



GTSAB REPORT

Recombinant DNA Advisory Committee

September 11, 2013



National Institutes
of Health



Protocols Submitted for 3rd Quarter 2013

- **15 Total submissions**

Disease indications for the 11 protocols not selected:

- 4 for Cancer
- 1 for HIV
- 1 for peripheral artery disease
- 1 for brain injury
- 1 for elimination graft vs. host
- 1 for wound healing
- 1 for arthritis
- 1 for muscular dystrophy

Vectors	
2 Retroviruses	4 Plasmids
2 Lentiviruses	1 modified <i>Listeria monocytogenes</i>
1 AAV	1 VEE replicon



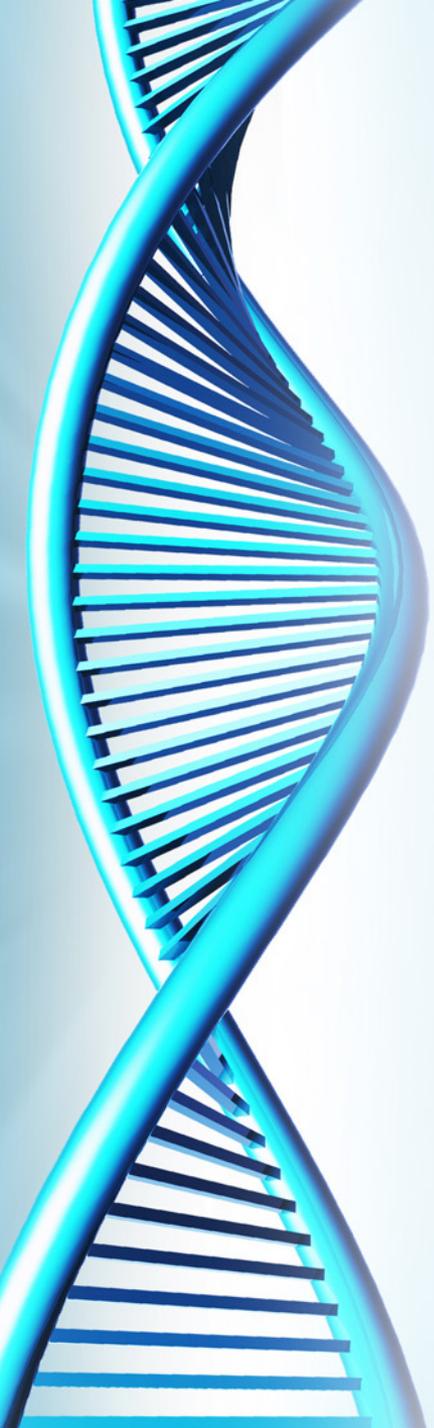
Serious Adverse Events

23 serious adverse events were reviewed by the GTSAB from 13 protocols, including initial and follow-up reports. No events will be discussed today.



Opening of New Protocols 2nd Quarter 2013

- **Six protocols notified OBA of enrollment (MIC1 submission).**
- **None of the six were publicly reviewed**



**A Largely Random AAV Integration Profile after LPLD Gene Therapy.
Kaepffel, C., et al., (2013) Nat. Med. 19:
89 19:890-892.**



Previous Integration Profile of AAV Vectors

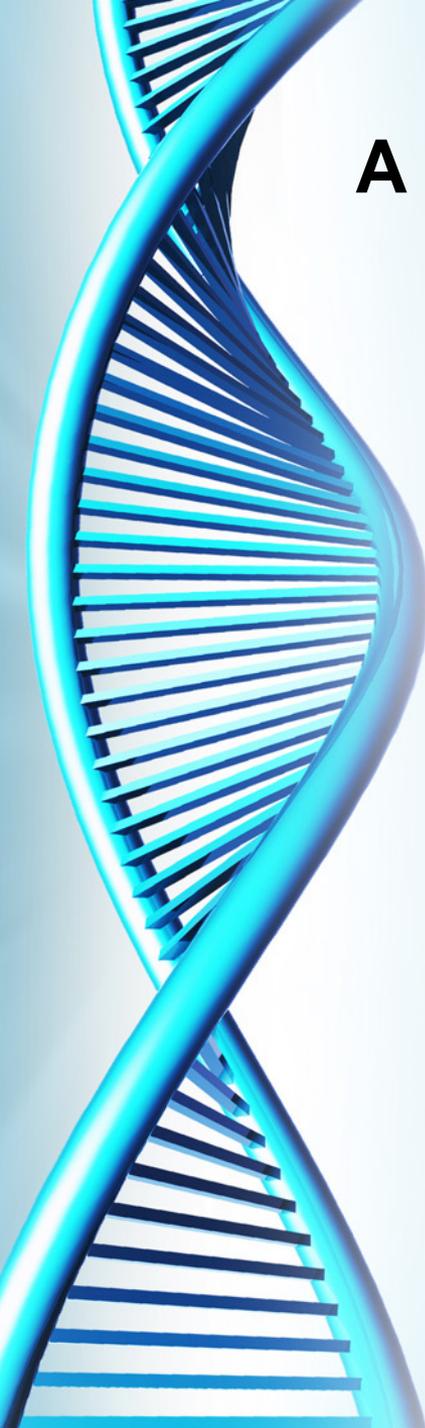
- Previous integration site studies utilized transformed cell lines, mouse, NHP tissues & human fibroblasts
- Most intracellular rAAV genomes are episomal, however, integration also occurs at low frequencies
- AAV vectors were previously reported to integrate into intergenic regions, introns, CpG islands, G/C-rich sequences, repeat sequences, rDNA and transcriptionally active DNA



A Largely Random AAV Integration Profile after LPLD Gene Therapy.

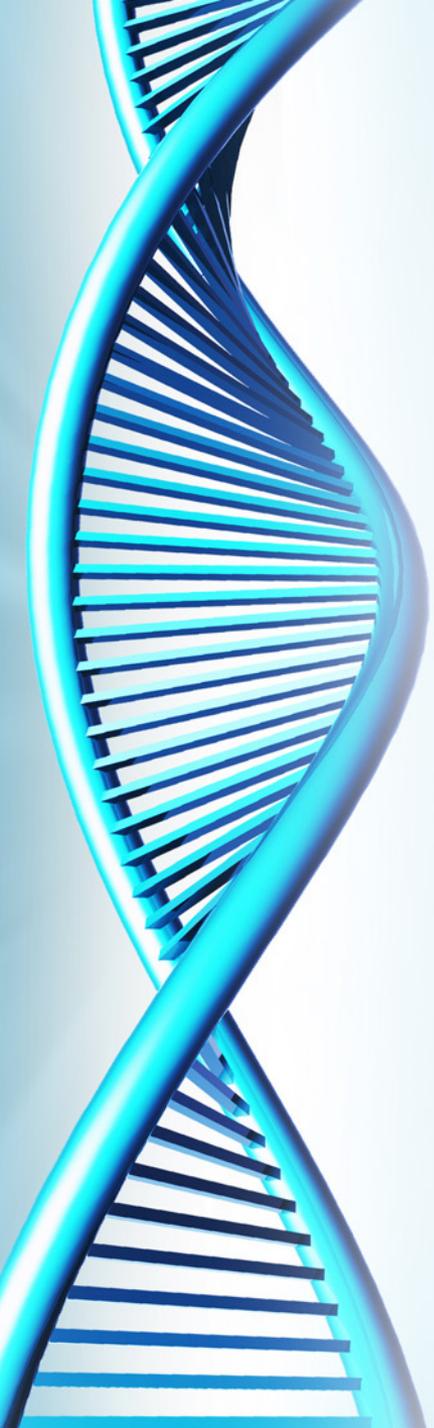
Kaepfel, C., et al., (2013) Nat. Med. 19:890-892.

- **First AAV vector integration site analysis of clinical samples – 5 subjects with LPL Deficiency – treated with intramuscular injection of AAV1-LPLS447X, (Glybera, the 1st approved gene therapy product in Europe)**
- **LAM-PCR / deep sequencing of muscle biopsies**
- **AAV integration was random**
- **No preferential integration observed into genes, CpG islands, palindromes or ribosomal DNA**
- **AAV vector frequencies: 0.74-84 vg/cell**
- **Integration frequencies: 10^{-4} to 10^{-5}**

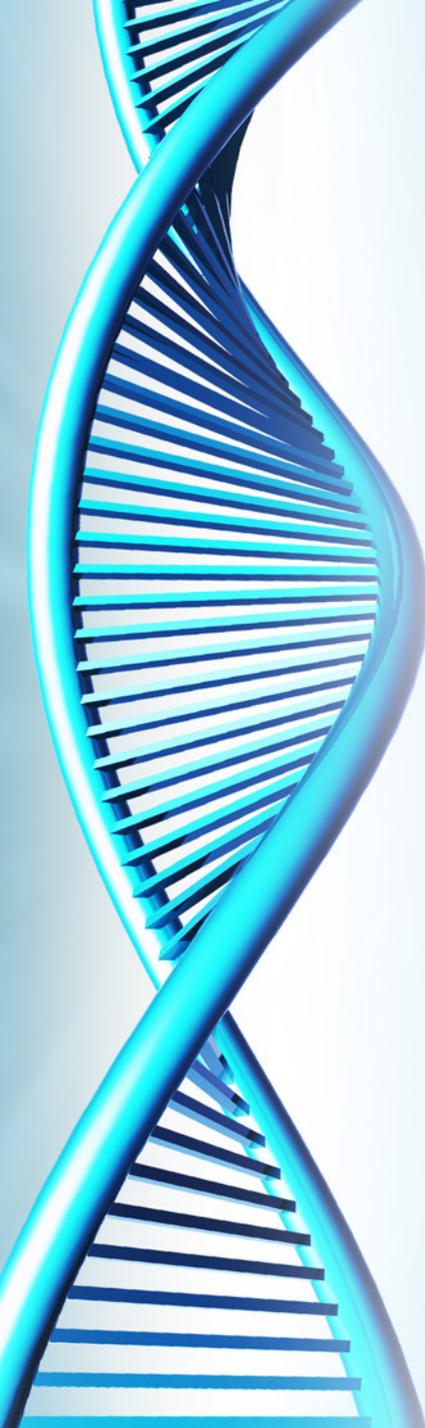


A Largely Random AAV Integration Profile

- **The most frequent common integration sites mapped to human mitochondrial DNA**
- **Chromosome-AAV junctions were found throughout the length of the vector – breaks were not limited to the ITRs**
- **Integration frequencies were 10-fold higher than previous estimates, but well below that of retroviral vectors**
- **No integration into hepatocellular carcinoma locus was observed**



Questions?



PROTOCOLS INITIATED THIS QUARTER

0901-962 A Phase I Open-Label Dose Escalation Safety Study of Convection-enhanced Delivery (CED) of Adeno-Associated Virus Encoding Glial Cell Line-Derived Neurotrophic Factor (AAV2-GDNF) in Subjects with Advanced Parkinson's Disease

1201-1142 Adoptive Immunotherapy for B-cell Chronic Lymphocytic Leukemia Using Sleeping Beauty Transposition to Express a CD19-specific Chimeric Antigen Receptor in Autologous Ex Vivo Expanded T-cells

1207-1175 A Phase I/II Study of BPX-201 Vaccine plus AP1903, in Patients with Metastatic Castrate Resistant Prostate Cancer (mCRPC)

1210-1195 A Phase III Study of FOLFIRINOX With or Without HyperAcute®-Pancreas (algenpantucel-L) Immunotherapy in Subjects with Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer

1301-1201 A Phase I Trial of Autologous T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients with Relapsed B-Cell Acute Lymphoblastic Leukemia

1303-1213 Phase I/II Study of Immunotherapy for Advanced CD19+ B Cell Malignancies with Defined Subsets of Autologous T Cells Engineered to Express a CD19-Specific Chimeric Antigen Receptor