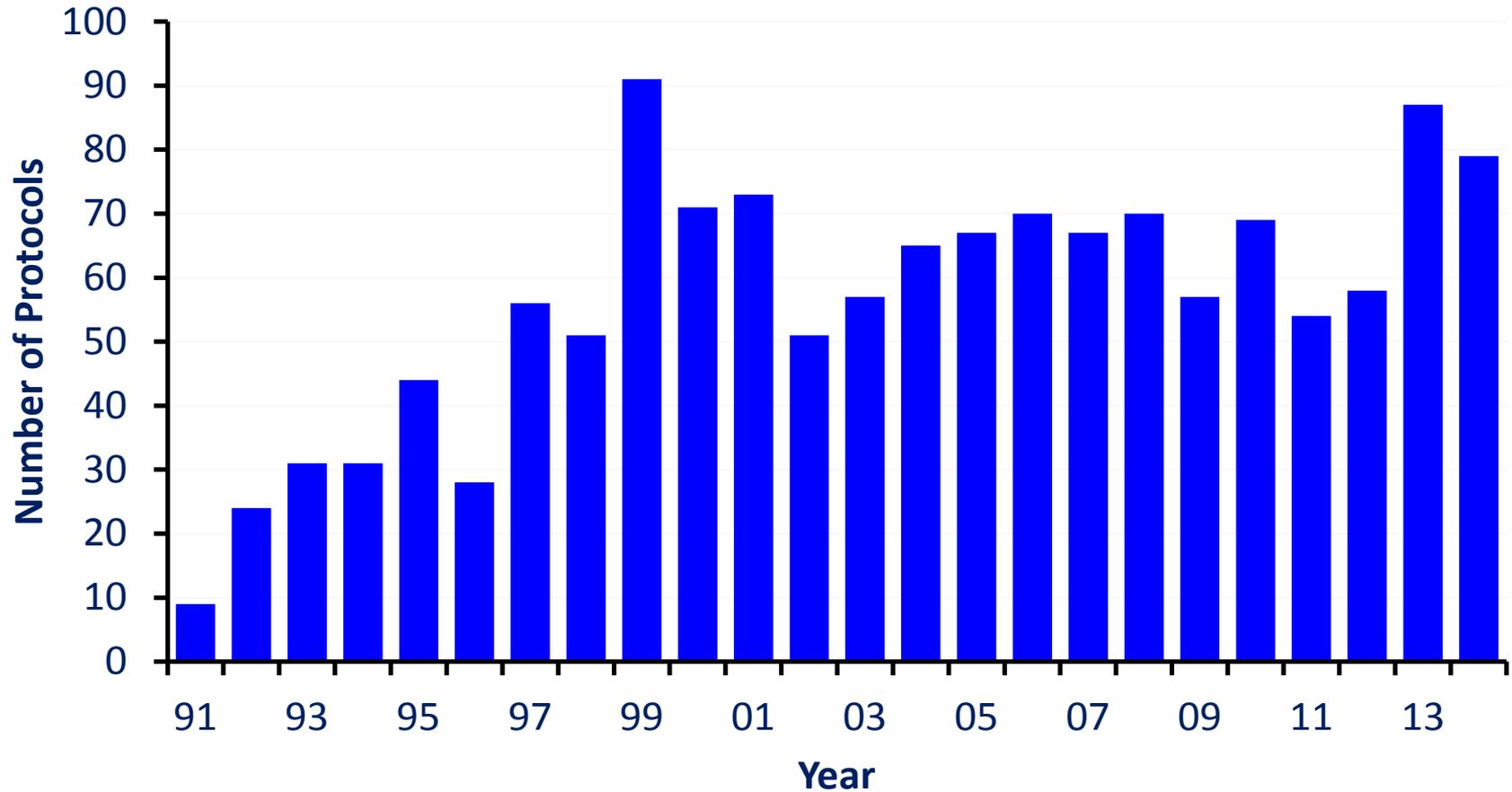
Diseases		
12 cancer	2 monogenic diseases	1 heart failure
Vectors		
1 Retrovirus	2 Plasmids	2 RNA
2 Lentiviruses	2 Adenovirus	1 attenuated <i>Listeria monocytogenes</i>
1 HSV	3 AAV	1 Measles



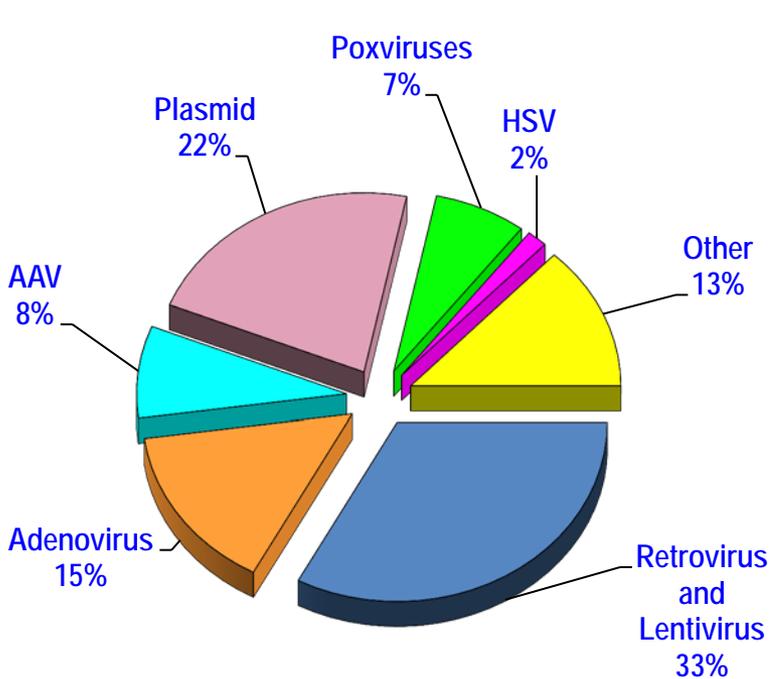
Overview of Human Gene Transfer Trials

Number of Protocols Registered with NIH from 1991 to 2014

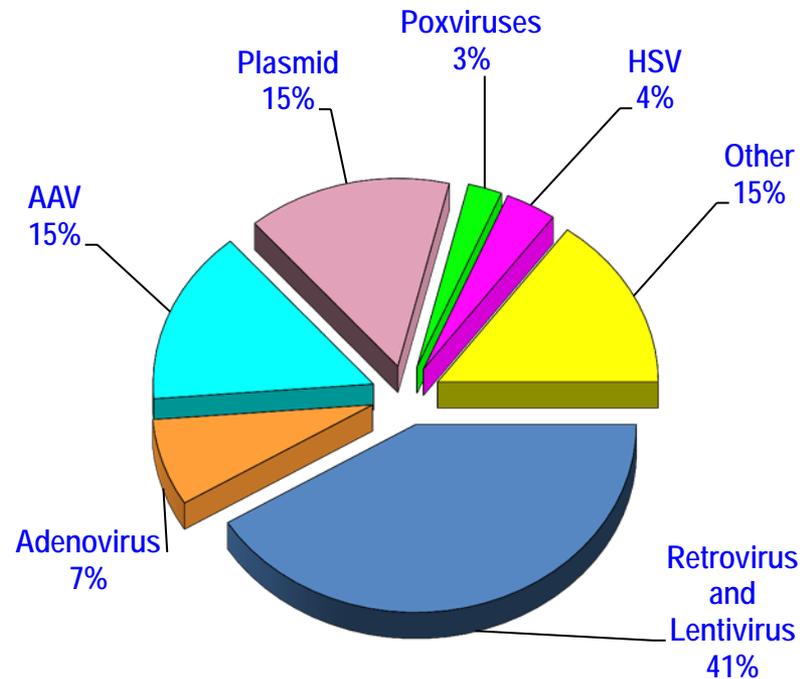
N=1360



Gene Transfer Vectors

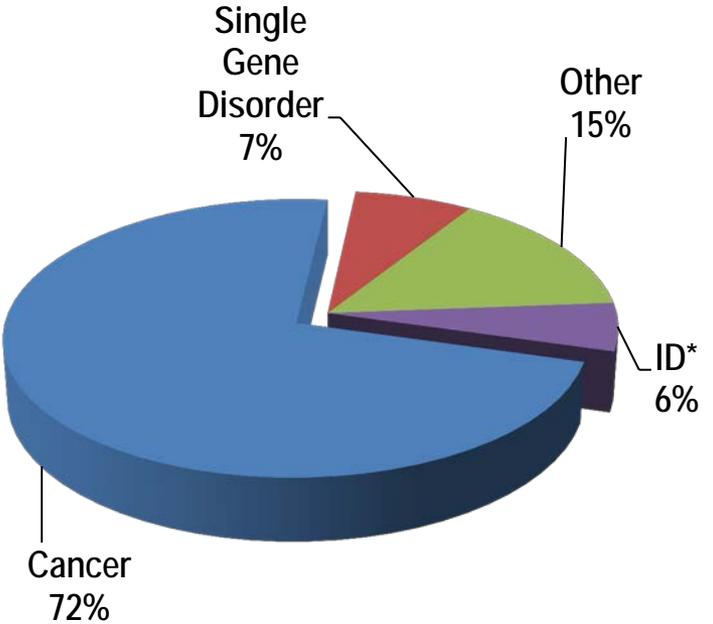


2010 - 2013

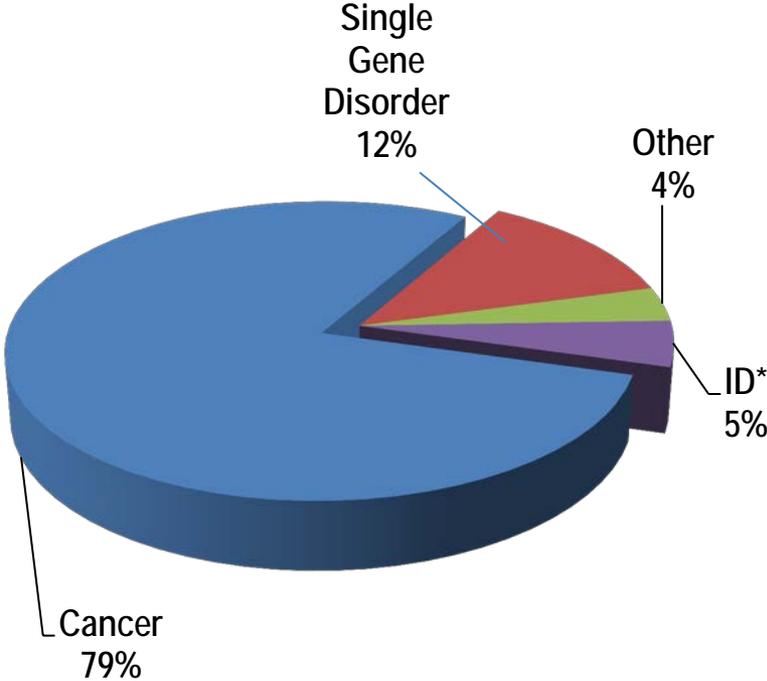


2014

Gene Therapy: A Snapshot by Application



2005 - 2013



2014

* ID: Infectious Diseases



Serious Adverse Events

17 serious adverse events were reviewed by the GTSAB from 15 protocols, including initial and follow-up reports.

Abbreviated public web summaries are available with the RAC meeting materials on the OBA website and in the future will be available in GeMCRIS



Opening of New Protocols Fourth Quarter 2014

- 11 protocols notified OBA of enrollment (MIC1 submission), 4 were publicly reviewed.
- In 2014, 49 protocols informed OBA of enrollment



A Three-part, Multicenter, Open Label, Single Dose Study to Assess the Safety, Tolerability, and Efficacy of Intralabyrinthine (IL) CGF166 in Patients with Severe Hearing Loss (OBA Protocol #1260 Reviewed December 2013)

- **Disposal of any fluid that leaks from the inner ear during the surgical procedure will be in accordance with protocols for BL2 agents.**
- **The informed consent forms have been modified clearly indicate that this is a gene transfer approach and that once the vector is surgically administered it is not possible to remove the agent.**



Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering the Survival Motor Neuron Gene by Self-complementary AAV9 (OBA Protocol #1188 Reviewed December 2010)

- **Previous definition of dose-limiting toxicity included two Grade II* related toxicities, but the protocol has been changed to state that an unacceptable toxicity is now defined as the occurrence of any Grade III or higher related event.**
- **The RAC had expressed concern that the starting dose might not be high enough to provide potential benefit in this first-in-human pediatric study. The starting dose was not changed for two reasons. First, all dose escalation trials must start with the minimally effective dose. Second, the highest planned dose is currently at the maximally achievable dose.**

* Common Terminology Criteria for Adverse Events



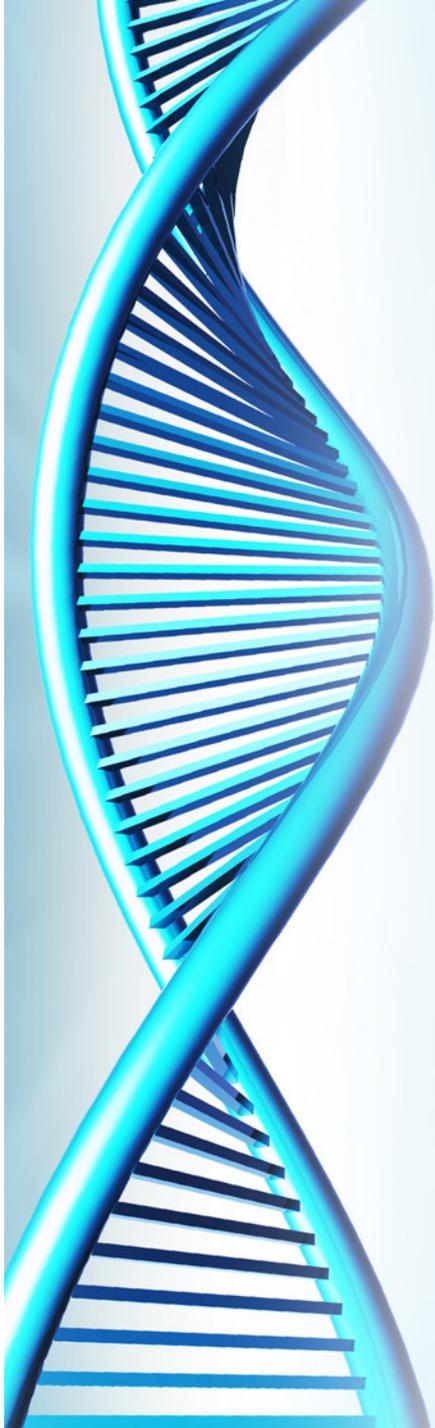
A Phase I/II, Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of Single Doses of TT-034 in Patients with Chronic Hepatitis C (CHC) Infection (OBA Protocol #1219 Reviewed June 2013)

- **In order to monitor for changes that would not be expected with chronic hepatitis C infection, tissue obtained by liver biopsy will be evaluated for unusual areas of fibrosis or necrosis or eosinophilia as recommended by the RAC.**



An Open-label Dose Escalation Study of An Adeno-Associated Virus Vector (scAAV2-P1ND4v2) for Gene Therapy of Leber's Hereditary Optic Neuropathy (LHON) Caused by The G11778A Mutation in Mitochondrial DNA (OBA Protocol #1306 Reviewed June 2014)

- **In animal models of this disease, vision was rescued only when the vector with the mutated capsid was used. Future studies will attempt to better understand the mechanism as to why mutations in three tyrosine residues (to phenylalanine) in the capsid led to these results.**
- **Development of an assay for detection of the wild type protein will be pursued in the future.**



Recent Publication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

A.C. Nathwani, U.M. Reiss, E.G.D. Tuddenham, C. Rosales, P. Chowdary, J. McIntosh, M. Della Peruta, E. Lheriteau, N. Patel, D. Raj, A. Riddell, J. Pie, S. Rangarajan, D. Bevan, M. Recht, Y.-M. Shen, K.G. Halka, E. Basner-Tschakarjan, F. Mingozzi, K.A. High, J. Allay, M.A. Kay, C.Y.C. Ng, J. Zhou, M. Cancio, C.L. Morton, J.T. Gray, D. Srivastava, A.W. Nienhuis, and A.M. Davidoff

N Engl J Med 2014;371:1994-2004.



Gene Transfer for Hemophilia

(OBA Protocol # 864; ClinicalTrials.gov number, NCT00979238*)

- 10 patients with severe hemophilia received a single IV infusion of a serotype 8 pseudotyped, self-complementary AAV vector expressing codon-optimized Factor IX (scAAV2/8-LP1-hFIXco). A dose-dependent increase in factor IX (1-6% of normal value) was seen over a median period of 3.2 years.
- In the six subjects in the high-dose group (2×10^{12} vg/kg), the consistent increase in factor IX resulted in >90% reduction in both bleeding episodes and use of factor IX concentrate.
- A transient increase in the mean alanine aminotransferase level (ALT) levels to 86 IU/L (range 36 to 202) occurred during week 7 and 10 in 4 of 6 patients in the high-dose group, which resolved over a median of 5 days (range, 2 – 35) after prednisolone therapy.
- With a follow-up period of up to 3 years, no late toxic effects from the therapy were reported.

*Funded by the NHLBI and others



Questions?



PROTOCOLS INITIATED THIS QUARTER

1108-1121 A Phase III Double-Blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of AMG0001 (HGF Plasmid) in Subjects with Critical Limb Ischemia (AG-CLI-0206)

1302-1211 An Integrated Phase II/III, Open-Label, Randomized and Controlled Study of the Safety and Efficacy of CG0070 Oncolytic Vector Regimen in Patients with Non-Muscle Invasive Bladder Carcinoma In Situ Disease (“NMIBCis”, meaning Cis and Cis with Ta and/or T1) and Who have Failed BCG Therapy and Refused Cystectomy

1304-1221 Vaccination to Enhance the Anti-tumor Activity of GD2 Chimeric Antigen Receptor-Expressing, VZV-Specific T cells in Subjects with Advanced Sarcomas



PROTOCOLS INITIATED THIS QUARTER

1311-1276 Phase I Study of Activated T Lymphocytes Expressing Chimeric Antigen Receptors for Therapy of Relapsed CD19-Positive Malignancies Post-Allogeneic Hematopoietic Stem Cell Transplantation Infused Only after Engraftment (CARPASCIO)

1312-1280 Phase I Trial of T Cells Expressing an anti-GD2 Chimeric Antigen Receptor in Children and Young Adults with Non-neuroblastoma, GD2+ Solid Tumors

1312-1284 Pilot 2-Part Prospective Study of HPV Specific Immunotherapy in Subjects with HPV Associated Head and Neck Squamous Cell Carcinoma (HNSCCa)

1403-1295 A Phase 3b, Multicenter, Open-label, Single-Arm, Expanded Access Protocol of Talimogene Laherparepvec for the Treatment of Subjects with Unresected, Stage IIIB to IVM1c Melanoma