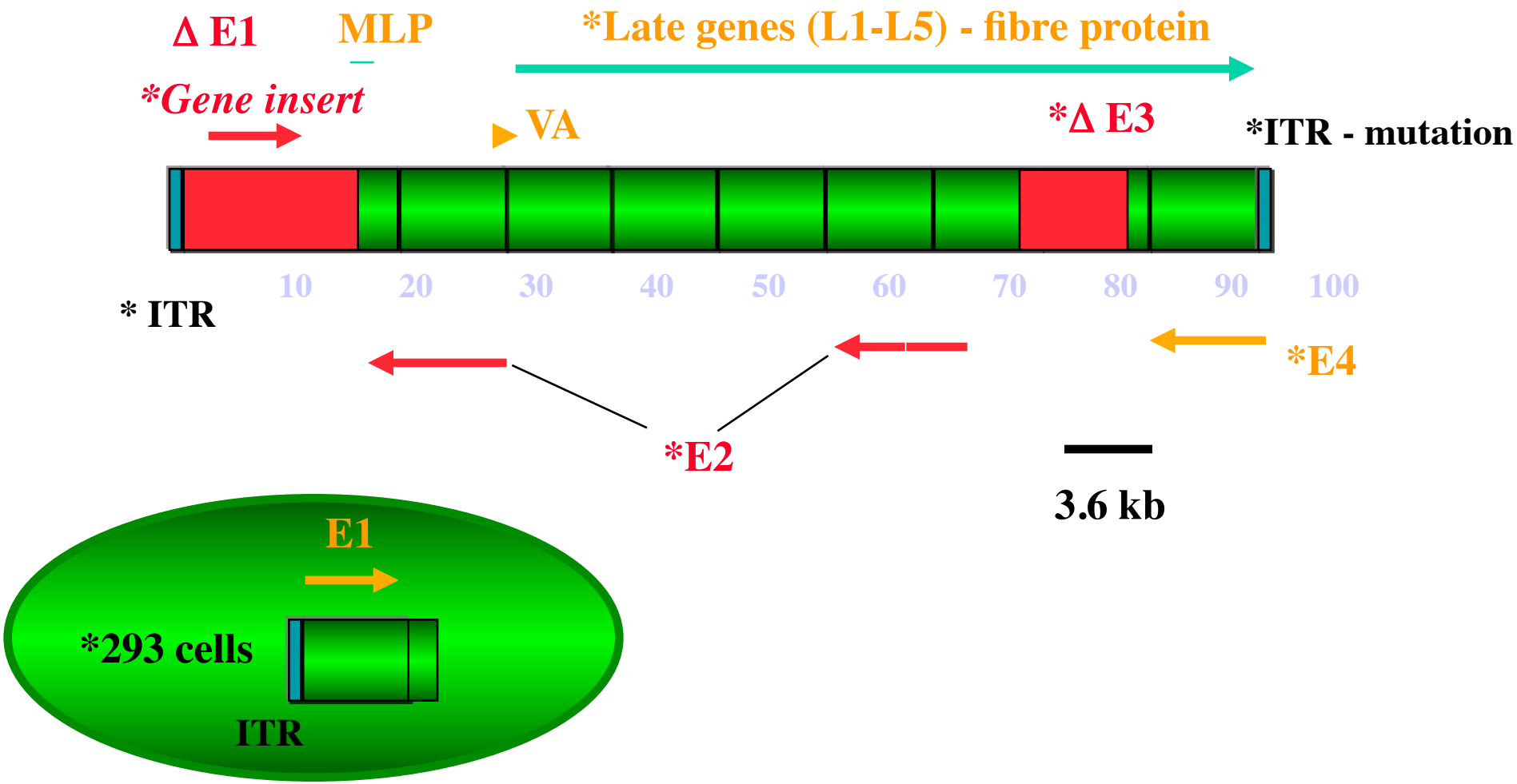
2nd generation adenoviral vectors



Adeno-death
(clinical trials Wilson)

- 18 year old boy
- To correct ornithyne transcarbamylase deficiency (OCT), a metabolic disease that can induce ammonia accumulation in the body
- Ad-OCT 3.8 x10e13 2nd generation vector (E1-deleted, E2A-temperature-sensitive) in the hepatic artery
- Patient dyes 4 days after injection

Why?

CLINICAL TRIALS

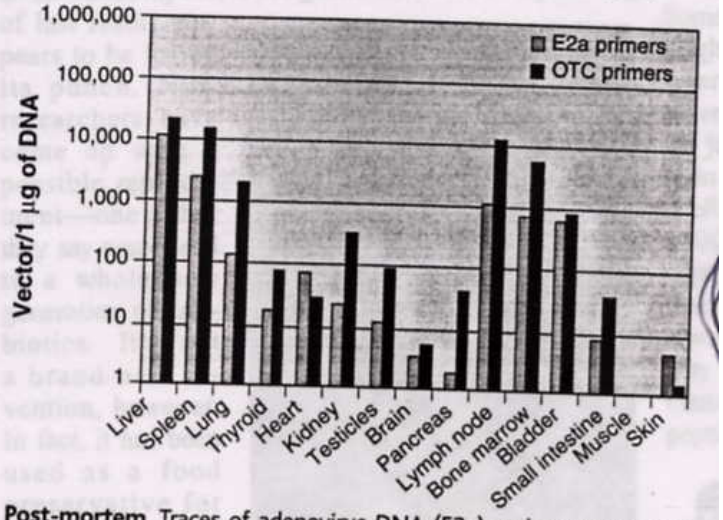
Gene Therapy Death Prompts Review of Adenovirus Vector

For the past 3 months, one-third of the 250 faculty and staff members connected with the University of Pennsylvania's Institute for Human Gene Therapy have been studying a single case. They've been trying to understand why Jesse Gelsinger, a relatively fit 18-year-old with an inherited enzyme deficiency, died on 17 September, 4 days after doctors at Penn injected a genetically altered virus into his liver.

Gelsinger was the first patient in a gene therapy trial to die of the therapy itself, as James Wilson, who heads the Penn institute, confirmed at a public meeting last week. His death is the latest blow to a field that has been struggling to live up to the promise and hype surrounding the first gene therapy trials a decade ago. And Penn isn't the only one investigat-

Gelsinger had died. It was a tense session.

After releasing stacks of clinical data and answering questions for 2 days, however, Wilson and colleagues said that they didn't fully understand what had gone amiss. They report-



Post-mortem. Traces of adenovirus DNA (E2a) and a curative gene (OTC) it carried turned up in many tissues outside the patient's target organ, the liver.

Science 1999 Marschall

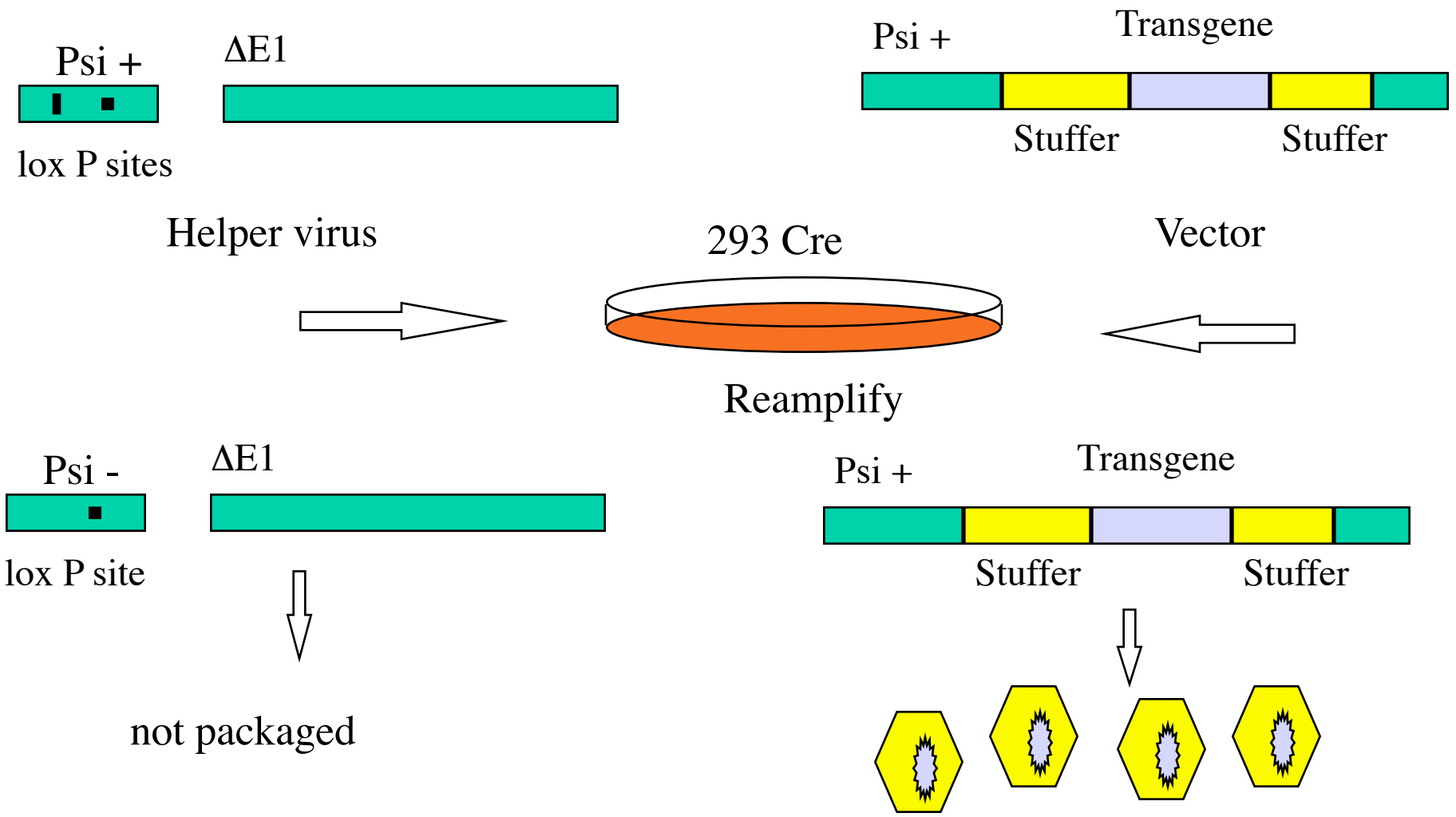
Sanctions agreed over teenager's gene therapy death

- 5 year investigation
- According to an investigation by the university, Gelsinger died from an immune reaction to the adenovirus vector.
- The justice department alleged that the researchers and their institutions made false statements regarding the safety of the trial to the National Institutes of Health, the Food and Drug Administration, and the institutional review board that oversaw the research.
- 3 researchers will pay 1 million $
- The terms of the settlement state that a monitor will supervise Wilson's work in humans for three years, and he will be allowed to conduct only one trial at a time. Any of Wilson's animal research that could affect patient safety will also be supervised
- Wilson : retraining for clinical trial, clinical trials in 2010

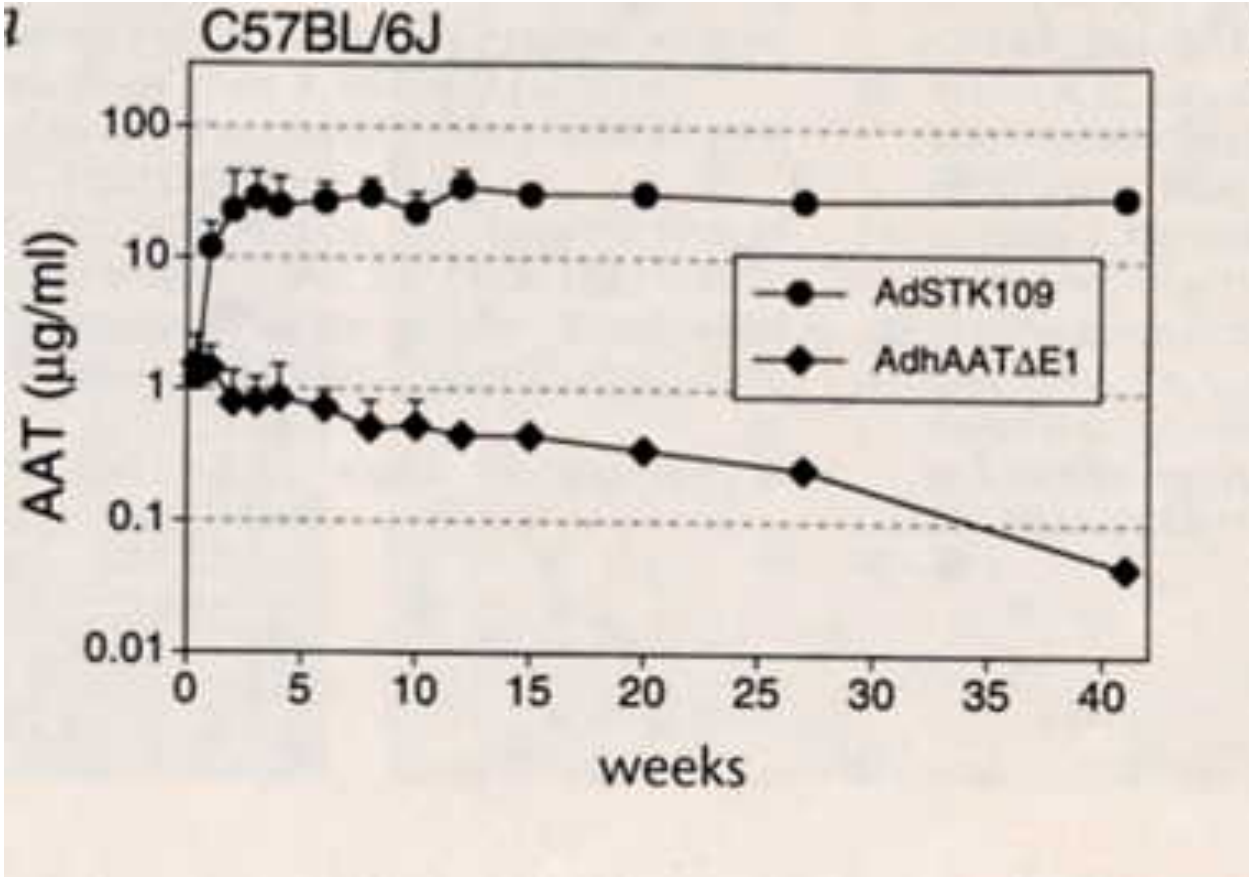
Nature, 2005

http://www.nih.gov/catalyst/2000/00.01.01/page1.html

3rd generation Ad- vectors

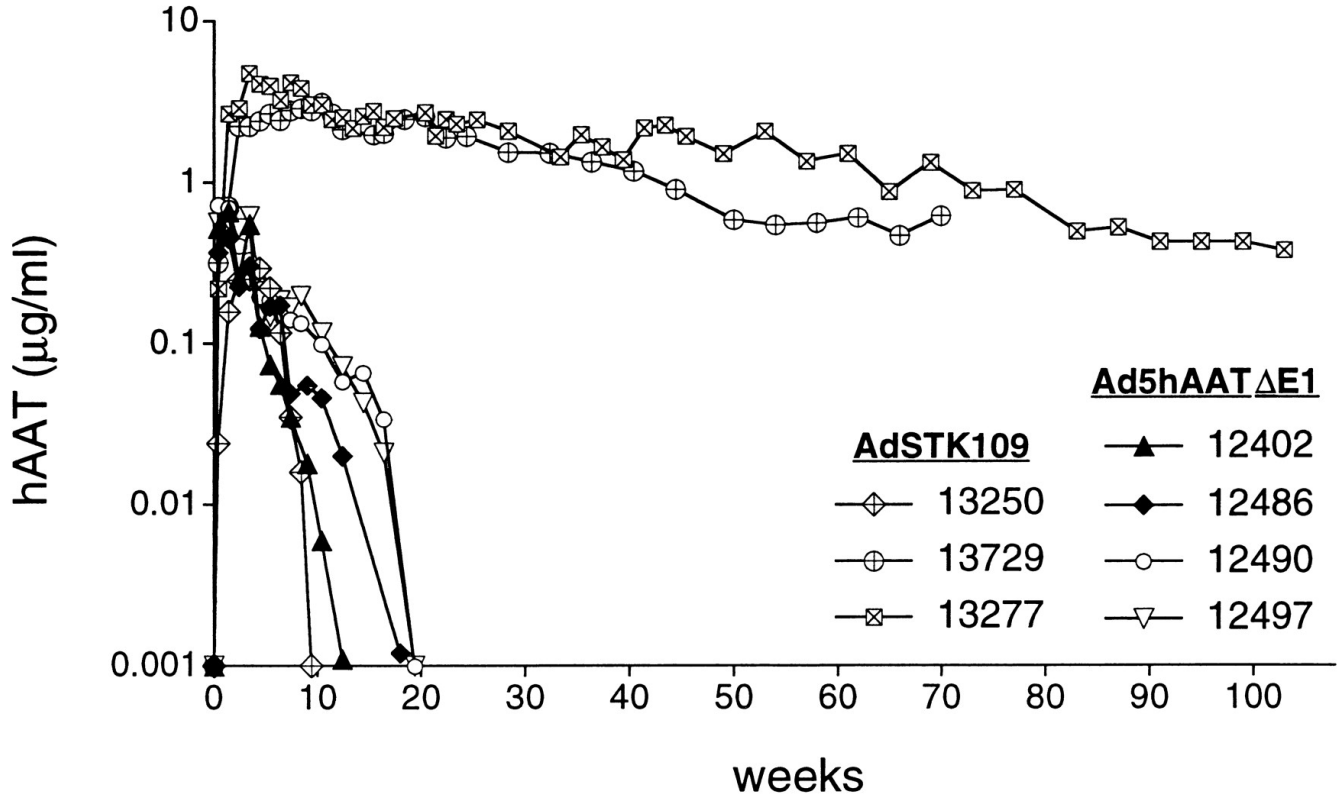


Ad gutless in mice



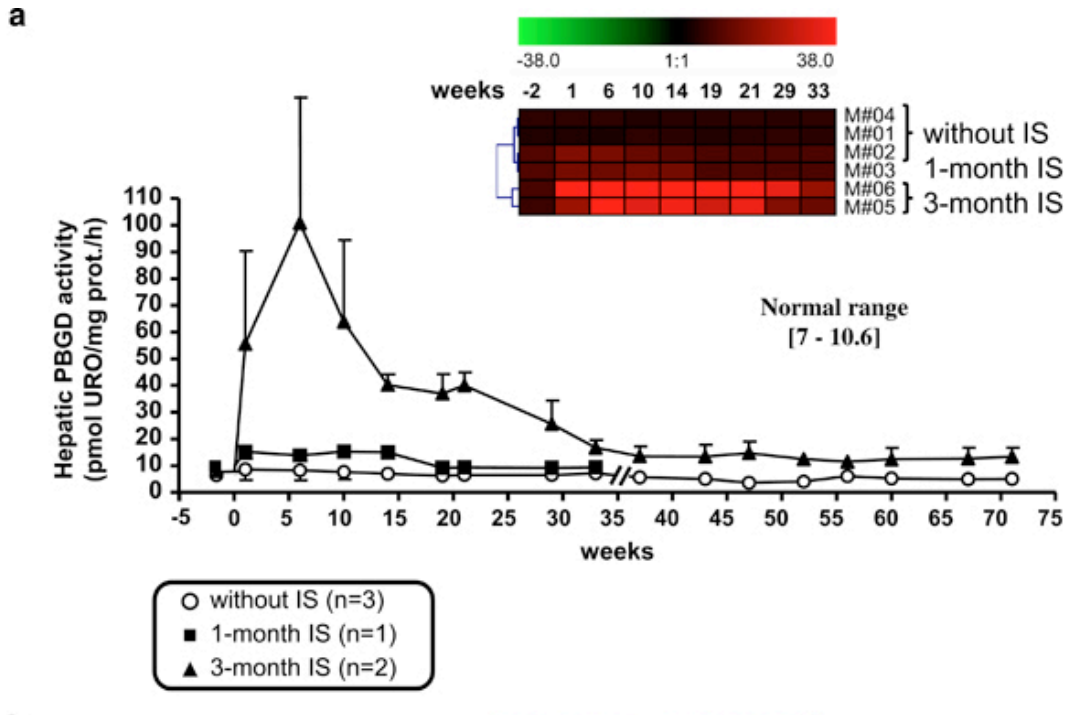
Shiedner et al Nat Gen 1998

Ad gutless in baboons



Morral et al PNAS 99

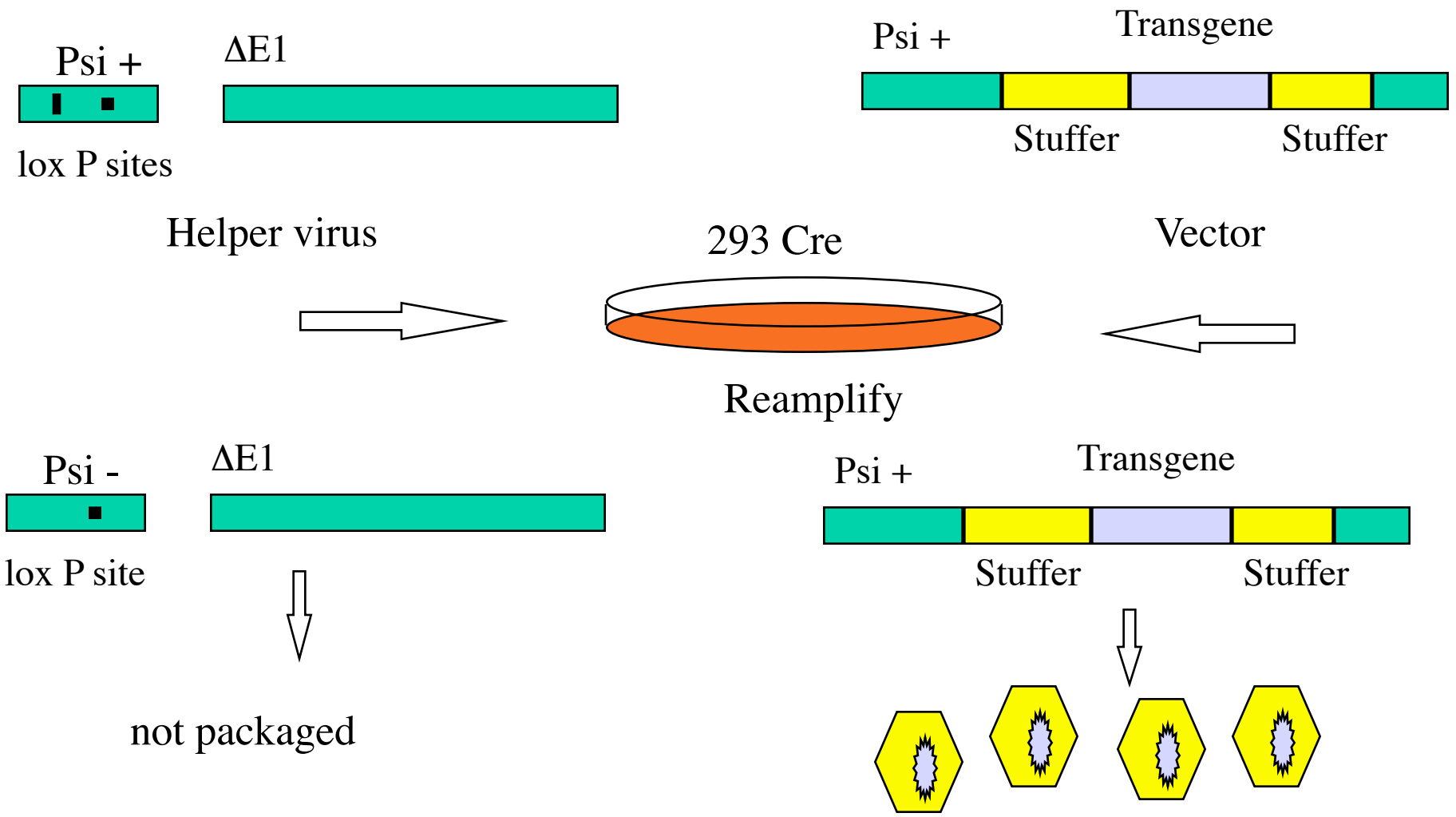
Ad gutless in primates – porphyria disease



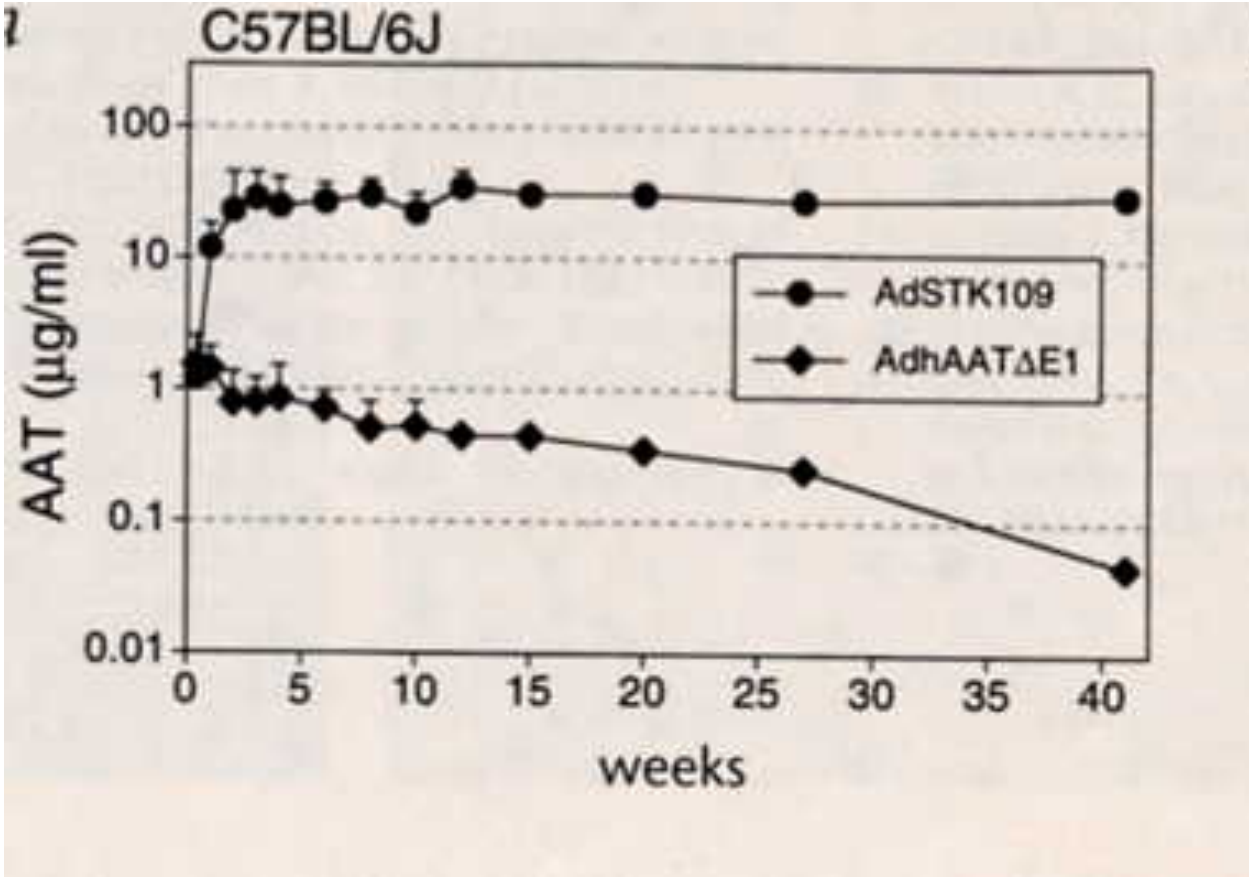
Helper-dependent adenovirus achieve more efficient and persistent liver transgene expression in non-human primates under immunosuppression

Gen Ther Unzu et al 2015

3rd generation Ad- vectors

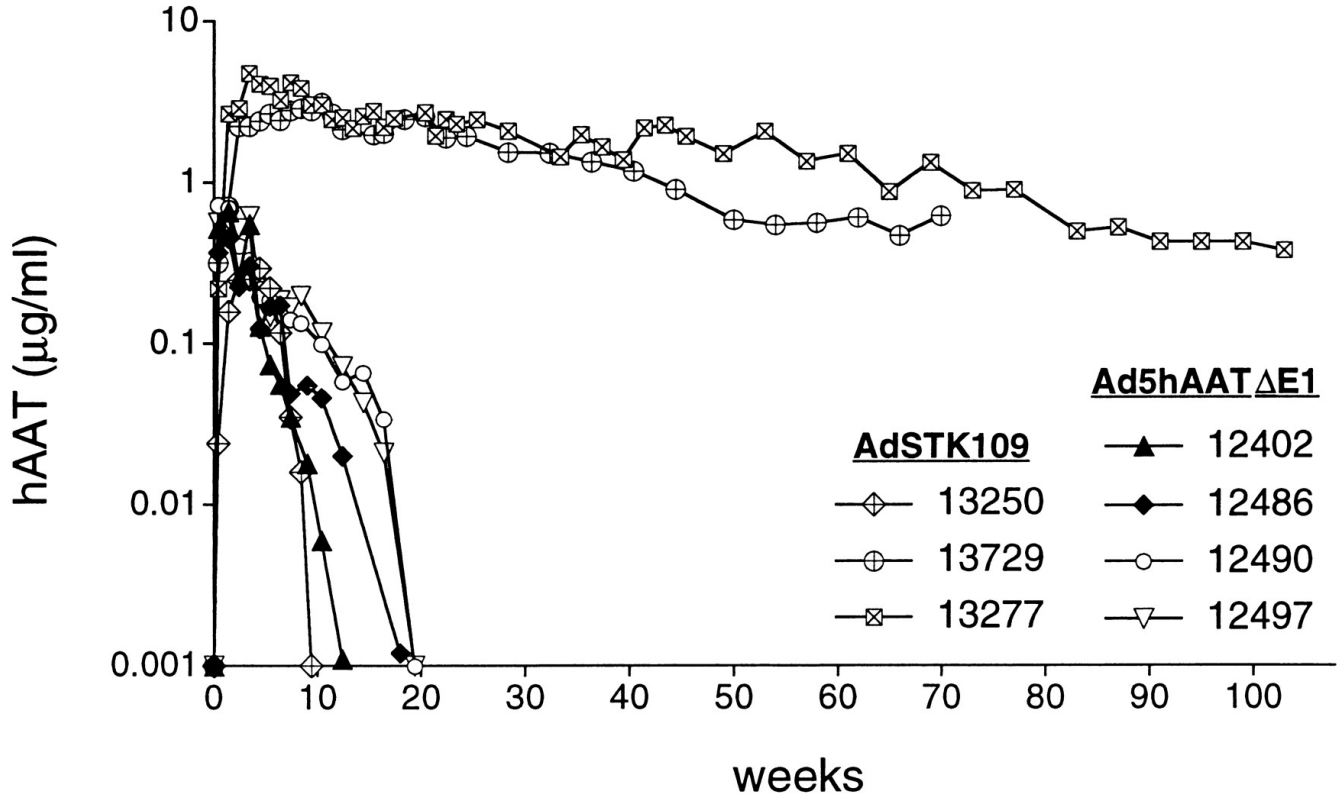


Ad gutless in mice



Shiedner et al Nat Gen 1998

Ad gutless in baboons



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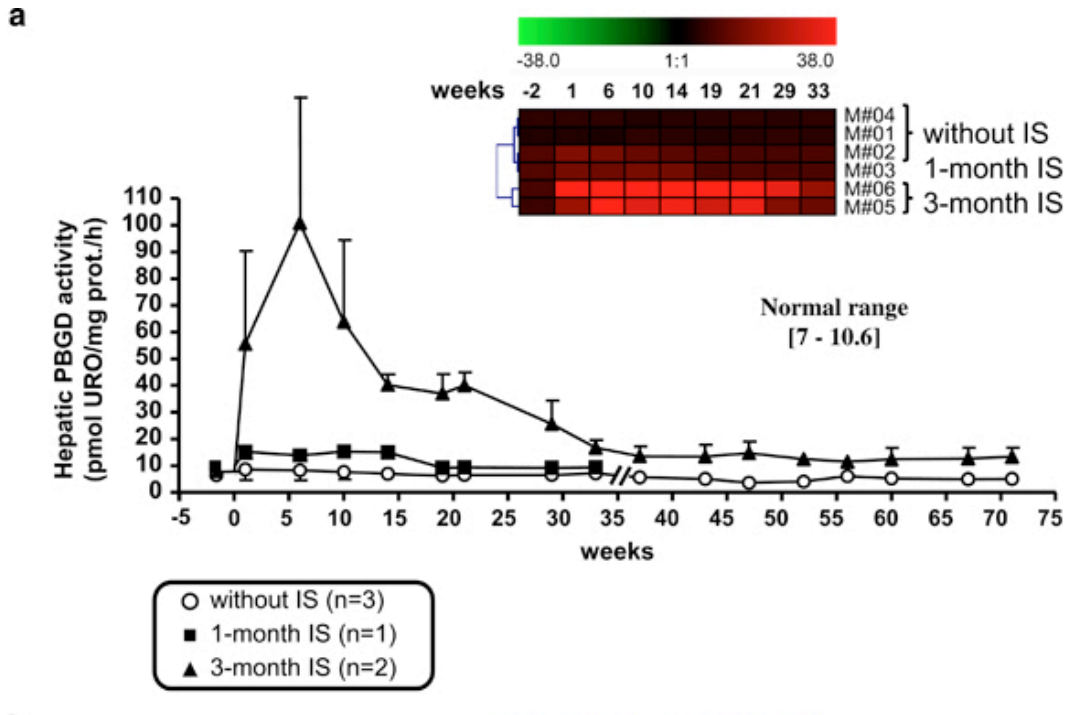
Ad gutless in primates – porphyria disease



Helper-dependent adenovirus achieve more efficient and persistent liver transgene expression in non-human primates under immunosuppression

Gen Ther Unzu et al 2015

Adenovirus and vaccination

Attenuated adenovirus expressing
Gag, nef, pol immunogens.

Ongoing Trials: Phase II

Protocol Number	Status as of December 2007	Prime			
		Class	Producer	Product	Adjuvant
HVTN 502/Merck 023 (Step) (n=3000)	Closed to accrual	Nonreplicating adenoviral vectors (clade B Gag-Pol-Nef)	Merck	MRKAd5 trivalent	

Adenovirus and vaccination

Higher infection

anti-Ad5 antibody titer	HIV incidence rate (%) vaccine	placebo
<18	4.0	4.0
19 – 200	4.4	2.2
201 – 1000	6.1	3.0
>1000	4.4	1.2

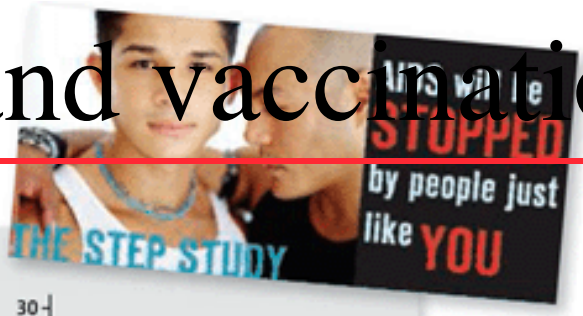
Table 3. HIV incidence rates during STEP trial. *This table shows the HIV incidence observed in vaccine and placebo recipients during the STEP trial, according to Ad5 antibody titer.*

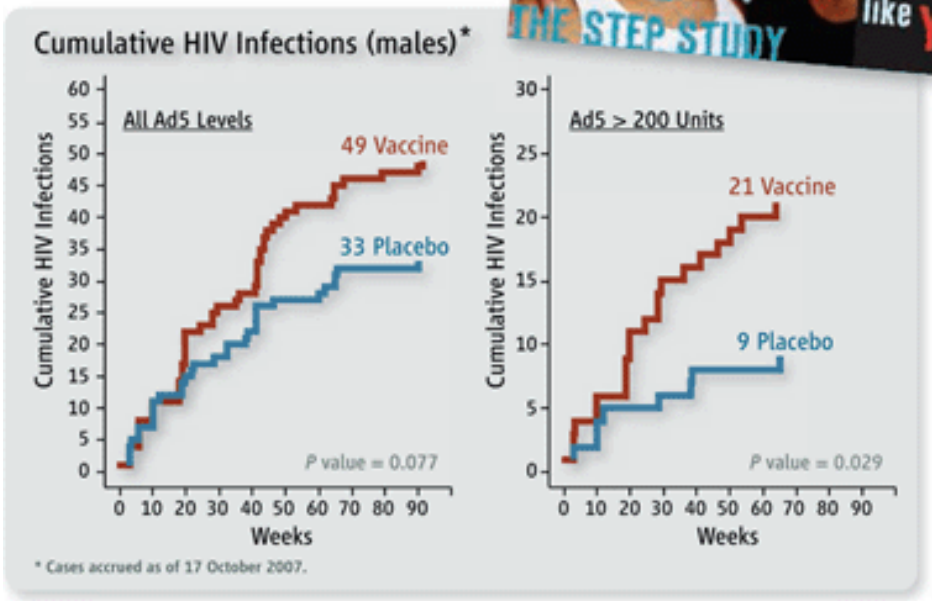
	Ad5 antibody titer			
	<18	<18<Ad5≤200	200<Ad5≤1,000	Ad5>1,000
Vaccine	20/382	8/140	14/229	7/163
Placebo	20/394	4/142	7/229	2/157

Table 1. Number of HIV infections according to Ad5 antibody titer. *Number of HIV-infected individuals, out of the total number of vaccine and placebo recipients, according to increasing Ad5 antibody titer. This data, from the post-hoc analysis of the STEP trial, was presented at the HVTN meeting by Mike Robertson of Merck.*

Adenovirus and vaccination

science





Two prominent hypotheses have emerged to explain the observed trend of increased HIV infections among some vaccinated Step participants: the first suggests that rAd5 activates memory Ad5-specific CD4 T cells in Ad5-seropositive individuals, expanding the potential targets for incoming HIV virions; the second suggests that preexisting nAb to Ad5 can form immune complexes with an rAd5 vaccine vector and promote infection of target CD4 T cells with HIV.

2010

Adenovirus and vaccination

BBC NEWS

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Last Updated: Friday, 21 September 2007, 21:52 GMT 22:52 UK

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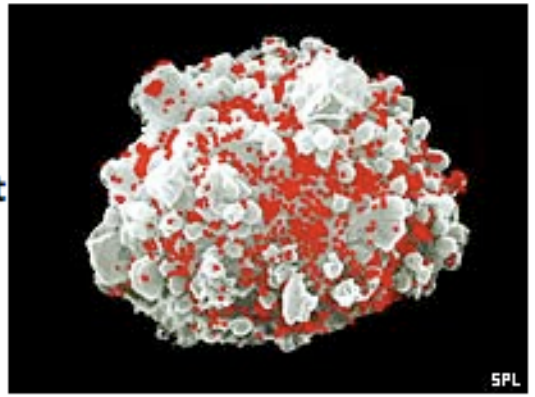
Merck abandons HIV vaccine trials

International drug company Merck has halted trials on an HIV vaccine that was regarded as one of the most promising in the fight against Aids.

Merck stopped testing the vaccine after it was judged to be ineffective.

In trials, the vaccine failed to



The vaccine was loaded with copies of three HIV genes

Simian Adenovirus

Science Translational Medicine Integrating Medicine and Science

2012

GENE THERAPY

Vaccine Vectors Derived from a Large Collection of Simian Adenoviruses Induce Potent Cellular Immunity Across Multiple Species

Stefano Colloca[1,*], Eleanor Barnes[2,3,*], Antonella Folgori[1], Virginia Ammendola[1], Stefania Capone[1], Agostino Cirillo[4,†], Loredana Siani[1], Mariarosaria Naddeo[1], Fabiana Grazioli[1], Maria Luisa Esposito[1], Maria Ambrosio[1], Angela Sparacino[1], Marta Bartiromo[1], Annalisa Meola[4], Kira Smith[2], Ayako Kurioka[2], Geraldine A. O'Hara[5], Katie J. Ewer[5], Nicholas Anagnostou[5], Carly Bliss[5], Adrian V. S. Hill[5], Cinzia Traboni[1], Paul Klenerman[2], Riccardo Cortese[1,6] and Alfredo Nicosia[1,6,‡]

EMERGENZA SANITARIA

Ebola, dall'Italia 10 mila dosi di vaccino per la sperimentazione in Usa

Falsa la notizia che l'Oms sarebbe intenzionata a chiedere una commessa di un milione di vaccini alla Okairos (che ha laboratori a Napoli) e all'Irbm di Pomezia

di Redazione Online Roma

ROMA — Le prime notizie su uno dei vaccini contro il virus Ebola si erano diffuse alla vigilia dell'estate e allora i riflettori si erano accesi su Okairos, con sede in Svizzera e laboratori a Napoli (presso Ceinge) e a Pomezia (in joint venture con l'Irbm Science Park). Circa 10mila dosi del prodotto saranno