

SV40 and Polio Vaccines

William M. Egan, Ph. D.

Deputy Director

Office of Vaccines Research and Review

CBER, FDA

The Presence of SV40 in Polio Vaccines

- SV40 in monkey kidney cells and vaccine seeds
 - Sweet and Hilleman, *Proc. Soc. Exp. Biol. Med.*, **105**, 420 (1960)
- SV40 not completely inactivated by formalin treatment used for IPV vaccine
 - Gerber, Hottle, and Grubbs, *Proc. Soc. Exp. Biol. Med.*, **108**, 205 (1961)

SV40 and Tumors in Hamsters

- Rhesus Monkey Kidney Cell Extracts can induce tumors in hamsters
 - Eddy, Borman, Berkeley, and Young, *Proc. Soc. Exp. Biol. Med.*, **107**, 191 (1961)
- Oncogenic Substance in Cell Extracts is SV40
 - Eddy, Borman, Berkeley, and Young, *Virology*, **17**, 65 (1962)

SV40 Tumor Induction

- Tumor incidence dependent on age
 - Newborns (96%)
 - 7 Days (60%)
 - 1 month (23%)
 - 3 months (0%)
- Tumor incidence dependent on virus dose
 - 320,000 TCID₅₀ (96%)
 - 3,200 TCID₅₀ (18%)
 - 32 TCID₅₀ (0%)
 - 1000 TCID₅₀ (12%)

Girardi, Sweet, and Hilleman, *Proc. Soc. Exp. Biol. Med.*,
112, 662 (1963)

SV40 Tumor Induction (cont'd)

- Tumor incidence dependent serologic response to SV40
 - SV40 + pre-immune serum (96%)
 - SV40 + immune serum (0%)
- Tumor incidence diminished in SV40 immunized hamsters

Girardi, Sweet, and Hilleman, *Proc. Soc. Exp. Biol. Med.*, **112**, 662 (1963); Goldner, Girardi, Larson, and Hilleman, *Proc. Soc. Exp. Biol. Med.*, **117**, 851 (1964).

Epidemiological Studies

- No detectable increase in cancer risk in vaccinated children
 - Fraumeni, Ederer, Miller. *J. Amer. Med. Assoc.*, 185, 713 (1963); Mortimer, Lepow, Gold, Robbins, Burton, and Fraumeni, *New Engl. J. Med.*, **305**, 1517 (1981)
- NINDS Study of Pregnancies: increased risk to offspring of pregnant women immunized with IPV (relative to OPV or influenza)
 - Heinonen, Shapiro, Monson, Hartz, Rosenberg, and Slone, *Int. J. Epidemiol.*, **2**, 229 (1973)

SV40 in IPV and OPV

- "... no lots of poliomyelitis vaccine will be released in the absence of negative results of a valid tissue culture test for SV40." Roderick Murray memorandum of 6/30/61 to manufacturers of IPV
- "The seed material for each strain shall be demonstrated to be free of extraneous microbial agents." [42 CFR Part 73.110(3)]

Human Immune Response to SV40 in IPV and OPV

- **IPV induced a serum immunological response to SV40**
 - Sweet and Hilleman, *Proc. Soc. Exp. Biol. Med.*, **105**, 420 (1960); Magrath, Russell, Tobin, *Brit. Med. J.*, 287 (1961).
- **Intranasal administration of SV40 leads to immune response**
 - Morris, Johnson, Aulisio, Chanock, and Knight, *Proc. Soc. Exp. Biol. Med.*, **108**, 56 (1961)
- **SV40 in OPV: Sv40 is excreted; no immune response**
 - Melnick and Stinebaugh, *Proc. Soc. Exp. Med. Biol.*, **109**, 965 (1962).

1997 PHS Workshop on SV40

- Several epidemiological studies from the US and Sweden indicated no increased risk for cancer among recipients of SV40 containing IPV
- PCR analysis of OPV samples for SV40 sequences were negative

SV40-related Issues

- What is the role, if any, of SV40 in the development of the various tumors in which it has been detected? Is the presence of SV40 causal or coincidental in these tumors? The similarity in the types of tumors caused by SV40 in hamsters and the tumors in which SV40 sequences have been found in humans is suggestive of a causal link. Is there a similarity in mechanism between the hamster and human tumors and SV40? For example, is the amount of virus found in the respective tumors the same?

SV40 Related Issues (cont'd)

- To what extent is SV40 circulating in the human population? How did the individuals in whom SV40 has been detected in their tumors become infected with SV40? Is there a vertical or horizontal transmission of SV40, or both?

SV40 Related Issues (cont'd)

- To what extent, if any, was SV40 circulating in the human population prior to the introduction of polio vaccines? If SV40 was always in the population, did the polio vaccine exacerbate the consequences? In this regard, a further question arises: can we examine archived (pre 1955) tumor samples and serum samples to look for SV40?