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Feline immunodeficiency virus (FIV) vaccine efficacy and FIV neutralizing antibodies☆

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ABSTRACT

A HIV-1 tier system has been developed to categorize the various subtype viruses based on their sensitivity to vaccine-induced neutralizing antibodies (NAbs): tier 1 with greatest sensitivity, tier 2 being moderately sensitive, and tier 3 being the least sensitive to NAbs (Mascola et al., J Virol 2005; 79:10103–7). Here, we define an FIV tier system using two related FIV dual-subtype (A+D) vaccines: the commercially available inactivated infected-cell vaccine (Fel-O-Vax® FIV) and its prototype vaccine solely composed of inactivated whole viruses. Both vaccines afforded combined protection rates of 100% against subtype-A tier-1 FIV_{Pet}, 89% against subtype-B tier-3 FIV_{FC1}, 61% against recombinant subtype-A/B tier-2 FIV_{Bang}, 62% against recombinant subtype-F′/C tier-3 FIV_{NZ1}, and 40% against subtype-A tier-2 FIV_{UK8} in short-duration (37–41 weeks) studies. In long-duration (76–80 weeks) studies, the commercial vaccine afforded a combined protection rate of at least 46% against the tier-2 and tier-3 viruses. Notably, protection rates observed here are far better than recently reported HIV-1 vaccine trials (Sanou et al., The Open AIDS J 2012; 6:246–60). Prototype vaccine protection against two tier-3 and one tier-2 viruses was more effective than commercial vaccine. Such protection did not correlate with the presence of vaccine-induced NAbs to challenge viruses. This is the first large-scale (228 laboratory cats) study characterizing short- and long-duration efficacies of dual-subtype FIV vaccines against heterologous subtype and recombinant viruses, as well as FIV tiers based on *in vitro* NAb analysis and *in vivo* passive-transfer studies. These studies demonstrate that not all vaccine protection is mediated by vaccine-induced NAbs.

1. Introduction

The mechanism(s) of vaccine protection against AIDS lentiviruses such as human (HIV) and feline (FIV) immunodeficiency viruses are still unclear even after completion of four major Phase IIb-III trials on HIV-1 vaccines and after 10 years of commercial FIV vaccine release (Fel-O-Vax® FIV, Fort Dodge Animal Health (FDAH), Fort Dodge, IA) in the U.S. [1–6]. The failed Phase-III AIDSVAX vaccine trials tested the HIV-1 recombinant envelope (Env) protein vaccine for generating predominantly anti-HIV-1 antibody-mediated immunity [3], while the failed Phase-IIb STEP trial tested an adenovirus-vectored HIV-1 *gag/pol/nef* for inducing anti-HIV cell-mediated immunity (CMI) [2]. A more recent phase-III RV144 trial, consisting of canarypox virus-vectored HIV-1 *gag/pr/env* priming and AIDSVAX vaccine boosts, induced both CMI and humoral immunity and showed a modest overall vaccine efficacy of 31.2% [4]. However, these human trials did not use inactivated whole virus (IWV) approach due to safety concerns raised over potential incomplete inactivation [1,6]. The IWV approach is currently being used for commercial veterinary vaccines against retroviruses such as, feline leukemia virus, equine infectious anemia virus, and FIV [7–11]. No cases of breakthrough infections caused by incomplete inactivation of the FIV vaccine viruses have been reported for the Fel-O-Vax® FIV [11].

FIV causes a fatal acquired immunodeficiency syndrome (AIDS) in domestic cats and is an animal model for human AIDS [5,9]. Like HIV-1 with at least seven subtypes and numerous intersubtype recombinants [12], FIV has at least five subtypes (A–E, Fig. 1)

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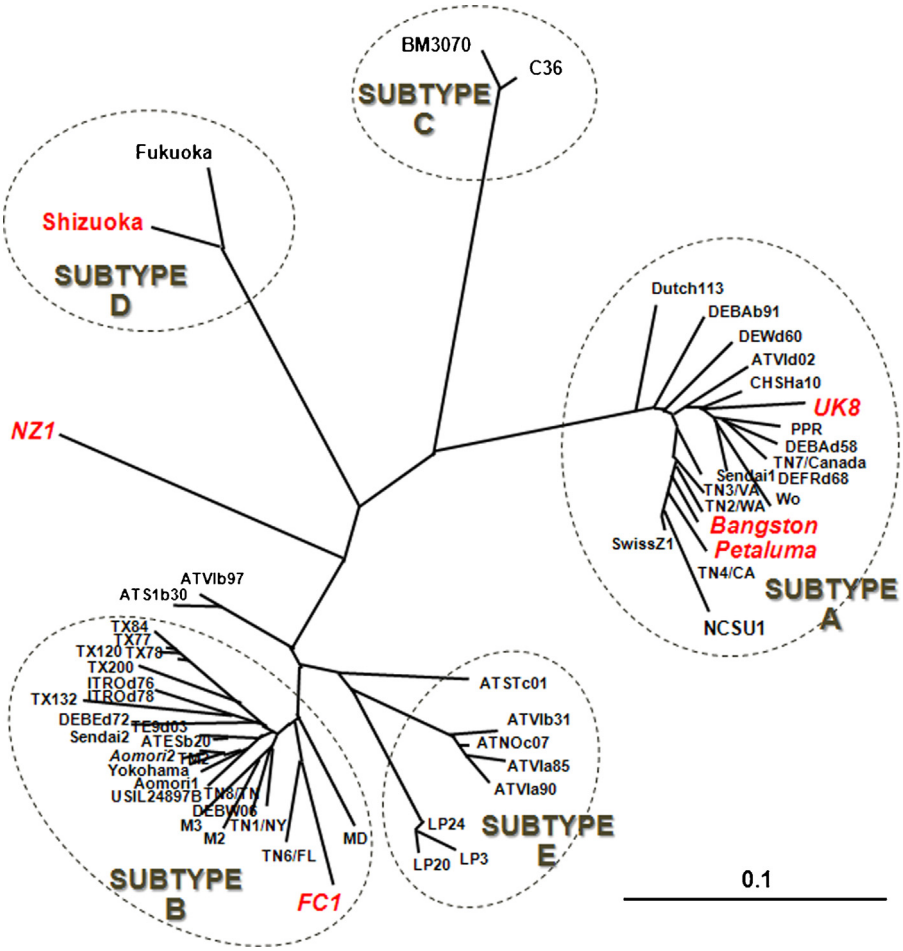

Fig. 1. FIV *gag* phylogenetic distribution of the vaccine and challenge viruses. The subtype designations of the inoculum and vaccine viruses (subtype-A FIV_{Pet} and subtype-D FIV_{Shi}) were previously determined by proviral sequence and phylogenetic comparisons [49,50] of the FIV *env* [10], *gag* (Fig. 1), and *pol* (data not shown). As shown for the first time, FIV_{NZ1} is a recombinant that belongs to a new subtype F′ at Gag (Gag-p24 shown; GenBank accession: GQ406242) and Pol (data not shown; GenBank accession: GQ996603), while its envelope (GenBank accession: GQ406243) has previously been described to belong to subtype C [10,15]. The full sequence analysis demonstrates FIV_{Bang} to belong to subtype A (Gag-p24 shown for the first time) except for the envelope V4-V9 which is subtype B [18]. FIV Gag-p24 phylogeny is based on 58 sequences derived from GenBank FIV strains with accession number: Petaluma (M25381), Bangston (AY684181), TM2 (E03581), FC1 (DQ365596), UK8 (GU055218), BM3070 (AF474246), Shizuoka (AY679785), NZ1 (GQ406242), *Yokohama* (D37819), *Aomori1* (D37823), *Fukuoka* (D37822), MD (AF361320), C36 (AY600517), PPR (M36968), *Sendai1* (D37820), *Sendai2* (D37821), SwissZ1 (X57002), Wo (L06311), *ATESb20* (AF531049), *ATESd03* (AF531050), *ATNOc07* (AY196330), *ATSTb30* (AF531054), *ATSTc01* (AF531058), *ATVIa85* (AF531061), *ATVIa90* (AF531059), *ATVIb31* (AF531063), *ATVIb97* (AF531055), *ATVId02* (AF531075), *CHSHa10* (AF31069), *DEBAb91* (AF531069), *DEBAd58* (AF531070), *DEBEd72* (AF531051), *DEBWa06* (AF531048), *DEFRd68* (AF531071), *DEWd60* (AF531072), Dutch113 (X68019), USIL24897B (U11820), *ITROd76* (AF531052), *ITROd78* (AF531053), *M2* (Y13867), *M3* (Y13866), NCSU1 (I64733), TN1 (DQ365589), TN2 (DQ365590), TN3 (DQ365591), TN4 (DQ365592), TN6 (GQ422126), TN7 (GQ422127), TN8 (DQ365595), *TX77* (AY139106), *TX78* (AY139107), *TX84* (AY139108), *TX120* (AY139105), *TX132* (AY139112), *TX200* (AY139110), *LP3* (AB027302), *LP20* (AB027303), *LP24* (AB027304), *Aomori2* (D37824). Twenty-three sequences are full length (224 aa), and the remaining 35 sequences in italics are partial sequences ranging from 190 to 221 aa, with exception of the three subtype-C viruses (LP3, LP20, LP24), which have only 113 aa.

with subtypes A and B being most prevalent globally followed by subtype C [9,13]. Thus, an effective FIV vaccine needs to confer protection against the predominant circulating FIV subtypes (A–C), as well as, the circulating recombinant forms (CRF) of FIV CRF-A/B, CRF-A/C, and CRF-B/C [13–15].

The prototype (dual-subtype IWVs) and Fel-O-Vax® FIV (dual-subtype IWVs plus infected cells) vaccines conferred protection against non-vaccine subtype-B viruses [16–18]. However, little is known about the duration, magnitude, and mechanism(s) of the vaccine protection against other subtype and recombinant viruses as well as the virus tiers based on virus neutralizing antibodies (NAbs) as described for HIV-1 [19]. Thus, the current studies assessed the efficacy of these vaccines and their vaccine-induced NAbs against virus strains from subtypes A, B, A/B, and F′/C.

2. Materials and methods

2.1. Animals

Specific pathogen free (SPF) cats were purchased from Liberty Research, Inc. (Waverly, NY), Harlan Sprague Dawly, Inc. (Madison, WI), Cedar River Laboratories (Mason City, IO), or were bred in the Laboratory of Comparative Retrovirology and Immunology at the University of Florida. Based on the Institutional Animal Care and Use Committee (IACUC) policy to minimize the animal use, Study 8 used the vaccinated/protected cats from Study 3 (Group 3B). Cats challenged with FIV_{FC1} (subtype-B) were 8 weeks of age, while all other cats were 12–16 weeks old. All cats were maintained and utilized according to the policy and protocols approved by IACUC.

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