The National Gene Vector Biorepository's Pharm/Tox Database

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The National Center for Research Resources has funded a new program to support preclinical and clinical gene therapy efforts. The National Gene Vector Biorepository (NGVB) will bring a variety of programs online during the next year. One of the resources will be a continuation of the Pharmacology/Toxicology (Pharm/Tox) Database formerly maintained by the National Gene Vector Laboratory. The purpose of the database is to provide gene therapy investigators with a catalog of gene therapy biodistribution and toxicology studies on file with the US Food and Drug Administration (FDA).

Pharm/tox refers to any *in vitro* or animal study that seeks to determine the therapeutic or toxic effect of a drug product (including gene therapy). Pharm/tox studies are designed to estimate the dose and dosing schedule as well as to identify the potential toxicity of drug products before they are administered to humans. These studies, which are required by the FDA, are submitted in an Investigational New Drug (IND) application—the established mechanism for FDA oversight of investigational drug development. The IND application must outline what is known about the drug, how the drug will be manufactured, the clinical protocol under which the drug will be administered, and how the patients will be informed about potential risks; in addition, it must include the results of pharm/tox studies.

The type and scope of a pharm/tox study will depend on several factors, including the product itself, the route of administration, the disease being treated, and the availability of suitable animal models. Given the complexity of products and disease indications, a customized pharm/tox plan is usually required. Therefore, investigators are well advised to draft a detailed pharm/tox plan, then engage the FDA via a Pre-Pre-IND or Pre-IND meeting before initiating the study, to minimize the chance that the study will be inadequate or insufficient to support the IND application.

Why is the Pharm/Tox Database needed? There are at least three reasons to provide a public catalog of pharm/tox studies. First, the results of such studies are generally not available. Many go unpublished because they are not viewed as hypothesis-driven research, and studies that support clinical trials generally have no significant findings. The second need for the database is financial. These studies, especially when done in nonhuman primates, are expensive and use valuable animal resources. Because the costs of the studies can exceed the cost of vector production and testing, there is a financial incentive for academic investigators and the National Institutes of Health (NIH) to avoid unnecessary duplication of studies. Third, the time needed to admit new products into clinical trial may be shortened if duplicative pharm/tox studies are avoided.

How can the database decrease costs? To protect the proprietary information of commercial sponsors, the FDA is prohibited by law from disclosing or using pharm/tox data submitted by one investigator for the benefit of another. An exception can be made when the FDA is given permission by the individual who submitted the original data. This is done with a "letter of cross-reference" written by the owner of the pharm/tox data. The letter authorizes the FDA to utilize the data in its deliberation of a specified IND application. By allowing the FDA to consider studies it has on file, it is hoped that subsequent gene therapy IND applications will not be viewed in isolation but can build on existing pharm/tox data and provide more focused (and less expensive) studies.

Generally, an individual who obtains a letter of cross-reference from a commercial or academic institution is not shown the primary data contained in the referenced file. Because it is ultimately the FDA that decides whether existing data can be used in support of an IND application, not sharing the primary data protects confidentiality and proprietary information while still accomplishing the goal of permitting the FDA to reference the data. The NGVB Pharm/Tox database was designed with similar considerations; primary data are not contained in the database, but detailed information is provided to investigators so that they can identify studies of relevance to their IND application.

What is contained in the database? It contains information regarding the study design and methodology, dose level, assessment vector type and manufacturing grade, species used in animal studies, route of administration, and detailed lists of analyses performed. For each study there are details on the number of animals evaluated and the dosing, as well as summary information about the results and implications of the study. The site and sponsor of the study are also listed.

Who should use the database? Investigators who have not previously submitted a pharm/tox study to the FDA will find the database an excellent educational resource. The studies can serve as examples and help identify the scope of work required for previous studies that had similar routes of administration, vector systems, and/or transgenes. A tutorial is being developed to provide additional guidance on study design and interacting with the FDA.

The database should be reviewed by anyone submitting an IND application to determine whether prior work can be used to decrease the scope (and cost) of the pharm/tox studies. For example, a review of the database may identify an

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Table 1 Current and pending studies listed in the National Gene Vector Biorepository Pharmacology/Toxicology Database

	Study	Institution	Indication	Animal (no.)	Delivery route
1	Safety and Germline Transmission of rAAV2-hAAT Vector After IM Injection in the Baboon	University of Florida	α_1-Antitrypsin deficiency	Baboon (*Papio* spp.) (10)	i.m.
2	Single Dose 6-Month Toxicity Study of Adeno-Associated Virus–Cystic Fibrosis (AAV-CFTR) Gene Vector in the Rhesus Monkey	University of Florida	Cystic fibrosis	Rhesus (16)	i.b.
3	Toxicity and Biodistribution Study of rAAV-1-CB-hAAT in New Zealand White Rabbits	University of Florida	α_1-Antitrypsin deficiency	New Zealand white rabbit (24)	i.m.
4	Toxicology and Biodistribution Study of rAAV-AAT Vectors in Rabbit Tissues	University of Florida	α_1-Antitrypsin deficiency	New Zealand white rabbit (31)	i.m.
5	Effect of HCV Infection in Safety and Efficacy of Liver Delivery of rAAV-AAT	University of Florida	Hepatitis C	Chimpanzee (6)	Portal vein
6	Single Dose Biodistribution Study of AAV-CB-AAT Comparing IM and IV Routes of Vector Administration in the C57/B16 Mouse	University of Florida	α_1-Antitrypsin deficiency	Mouse (36)	i.m. and i.v.
7	Toxicology and Biodistribution Study of AAV-Mediated Gene Therapy for Muscular Dystrophy	University of Florida	Muscular dystrophy	Mouse C57BL/6-α-SG (130)	i.m.
8	60-Day Subcutaneous Toxicity Study of Recombinant Adenovirus Expressing PDGF-B in C57B1/6 Mice.	University of Pennsylvania	Venous leg ulcer	Mouse (144)	s.q.
9	Single Dose Subcutaneous Biodistribution Study of Recombinant Adenovirus Expressing PDGF-B in C57B1/6 Mice.	University of Pennsylvania	Venous leg ulcer	Mouse (32)	s.q.
10	Single-Dose 3-Month Toxicity Study of Adeno-Associated Virus ATT Gene Vector in the C57/BL6 Mouse	University of Florida	α_1-Antitrypsin deficiency	Mouse (48)	i.m.
11	Toxicity and Vector Distribution Study in Rats Following a Single Injection into the Submandibular Duct (test article Adenovirus/AdCMVH3)	NIDR/NIH	Diabetes	Wistar rat (120)	
12	A 12-Week Toxicity Study of DNA Vaccine (pTVG-HP) Encoding Human Prostatic Acid Phosphatase (PAP) Administered Intradermally to Male Lewis Rats	University of Wisconsin–Madison	Prostate cancer	Lewis rat (75)	i.d.
13	28-Day Prechronic Toxicity Biodistribution and Transgene Expression Study in Fischer 344 Rats for Single Submandibular Gland Injections of an Adenoviral Vector Carrying the Human Growth Hormone Gene (Ad-hGH)	NIDR/NIH	Diabetes	Fischer rat (144)	
14	Evaluation of Potential Toxicity of Electroporation Mediated Delivery of a Plasmid Encoding for IL-12 in a Mouse Melanoma Model	H. Lee Moffit Center, Florida	Cancer; melanoma	Mouse (250)	s.q.
15	Dose Response of H5.001RSVTK in C57BL/6 Female Mice after Intraperitoneal Inoculation, With Ganciclovir on Days 2 to 15 Delivered Intraperitoneally (Ovarian Cancer Project)	University of Alabama	Ovarian cancer	Mouse (88)	i.p.
16	Toxicological Safety Evaluation of DNA Plasmid Vaccines Against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile Virus Is Similar Despite Differing Plasmid Backbones or Gene-Inserts	VRC/NIAID/NIH	Multiple HIV/Ebola/ ARDS/WNV	Rabbit (100)	i.m.
17	Biodistribution of DNA Plasmid Vaccines Against HIV-1, Ebola, Severe Acute Respiratory Syndrome, or West Nile Virus Is Similar, Without Integration, Despite Differing Plasmid Backbones or Gene Inserts	VRC/NIAID/NIH	HIV	Rabbit and mouse (163)	i.m.
18	Myocarditis Following Adeno-Associated Viral Gene Expression of Human Soluble TNF Receptor (TNFRII.Fc) in Baboon Hearts	University of Pittsburgh	Congestive heart failure	Baboon (*Papio anubis*) (6)	Direct heart
19	A Single-Dose 90 Day Biodistribution Study of Viral Test Article HSV-NP2 Administered Subcutaneously in BALB/C Mice	University of Pittsburgh; Diamyd	Cancer pain	Mouse (96)	s.q.
20	A Single-Dose Toxicology Study of HSV-NP2 Administered Subcutaneously in BALB/C Mice with 90 Day Follow-up	University of Pittsburgh; Diamyd	Cancer pain	Mouse (320)	s.q.
21	Canine Biodistribution Study AAV6-CMV-SERCA2a	University of Pittsburgh	Congestive heart failure	Dog (28)	Cardiac
22	Adenylyl Cyclase VI Gene Transfer for Congestive Heart Failure hAd5.hACVI	University of California, San Diego	Congestive heart failure	Yorkshire–Landrace farm pig, (*Sus scrofa*) (48)	Intracoronary

Table 1 continued on next page

Table 1 Current and pending studies listed in the National Gene Vector Biorepository Pharmacology/Toxicology Database (continued)

	Study	Institution	Indication	Animal (no.)	Delivery route
23	Final Biodistribution Report for One-Week Biodistribution Study of rAAV-RPE65 Following a Single Subretinal Injection in Cynomolgus Monkeys—0406SU20.0 AAV2	University of Florida	Retinal degeneration	Cynomolgus monkey (6)	Subretinal
24	Biodistribution Report for Three Month Biodistribution Study of rAAV-RPE65 Following a Single Subretinal Injection or Intravitreal Injection in Cynomolgus Monkeys	University of Florida	Retinal degeneration	Cynomolgus monkey (11)	Subretinal or intravitreal
25	Biodistribution of Adenovirus Type 5 and Type 35 Vector Vaccines Against Human Immunodeficiency Virus-1 (HIV-1), Ebola, or Marburg Are Similar Despite Differing Adenovirus Serotype Vector, Manufacturer's Construct, or Gene Inserts	VRC/NIAID/NIH	HIV-1; multiple	Rabbit (52)	i.m.
26	Toxicological Safety of Adenovirus Type 5 and Type 35 Vector Vaccines Against Human Immunodeficiency Virus-1 (HIV-1), Ebola, or Marburg Are Similar Despite Differing Adenovirus Serotype Vector, Manufacturer's Construct, or Gene Inserts	VRC/NIAID/NIH	HIV-1; multiple	Rabbit (181)	i.m.
27	Biodistribution of rAAV-1 in Primate Tissue	University of Florida	α_1-Antitrypsin deficiency	Rhesus macaque (6)	i.p.
P	Phase I/II Trial of Intrathoracic Delivery of Recombinant rAAV1-CBd300 GAA to the Diaphragm in Pompe Disease	University of Florida	Pompe disease	Mouse (150)	i.m.
P	Preclinical Study of AAV Mediated Gene Therapy for Pompe Disease by Direct Injection Into the Diaphragm of New Zealand White Rabbit	University of Florida	Pompe disease	Rabbit (*Oryctolagus cuniculus*) (12)	Diaphragm
P	Toxicology and Biodistribution Study of rAAV-1-CB-hAAT: Summary and Findings	University of Florida	α_1-Antitrypsin deficiency	Mouse (172)	i.m. and i.v.
P	Canine Toxicology Study AAV6-CMV-SERCA 2a	University of Pittsburgh	Congestive heart failure	Dog (28)	Direct heart
P	Direct Comparison Analysis of rAAV1 and rAAV5 Pseudotyped Vectors Using Aerosol Delivery of Firefly and *Renilla* Luciferase Reporters Co-delivered to the Lungs of Chimpanzees	University of Florida	Cystic fibrosis	Chimpanzee (8)	Bronchial aerosol
P	Toxicology and Biodistribution Study of NUREL C3 in BALB/c Mice	University of Pittsburg	Brain tumors	Mouse (420)	Intracranial

i.b., intrabronchial; i.d., intradermal; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous; NIAID, National Institute of Allergy and Infectious Diseases; NIDR, National Institute of Dental Research; NIH, National Institutes of Health; P, pending studies; s.q., subcutaneous; VRC, Vaccine Research Center.

existing study using a different transgene but a similar vector, manufacturing methodology, and route of administration. Although the FDA may require a toxicological assessment of the transgene, it might allow a limited biodistribution study based on information already on file in another IND application. The NGVB can facilitate the letter of cross-reference, and it is the expectation of NIH that letters will be provided to academic investigators for studies supported with NIH funds. For commercial entities that participate in this resource, the decision about whether to share this information is at their discretion.

The database can also serve as a resource for grant reviewers and NIH program officers to determine whether grant applicants are seeking funds for duplicative work.

A list of current and pending studies recorded in the database is provided in Table 1. The database search site can be viewed at http://www.ngvl.org/include/tox/index.php, where short abstracts of the studies can be accessed. Access to the full contents of the database can be obtained by registering with the NGVB Coordinating Center. Academic, commercial, or other interested parties are welcome to register and view the database.

The NGVB also requests that anyone involved with important gene therapy pharm/tox studies contribute to the database. The Coordinating Center can assist in uploading the information and will make the process as easy as possible. Contact information is provided on the NGVB website, https://www.ngvbcc.org.

Finally, over the next year the NGVB will be developing a variety of other support resources for gene therapy investigators, including a reagents repository, assistance with vector insertion site assays and analysis, and archiving services for FDA-monitored samples and products.