

Docket # 2005D-0047

E-mail message

From: SherylBuster@webtv.net(Jesse Creel)
Date: Thu, May 19, 2005, 11:22am
To: SherylBuster@webtv.net (Jesse Creel)
Subject: Comments on DNA Vaccines: FDA Considerations/ Guidance for Industry

Dear Joseph L. Okrasinski, Jr,
Center for Biologics Evaluation and Research (HFM-17) FDA 1401 Rockville Pike
Rockville, MD 20852-1448

First let me apologize for the late date of this letter.

Regarding the FDA request for comments:
"Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious
Disease Indications."

Address:<http://www.fda.gov/cber/gdlns/plasdnvac.htm>

I submit the following:

Upon reading (The Scientist :: May 17, 2005 HIV-1 induces RNA silencing), attached below, some thoughts of possible importance for DNA Vaccine development came to mind:

1a) Could HIV-1 siRNA present a problem for HIV-1 DNA Vaccine development, possible siRNA silencing actions on the RNA transcripts of the DNA Vaccine, which could reduce vaccine efficacy?

b. Similarly for human cellular siRNA silencers of Viral DNA. (L.A. Pray, "Viroids, viruses, and RNA silencing," The Scientist, 18:23, August 30, 2004.) (C.Q. Choi, "Human RNA silences viral DNA," The Scientist, April 22, 2005.)

This being the case, this may be why no DNA Vaccine has shown significant efficacy in humans.

Thanking you in advance for consideration of these comments

Jesse Creel
Vaccine Research Advocate
6072 Cartier Ave
New Orleans, LA 70122
(504) 282-1353

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The Scientist :: May 17, 2005

HIV-1 induces RNA silencing
Report in Immunity is first of natural siRNAs triggered by the virus | By
Graciela Flores

Address:<http://www.the-scientist.com/news/20050517/01/printerfriendly>

HIV-1 elicits RNA silencing in human cells, but also contains a sequence that suppresses the process, researchers report in the May issue of Immunity.

"Nucleic acid-based immunity in mammalian cells has been found before, but to date, there has been no single report of a natural small interfering RNA [siRNA] that is

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2005D-0047

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triggered by HIV in human cells," coauthor Kuan-Teh Jeang of the National Institute of Allergy and Infectious Diseases in Maryland told *The Scientist*. The virus' "counter strategy" described in the paper is also unprecedented, according to Jeang. Coauthor Yamina Bennasser and her colleagues characterized a sequence in the HIV-1 genome that encodes a rare siRNA precursor, a short hairpin RNA that is processed by the Dicer (or by a Dicer-like) ribonuclease into small siRNAs. In addition, they found that the virus prevents RNA silencing through a suppressor present in its Tat protein, which interferes with Dicer's activity.

"It's a very nicely done and a very intriguing story," said Mario Stevenson of the University of Massachusetts, who did not participate in the study. "A number of groups, including ours, have looked at the question of whether HIV encodes RNAs that can form siRNAs. Jeang's group was able to reveal that it does before anyone else." But John Rossi of City of Hope Beckman Research Institute in Duarte, Calif., who was not involved in the research, questioned the physiological relevance of the results. "It doesn't make much sense that Dicer, a cytoplasmic enzyme, would be inhibited by Tat, which is exclusively a nuclear enzyme," Rossi told *The Scientist*. "And the 19 base-pair hairpins they describe are not substrates for Dicer." Rossi said that "dumping tons of Tat into the cells" can lead to "all sorts of nonspecific effects."

Stevenson, however, is not concerned by those questions. "We are learning of new substrates for Dicer all the time, and some groups have shown that RNA silencing can also be achieved in the nucleus, not only in the cytoplasm. The rules by which RNA interfering machinery works are continually being tweaked and modified as we understand more about the process," he said.

What did surprise Stevenson is the idea that HIV encodes siRNA and avoids being inactivated by it by encoding a suppressor. "It seems an incredible expenditure of effort," he said, but added, "viruses will not always subscribe to human logic." Stevenson is more interested in whether shRNAs can be effectively used against HIV as a suppressor mechanism. "If Jeang's results prove to be right, then the shRNAs therapeutic approach [which expresses a HIV specific shRNA to be processed by Dicer into an antiviral form] may not be optimal."

Jeang welcomed the debate. "What is science without criticism?" he asked. "The excitement that drives me to this work, other than the fact that it comments on an aspect of nucleic acid immunology, is that the sequence that we have characterized doesn't change. It's constantly eliciting siRNAs against the virus, forcing the virus to develop a completely new mechanism. This is telling us that there is a region in the virus' genome that, because of functional constraints, cannot mutate."

According to Jeang, HIV researchers' "holy grail" is the ability to find regions in the HIV genome that cannot mutate, and the sequence that he and colleagues have characterized seems to be one such region that cannot change for functional reasons.

Links for this article

Y. Bennasser et al., "Evidence that HIV-1 encodes an siRNA and a suppressor of RNA silencing," *Immunity*, 22 607-19, May 2005. <http://www.immunity.com/>

L.A. Pray, "Viroids, viruses, and RNA silencing," *The Scientist*, 18:23, August 30, 2004. <http://www.the-scientist.com/2004/8/30/23/1>

C.Q. Choi, "Human RNA silences viral DNA," *The Scientist*, April 22, 2005. <http://www.the-scientist.com/news/20050422/01>

Kuan-Teh Jeang

<http://gpp.nih.gov/Researchers/Members/NIAID/Kuan-TehJeang.htm>

Mario Stevenson <http://www.umassmed.edu/pmm/faculty/stevenson.cfm>

John J. Rossi <http://www.cityofhope.org/gradschool/faculty/jrossi.asp>

A. Adams, "RNA therapeutics enter clinical trials," *The Scientist*, 19:28, January 17,

2005. <http://www.the-scientist.com/2005/1/17/28/1>

C. Holding, "RNAi active in the nucleus?," The Scientist, January 11,
2005. <http://www.the-scientist.com/news/20050111/01> return to webpage