Human Gene Transfer: Single Subject Protocols and Vaccine Exemption Under the *NIH Guidelines*

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Overview

- Definition of Human Gene Transfer under the NIH Guidelines
- Single Subject Protocols: Where do they Fit?
- Vaccine Exemption: What is in and what is not?

Human Gene Transfer

- Section III-C-1: Experiments involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA derived from Recombinant DNA, into One or More Human Research Participants
  - No requirement for active expression of transgene
  - Transferred nucleic acids need only to be derived from rDNA
  - Applies to research with one subject

Single Subject Protocols

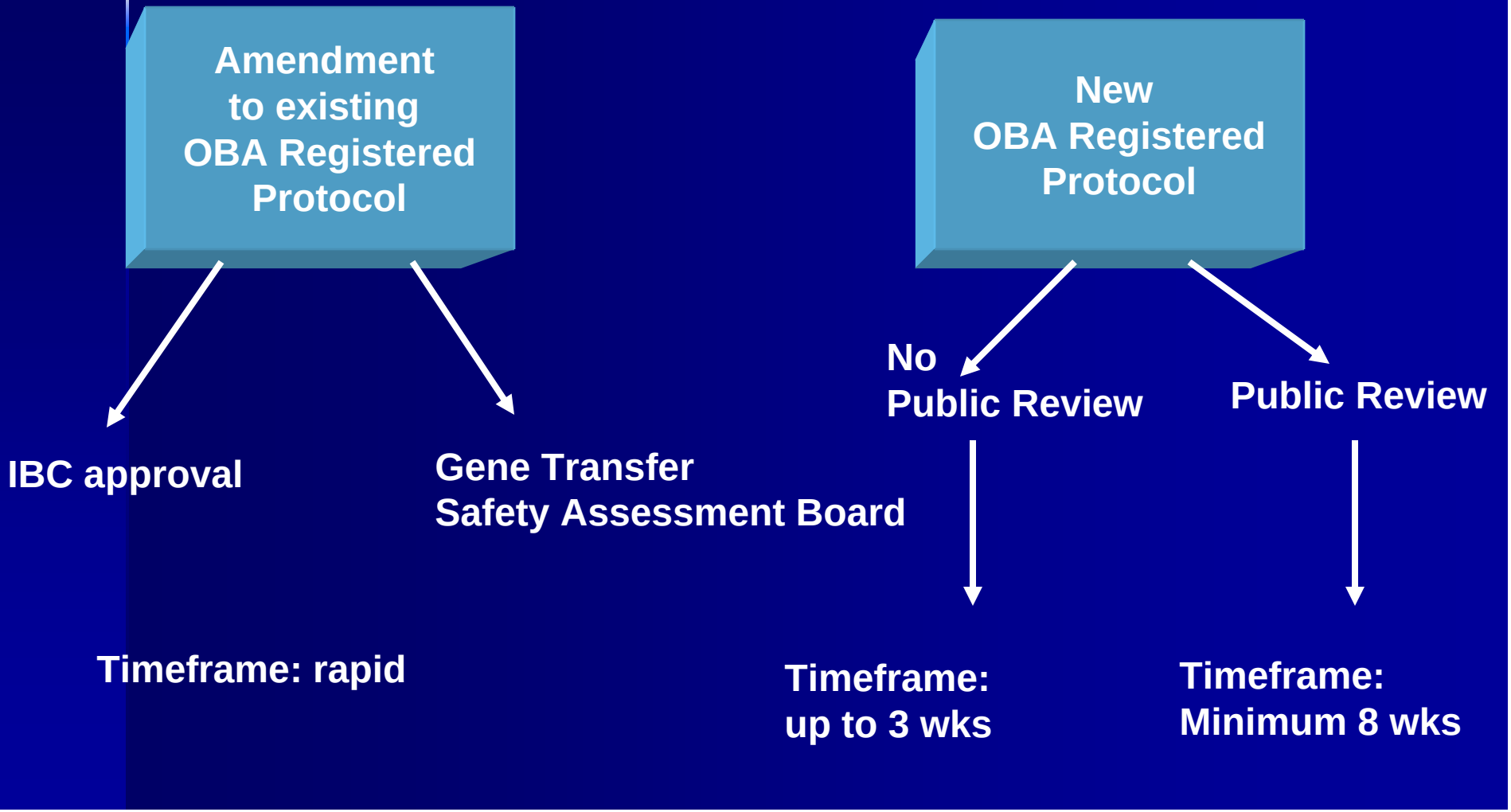
- Exemptions to reviewed protocol design
- Involve judgments about the suitability of gene transfer for an individual patient based on their unique clinical circumstances
- Usually Time Sensitive

RAC Review of Human Gene Transfer Protocols

- The RAC is an advisory body to NIH
- The RAC does not approve or disapprove protocols
- The RAC's primary focus is on research, including protocol design and safety
- The RAC process has mandated time frames

Current OBA Process

Single Subject Submissions



Single Subject Protocols 2003 - 2008

- 17 Notifications of approvals for redosing/minor deviations treated as amendments to existing protocols
- 23 New clinical protocols under IND
  - 18 Treated as amendment
  - 5 Treated as a new protocol
    - 2 used vectors that were not novel but disease indication significantly different from OBA registered trial
    - 3 novel vectors

Criteria for determining whether to Process as an Amendment

- Same vector has been used in a research protocol the RAC had the opportunity to review
- In almost all cases the parent protocol, modified as needed, is used for the single subject
- The decision to proceed for this individual patient is largely based on a clinical decision weighing the clinical risk/benefits
- OBA can consult with the clinicians on the RAC and provide feedback in a timely manner to the PI and IBC

When is it Likely to be Reviewed as a New Protocol?

- Vector not currently being used in OBA Registered Gene Transfer Protocol
- Significant difference in target disease or route of delivery that raise new safety issues
- At the request of PI or Sponsor

Single Subject Protocols

- The majority of single subject protocols will continue to be treated as amendments but certain single subject protocols will become new OBA registered protocols and sent for full RAC review
- When a protocol is treated as an amendment, OBA will consult with members of the RAC as needed and provide timely feedback to investigator
- If determined to be a new protocol, it will undergo initial RAC review and comments received from individual RAC members will be transmitted by OBA to PI, IBC, IRB and FDA

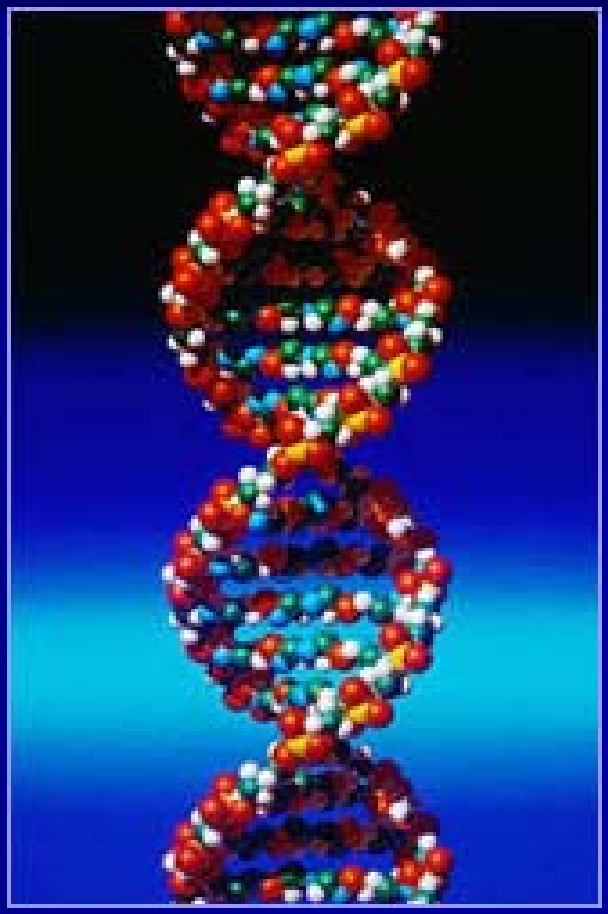
Single Subject Protocols

- Full RAC review and discussion at a public meeting will likely be the exception, *but it important to submit these protocols for review to OBA to determine whether it will be a new protocol or an amendment*

IBC Responsibilities

- If a new clinical protocol is submitted for IBC Review
  - Has the investigator notified OBA and a determination been made about whether this should be handled as a new submission or an amendment to an existing NIH OBA registered trial?

Vaccines and the *NIH Guidelines*



"Vaccine Exemption"

- **Section M-VI-A :** Human studies in which induction or enhancement of an immune response to a vector encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, are exempt from **Appendix M-I**, *Requirements for Protocol Submission, Review and Reporting – Human Gene Transfer Experiments*.

History of Amendment

- Adopted in 1994.
- Designed to foster the rapid development of vaccines against infectious agents with significant public health impact.
- Adopted at a time when HIV was an emerging infection and making new therapeutic options, including vaccines, available quickly was a public policy priority.

Examples of Studies that OBA has Determined Fall under Vaccine the Exemption

- *Phase I Study of the safety and Immunogenicity of rDEN3/4Δ30(ME), a Live Attenuated Virus Vaccine Candidate for the Prevention of Dengue Serotype 3*
  - attenuated virus
  - prevention of dengue infection
- *A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiple Strain Ebola Plasmid Vaccine, VRC-EBODNA012-00-VP, in Adults Volunteers*
  - plasmid vector
  - prevention of infection by Ebola

Examples continued

- *A Phase I, Randomized, Double-Blind Study to Evaluate the Tolerability, Safety, and Immunogenicity of LC002, a DermaVir Vaccine, in HIV-1-Infected Subjects Currently Under Treatment with Highly Active Antiretroviral Therapy (HAART)*
  - plasmid vector
  - individuals infected with HIV

What is not Included?

- The use of recombinant adjuvants (i.e. those expressed from a recombinant molecule) designed to boost the immune response, e.g. IL-12, even if combined with vector encoded immunogen
  - The adjuvant is not considered a vector encoded microbial immunogen

What is not Included ?

- The use of integrating vectors, such as lentiviral and retroviral vectors
  - Persistence of the vector encoded immunogen is expected

Cancer Vaccine Protocols: Where do we draw the Line?

- Human studies in which induction or enhancement of an immune response to a vector encoded microbial immunogen is the major goal . . .

Human Pampillomavirus Immunotherapy

- Transgene typically encodes polypeptides derived from the E6 and/or E7 genes of HPV strains 16 and/or 18.
- HPV 16 and 18 infection are responsible for the majority of cervical cancers worldwide
- The HPV transforming proteins, E6 and E7 have been shown to be the main contributors to the development of cancer of the cervix and cervical intraepithelial neoplasia (CIN)
- CIN 2 lesions may reveal low levels of E6 and E7 expression with replication episomally
- CIN 3 lesions (and invasive cancer) often display high level expression of E6 and E7, more often with integration of viral DNA into the host genome

HPV Protocols Registered with OBA

- OBA 595: A Phase I/II Clinical Trial of pNGVL4a-Sig/E7(detox)/HSP70 for the Treatment of Patients with HPV16+ Cervical Intraepithelial Neoplasia 2/3 (CIN2/3)
  - Vector: DNA plasmid with HPV 16 E7 cDNA with 2 point mutation to generate non-functional protein
  - Primary Endpoint: Evaluate feasibility and toxicity of vaccine
  - Secondary Endpoint: Evaluate changes in lesion size, HPV viral load and cellular and humoral immune response to vaccine

HPV Protocols, cont.

- OBA 592: A Phase I Study to Determine the Safety and Immunogenicity of Vaccination with Listeria monocytogenes Expressing Human Papilloma Virus type 16 E7 for the Treatment of Progressive, Recurrent and Advanced Squamous Cell Cancer of the Cervix
  - Vector: Listeria monocytogene containing cDNA for HPV 16 E7
  - Study Population: Patients with progressive, recurrent or advanced SCC of cervix that is metastatic or unresectable
  - Primary endpoint: Safety and feasibility
  - Secondary endpoint: Type of immunity induced and relationship to the number of organisms delivered in the vaccine and to monitor for survival
  - Reviewed publicly by the RAC in December 2003

Protocols that Use Oncogenic Viral Antigens

- The primary goal is to generate an immune response to an antigen, *however*, because the transgene is derived from an known viral oncogene and the major goal is to treat precancerous or cancerous lesions, these protocols are analogous to cancer vaccines and do not fall within the intent of the Vaccine Exemption under Section M-VI-A of the *NIH Guidelines*

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