

# ROLE OF IBC IN ASSESSING NOVEL THERAPIES UTILIZING RECOMBINANT DNA

- Gene transfer, both *in vivo* and *ex vivo*
- Oligonucleotide (antisense) strategies
- Gene repair using RNA/DNA  
chimeraplasty
- Stem cell therapeutics

# SCOPE OF IBC REVIEW

- Issues relating to recombinant DNA/RNA study agents
- Risks to public, health care workers as well as to individual study subject
- Working documents include the clinical protocol, Appendix M, SOPs, informed consent document, RAC correspondence, other documents if relevant
- Design of the clinical studies is not the focus of this review
- Working knowledge of pre-clinical safety and efficacy studies is critical for risk-benefit

# COMPOSITION OF IBC

- **Two community members**
- **Professor of Genetics**
- **Professor of Infectious Diseases**
- **Professor of Veterinary Medicine**
- **Two professors of Hematology**
- **Director of Environmental Health and Safety**
- **Research administration**

# **IBC REVIEW-PROCESS**

- **Chair and Director of EHS review at outset to determine if additional documents are required for full committee review**
- **IBC and IRB interface by chairs attending other committee's review**
- **Outside expertise is assembled as required, has included virology, infection control, pharmacy, occupational health**

# ISSUES OF INTEREST TO IBC

- Objectives and rationale of study
- Structure and characteristics of the biological study agent
  - Steps used to derive construct
  - Structure and composition of materials given to patient
  - Biodistribution of vector; intended target cells
  - Methods used to verify structure of rDNA/RNA

# ISSUES OF INTEREST TO IBC

- **Pre-clinical safety and efficacy**
- **Assessment of likelihood of generating RC virus, either in production or *in vivo***
- **Risk of horizontal transmission of study agent**
- **Risk of germline transmission**
- **Informed consent document**

# ISSUES OF INTEREST TO IBC

- **SOPs for study agent handling and accountability, including ordering, shipping, receipt and storage, dispensing, and disposition of unused material**
- **Pharmacy investigational drug data sheet, including drug dosing, description, storage conditions, dispensing procedures, record keeping**

# ISSUES OF INTEREST TO IBC

- **Nursing investigational drug data sheet, including dose form and strength, procedures for handling study agent, pharmacology/pharmacokinetics, administration, adverse effects, drug interactions, and contraindications**

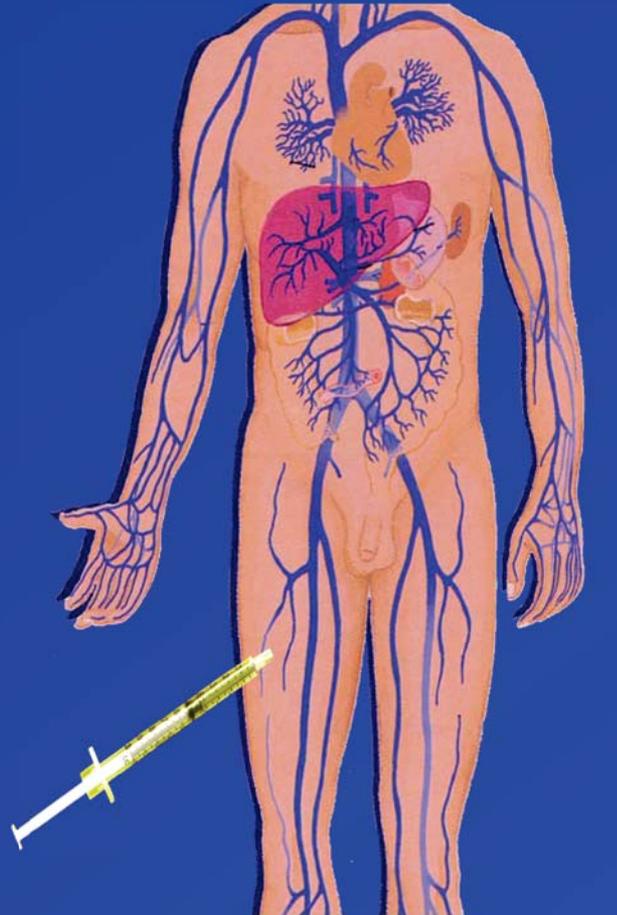
# CASE EXAMPLES

- **Development of guidelines for reducing risk of horizontal transmission of vector**
- **Pre-review of a gene transfer protocol where vector is used in a novel target tissue**
- **Education of health care workers at an off-site location**

# **DEVELOPMENT OF GUIDELINES FOR REDUCING RISK OF HORIZONTAL TRANSMISSION OF A NOVEL VECTOR**

- **Risks of vector shedding following parenteral administration of rAAV**
- **Based on pre-clinical studies in hemophilic and normal dogs, vector shedding in body fluids had been detected up to 24 hrs post-injection, but not beyond**
- **Subjects' body fluids were considered potentially infectious x 24 hrs. Standard precautions followed and pts housed in isolation rooms**

# AAV-F.IX muscle directed approach



**AAV – Factor IX  
Administration  
to skeletal muscle**

# **DEVELOPMENT OF GUIDELINES FOR REDUCING RISK OF HORIZONTAL TRANSMISSION OF A NOVEL VECTOR**

- **Serum, urine, saliva, semen and stool collected before and at serial time points after injection**
- **DNA extracted and assessed for vector sequences using a sensitive PCR assay**



# **ONGOING REVIEW OF DATA AND VALIDATION OF GUIDELINES FOR REDUCING RISK OF HORIZONTAL TRANSMISSION OF A NOVEL VECTOR**

- Results of vector shedding studies in humans confirmed animal studies and validated guidelines developed by investigators and approved by the IBC**

# CASE EXAMPLES

- **Development of guidelines for reducing risk of horizontal transmission of vector**
- **Pre-review of a gene transfer protocol where vector is used in a novel target tissue**
- **Education of health care workers at an off-site location**

# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **Administration of a vector that has been used in only a handful of studies, to a novel target tissue**
- **Previous experience with administration to this target tissue was confined to the work of these investigators at a different institution**

# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **Complex situation where vector was being produced at an academic center outside the US, with plans to move to a US commercial GMP manufacturing facility with no previous experience in manufacture of this vector**

# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **No SOPs provided for drug ordering, shipment conditions, receipt and storage, dispensing of study agent to subjects, including transport from Pharmacy, disposition of unused study agent**
- **No SOPs for procedures needed to prevent exposure of staff in pharmacy, OR, or ICU**

# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **Deficiencies in data on vector manufacture and characterization of material produced at the foreign academic center**
- **Requested that investigators supply IBC with a copy of the March 6, 2000 letter**

# **INFORMATION REQUESTED IN MARCH 6 LETTER**

- **List of all gene transfer products produced or generated in the facility**
- **List of all INDs that cross-reference this IND**
- **Lot release data and characterization for all lots used in clinical trials**
- **If lots were produced but not used, why?**
- **Summary of manufacturing QC and QA programs**

# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **Issues of greatest interest to the IBC**
  - **Stability studies on lot to be used at CHOP, including date of manufacture and serial studies of potency at intervals since manufacture under storage conditions used**
  - **Methods for assaying lot to lot variability of potency of vector**
  - **Particle:infectious unit ratio for all lots**

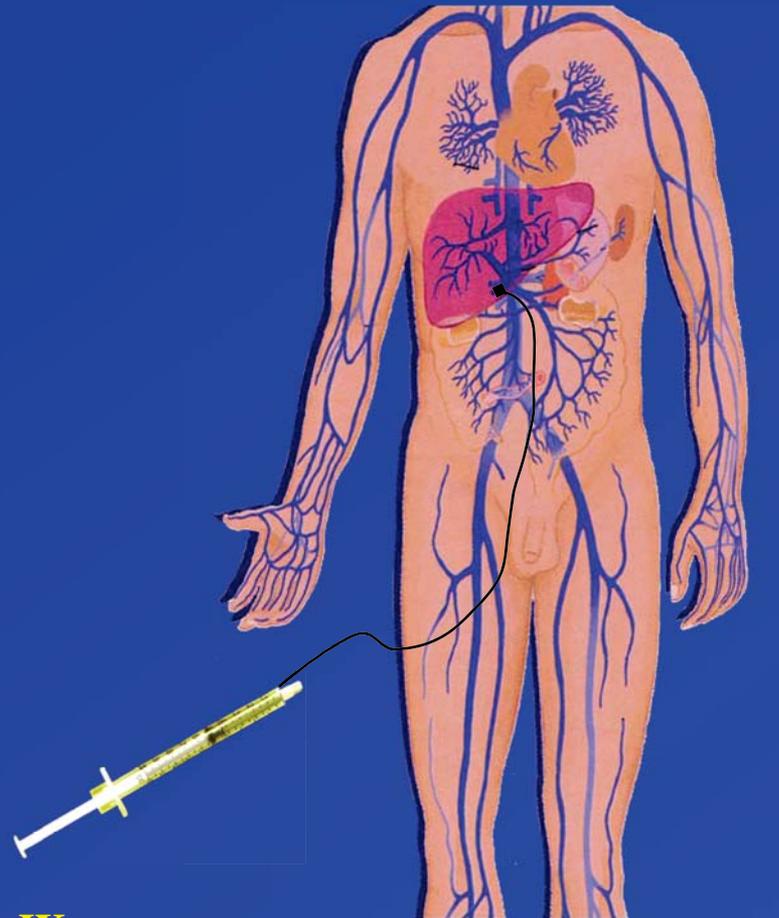
# **PRE-REVIEW OF A PROTOCOL INVOLVING USE OF A VECTOR IN A NOVEL TARGET TISSUE**

- **Recommended that a new Appendix M be submitted when manufacturer was changed from foreign academic medical center to US commercial facility manufacturing this vector for the first time**

# CASE EXAMPLES

- **Development of guidelines for reducing risk of horizontal transmission of vector**
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# AAV-F.IX liver-directed approach via arteriography



**AAV – Factor IX  
Administration  
to Liver via Hepatic Artery**

# **RESPONSIBILITIES OF IBC FOR PROTOCOLS CONDUCTED PARTLY OFF SITE**

- **Recombinant AAV vector is administered via hepatic artery either at Stanford or CHOP**
- **Subjects followed at treating hospital for first 3-5 days**
- **Additional follow-up, including collection of body fluids, is carried out at home hemophilia treatment center**

# **RESPONSIBILITIES OF IBC FOR PROTOCOLS CONDUCTED PARTLY OFF SITE**

- **OBA requested that CHOP IBC oversee part of protocol conducted at outside hemophilia centers**
- **Only safety issue, potential hazards to persons other than those being treated, i.e. are there precautions required to prevent spread of vector to other persons**
- **Based on pre-clinical studies, advised use of standard precautions**



# **Information sheet for health care workers**

- **Health care workers advised to maintain standard precautions when collecting samples on study**

# Subject A: Semen Analysis

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	BL	W1	W2	W3	W4	W5	W6	W7	W8	W10	W12	W14
Total Semen	Neg	Pos	Pos	Pos*	Pos	Pos	Pos	Pos	Neg	Pos	Neg	Neg

\* Week 3 sample fractionation: Motile sperm negative, seminal fluid positive, total semen positive

# **Information sheet for health care workers**

- **Health care workers advised to maintain standard precautions when collecting samples on study**
- **Subjects enrolled in trial should be advised to practice barrier contraception until they have been advised that semen is negative for vector sequences**

# **KEY FEATURES OF IBC FUNCTION**

- **Appropriate scientific and regulatory expertise**
- **Mechanisms to facilitate assembly and review of data that allow guidelines and SOPs to be validated and revised if necessary**
- **Working knowledge of organization and function of the clinical environment within the institution**
- **Knowledge of changing regulatory environment**