Advancing a Broadly Protective Vaccine for the Prevention of Fungal Infections

Karen A. Norris, PhD

Center for Vaccine and Immunology

1785
The University of Georgia

Disclosure:

Co-founder

Presentation Outline

- **Overview and Goals**
- **Background**
  - Invasive Fungal Infections– Unmet clinical Needs
- **Lead Vaccine Candidate: NXT-2 Vaccine**
  - Genesis of Pan-Fungal Vaccine Development
  - Key Pre-clinical Data
    - **Invasive Pulmonary Aspergillosis**
    - **Invasive Candidiasis**
    - ***Pneumocystis* Pneumonia**

GOAL

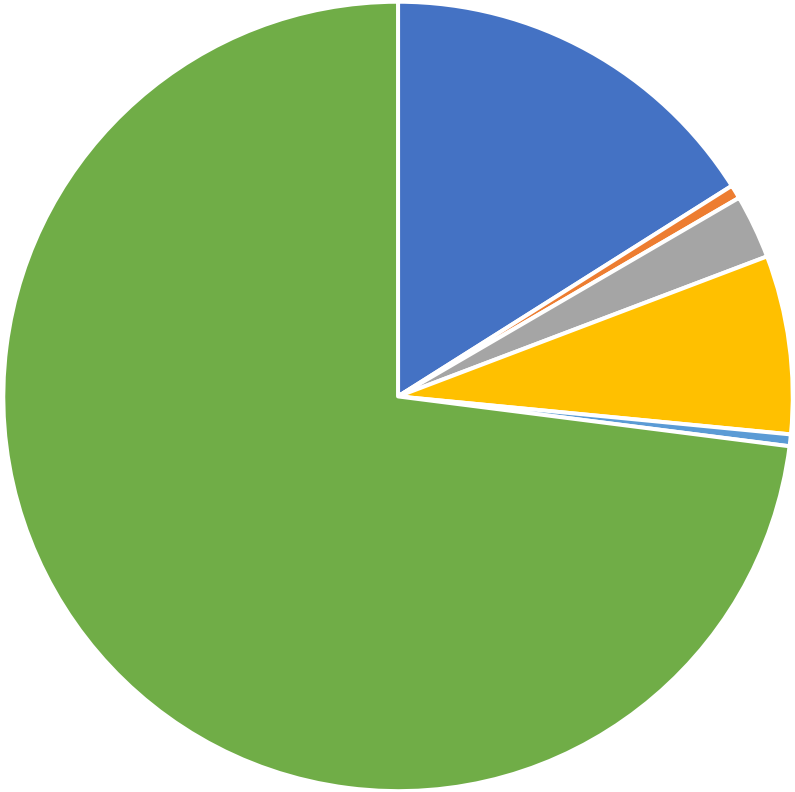
Development of a single vaccine for populations at risk of life threatening, **Invasive Fungal Infections (IFIs)**

Positive Public Health Outcomes:

- Reduction in morbidity and mortality of IFI in vaccinated populations
- Reduction in the need for prophylactic therapies in patients at risk of IFI.
- Reduction in the advancement of anti-fungal drug resistance

UNMET CLINICAL NEEDS:
INDIVIDUALS AT RISK OF INVASIVE FUNGAL INFECTIONS

36 million Immunocompromised Patients at Risk of IFIs (Global)



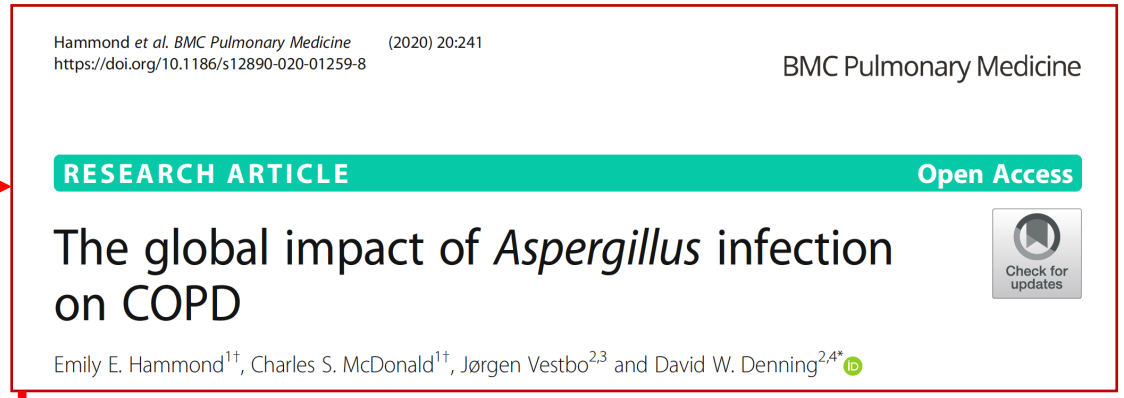
- Autoimmune diseases/Inflammatory disease/Immunosuppressive therapies
- HIV
- Solid Tumors
- Hematologic malignancies
- Solid organ transplant
- Hematologic Stem Cell Transplant
- Primary/Congenital Immunodeficiency

Source: https://www.gaffi.org/why/fungal-disease-frequency/

UNMET CLINICAL NEEDS:

ADDITIONAL CONDITIONS ASSOCIATED WITH INCREASED RISK OF IFIs

- Diabetes
- **COPD-Emphysema**
- Asthma
- Cirrhosis
- Influenza
- Renal Disease
- Cystic Fibrosis
- Tuberculosis
- COVID-19



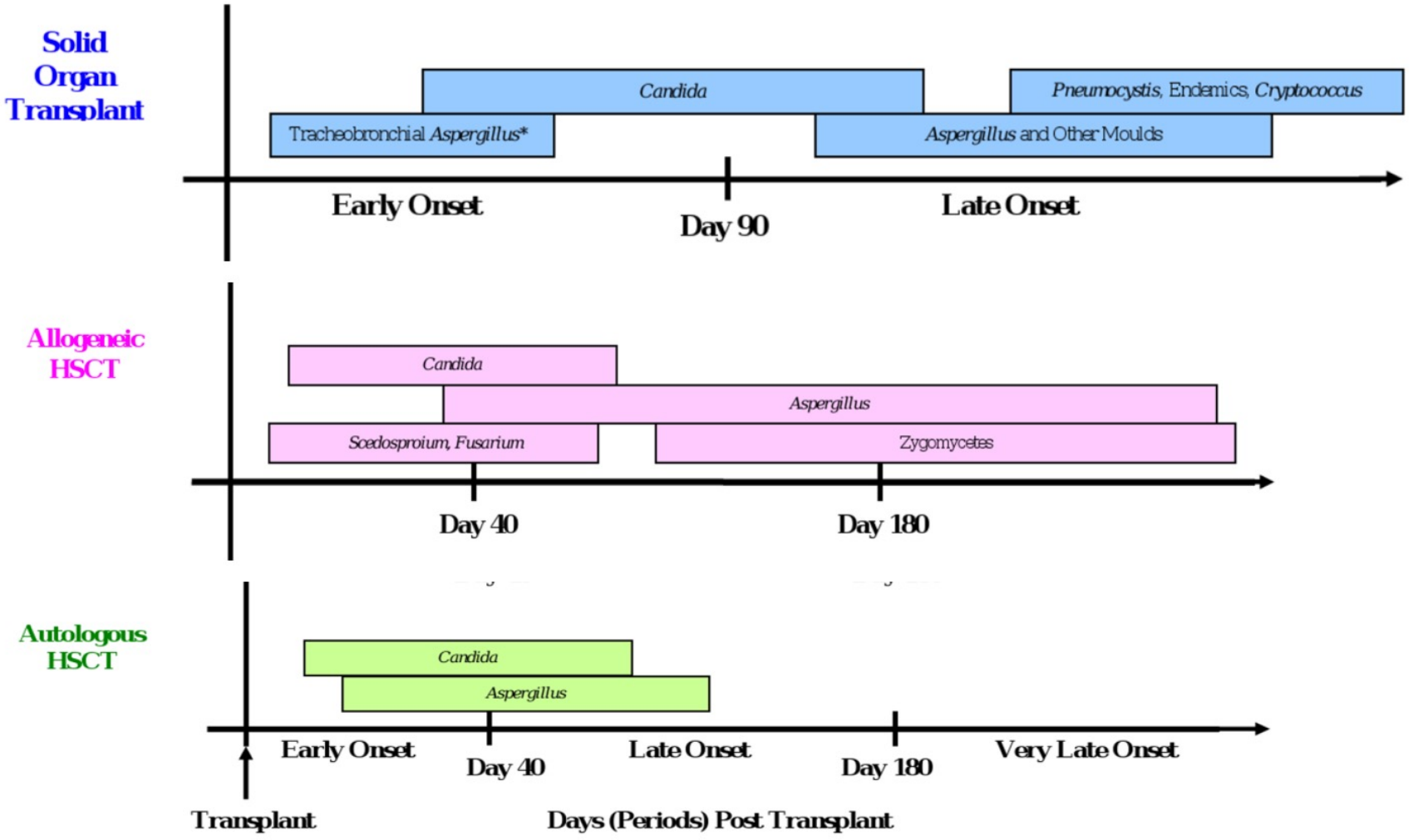
Prevalence of COPD **552,300,599 (global)**

57,991,563 (**10.5%**) COPD hospital admissions, annually…

…of these, **753,073** (**1.3%**) **to 2,272,322** (**3.9%**) develop **Invasive Aspergillosis**

540,451 to 977,082 deaths, annually (**44-72% mortality from IA**, Predicted)

One Challenge (of many) of Anti-Fungal Vaccine Strategy



Immunocompromised individuals are susceptible to multiple fungal pathogens

A single anti-fungal strategy may be inadequate

Person, AK, et al. Fungal Infections in Transplant and Oncology Patients. Infect. Dis. Clin. North Am. 2010. 24:439-459

Overview and Goals

Broadly Reactive Anti-Fungal Vaccine:

NXT-2, is a recombinant protein based on a conserved fungal protein that induces ***cross-protective immunity against the major life-threatening invasive fungal pathogens,***

- ***Aspergillus***
- ***Candida***
- ***Pneumocystis***

Rayens, E. at al. 2022. Immunogenicity and Protective Efficacy of a Recombinant Pan-Fungal Vaccine in Pre-Clinical Models of Aspergillosis, Candidiasis, and Pneumocystosis, PNAS Nexus, 1:1-15.

NXT-2 Anti-Fungal Vaccine

Patient Journey: Vaccination for the Prevention of Invasive Fungal Infections

- Vaccination of patients prior to solid organ or cell transplant
- Vaccination prior to initiation of immunosuppressive therapies for cancer, autoimmune and inflammatory disease
- Vaccination of populations at risk for HIV and at early-stage HIV
- Vaccination of early-stage COPD patients
- Vaccination for non-life-threatening fungal infections (e.g., VVC)

Key Pre-clinical Data

Vaccine-induced Protective Efficacy in Immunosuppressed Animal models of Invasive Fungal Infections

- Immunosuppressed murine models of **invasive pulmonary aspergillosis** and **invasive candidiasis**
- Simian immunodeficiency virus (SIV) immunosuppressed primates– model of ***Pneumocystis*** pneumonia

Mechanism of Action of Vaccine-Induced Protection

- Protective immunity correlates with IgG titers
- Vaccine-induced antibodies enhance fungal opsonic-phagocytic killing, *in vitro*
- Vaccine-induced antibodies inhibit *Candida* biofilm formation, *in vitro*
- Passive transfer of anti-NXT antibodies protects against IPA in immunocompromised mice

Rayens, E. et al. 2022. PNAS Nexus.

The Genesis of the Pan-Fungal Vaccine

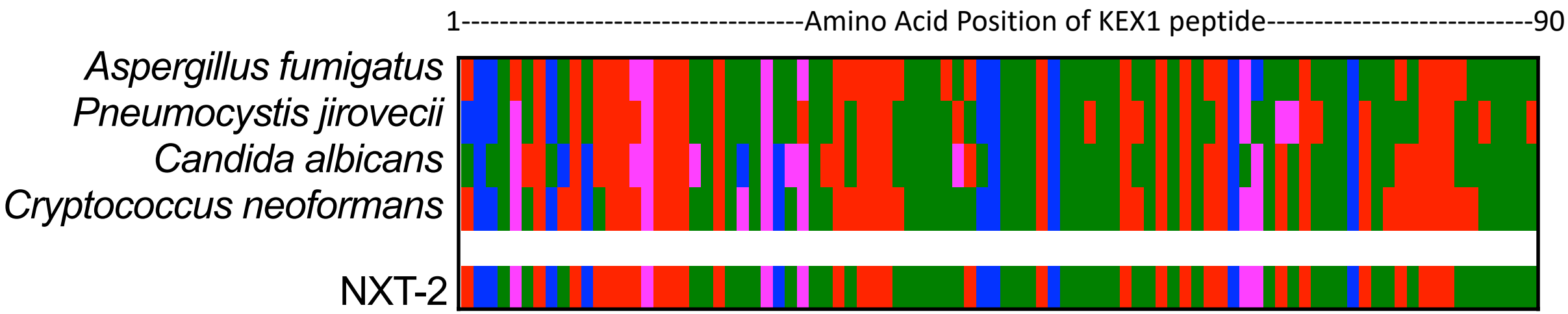
NXT-2 is a ***consensus 90 amino acid recombinant***, fungal protein that shares conserved amino acid sequence and cross-reactive antigenicity to a **kexin-related protein (KEX1)** present in several pathogenic fungal organisms including ***Aspergillus, Candida and Pneumocystis*.**

Species specific **KEX1 recombinant vaccine candidates** are *protective against fungal challenge in immunosuppressed murine and primate animal models.*

PC.KEX1, Pneumocystis jirovecii, ***Kling H and Norris, K. 2016 J.Infect.Dis***
AF.KEX1, Aspergillus fumigatus, ***Rayens et al. 2021, Front. Immunol***
CA.KEX1, Candida albicans, ***Rayens et al. 2022, PNAS Nexus***

NXT-2 Pan-fungal vaccine

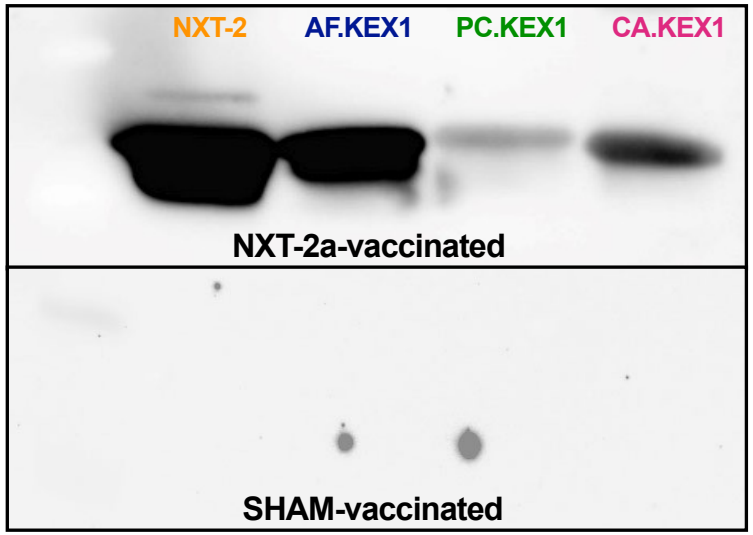
The Pan-Fungal **consensus peptide** generated based conserved KEX1 region in *Aspergillus, Candida, Pneumocystis and Cryptococcus* proteins



Rayens E, et al. (2022). Immunogenicity and protective efficacy of a pan-fungal vaccine in preclinical models of aspergillosis, candidiasis, and pneumocystosis. PNAS Nexus.

Anti-NXT-2 antibodies are cross-reactive with fungal KEX1 recombinant proteins

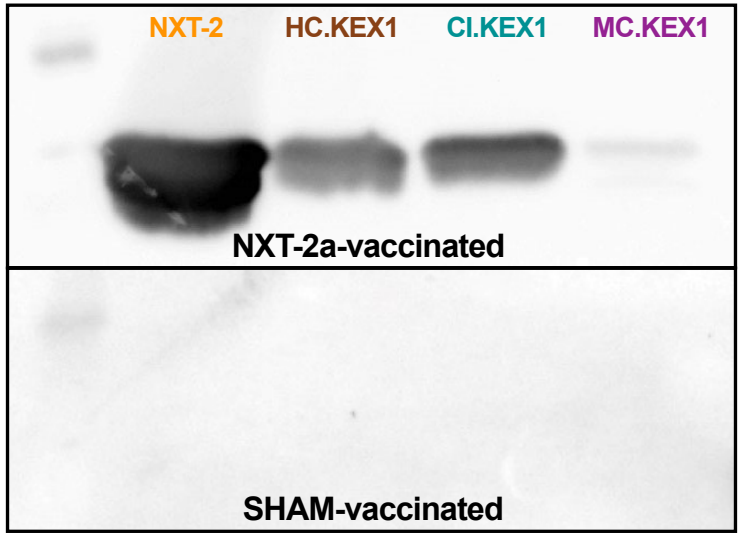
% Identity	NXT-2	AF.KEX1	PC.KEX1	CA.KEX1
NXT-2	100%	82.3%	68.5%	75.3%



AF.KEX1: *Aspergillus fumigatus*
PC.KEX1: *Pneumocystis jirovecii*
CA.KEX1: *Candida albicans*

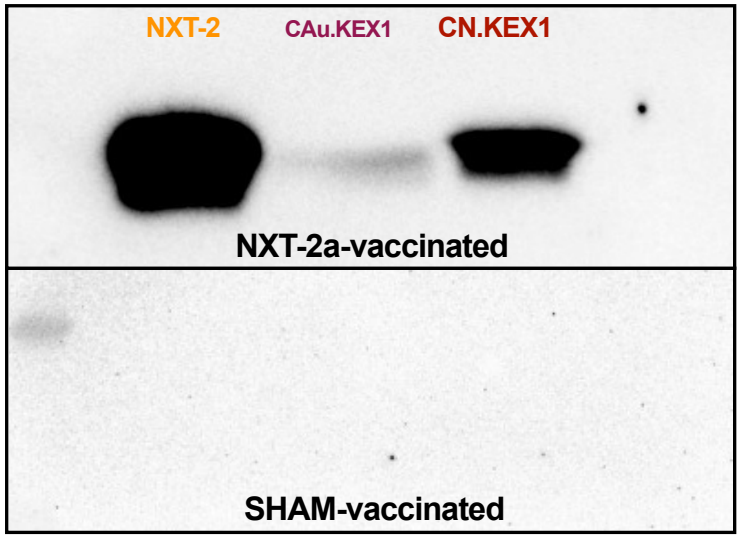
Represent 80-85% of fungal-related deaths and serious infections

% Identity	NXT-2	HC.KEX1	CI.KEX1	MC.KEX1
NXT-2	100%	74.7%	71.3%	68.5%



HC.KEX1: *Histoplasma capsulatum*
CI.KEX1: *Coccidioides immitis*
MC.KEX1: *Mucor circinelloides*

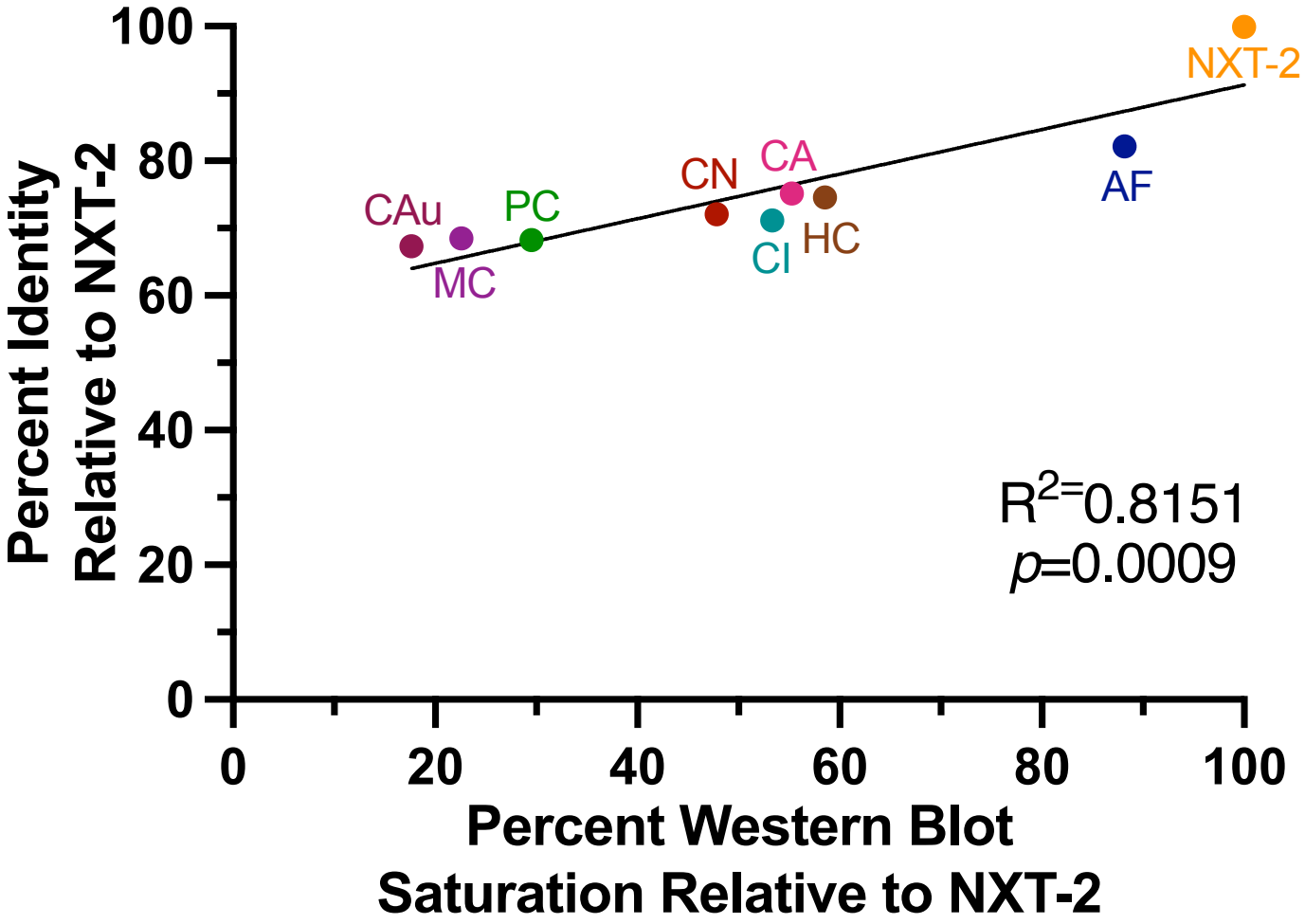
% Identity	NXT-2	CAu.KEX1	CN.KEX1	Empty pET28(+) Vector
NXT-2	100%	67.4%	72.2%	



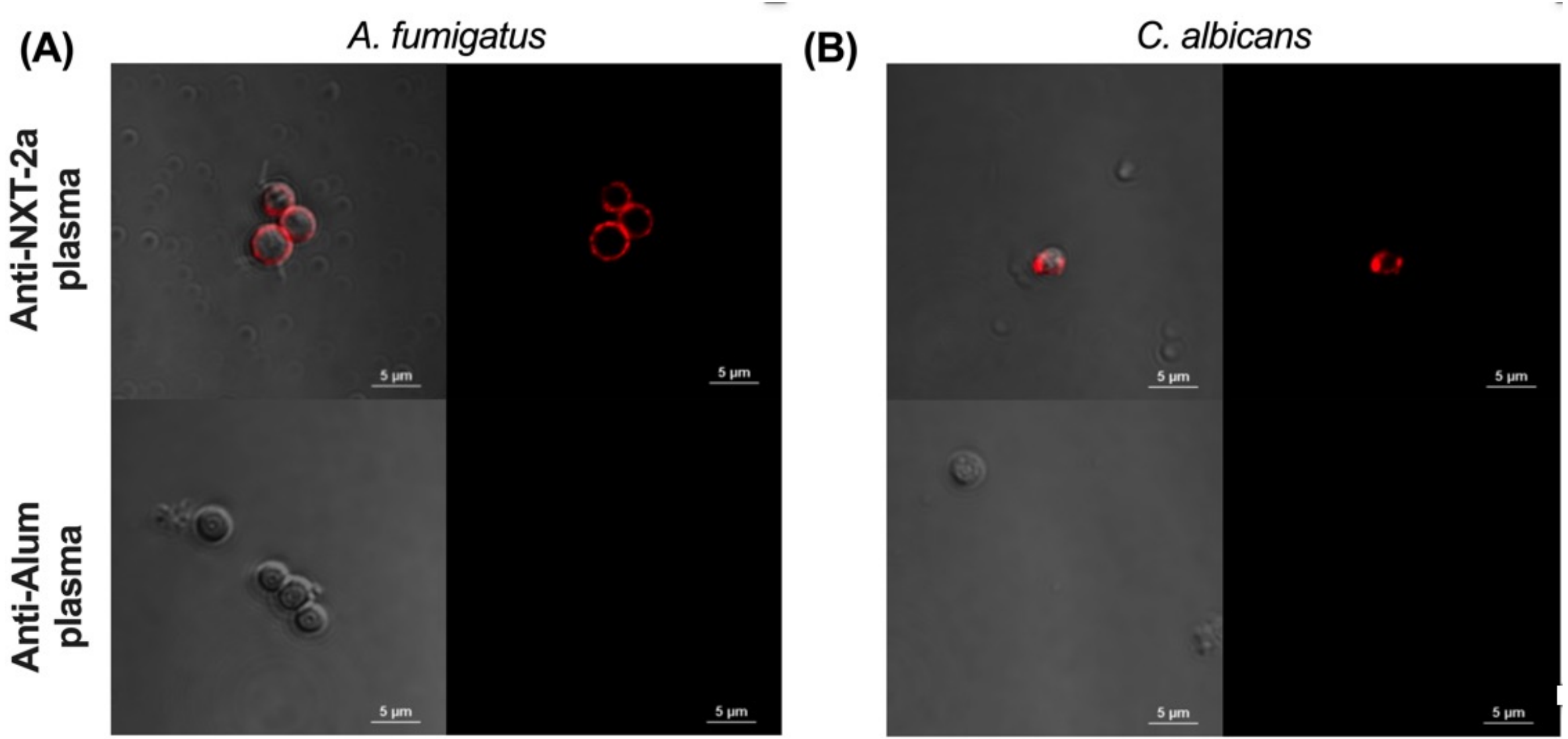
CAu.KEX1: *Candida auris*
CN.KEX1: *Cryptococcus neoformans*

Rayens E, et al. (2022). Immunogenicity and protective efficacy of a pan-fungal vaccine in preclinical models of aspergillosis, candidiasis, and pneumocystosis. PNAS Nexus.

Anti-NXT-2 antibodies are immuno-cross reactive with fungal KEX1 recombinant proteins



Anti-NXT-2 antibodies surface binding of fungal pathogens



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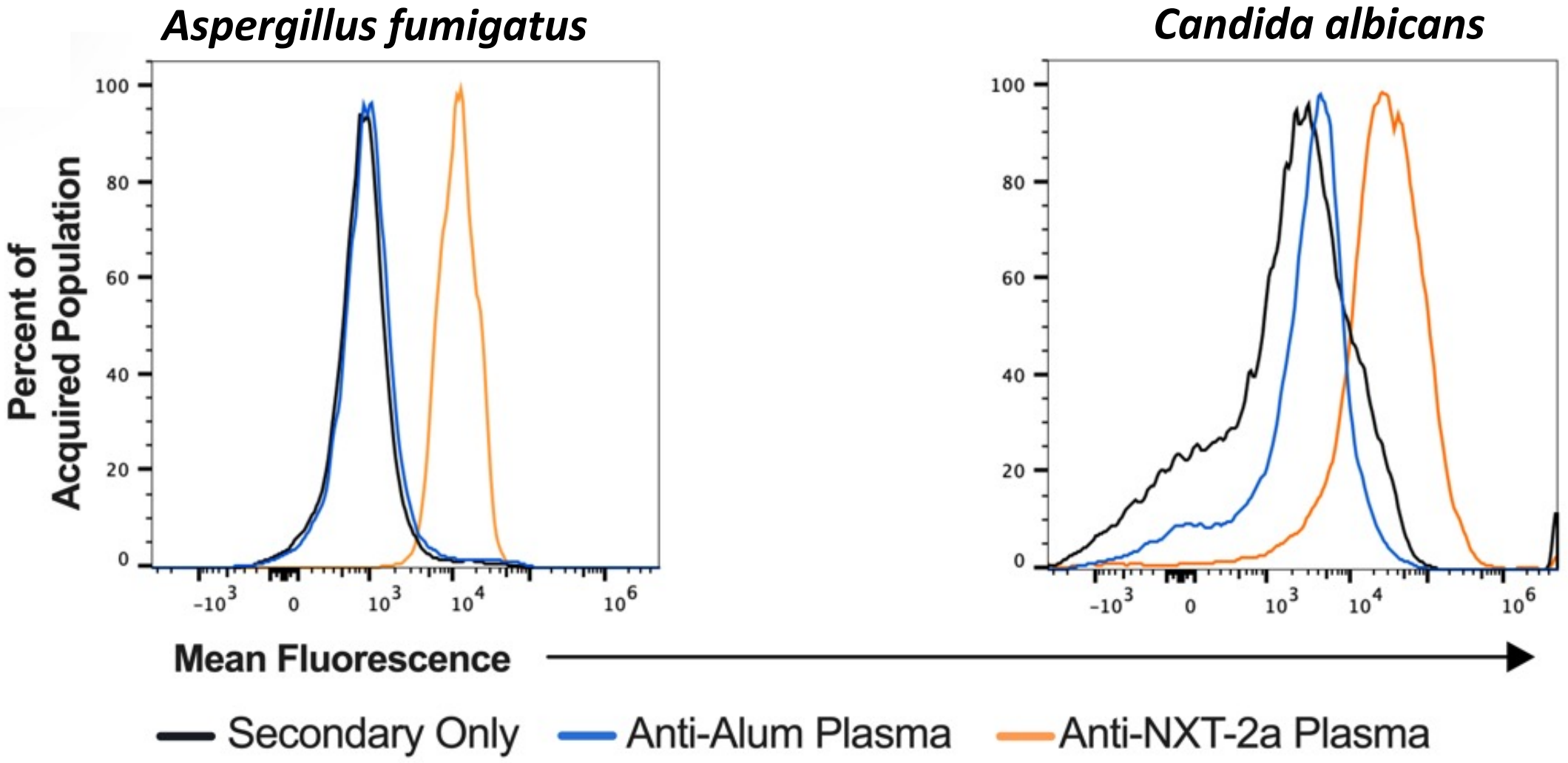


Immunization with NXT-2 vaccine induces protective immunity in experimental models of **immunosuppressed** animals.

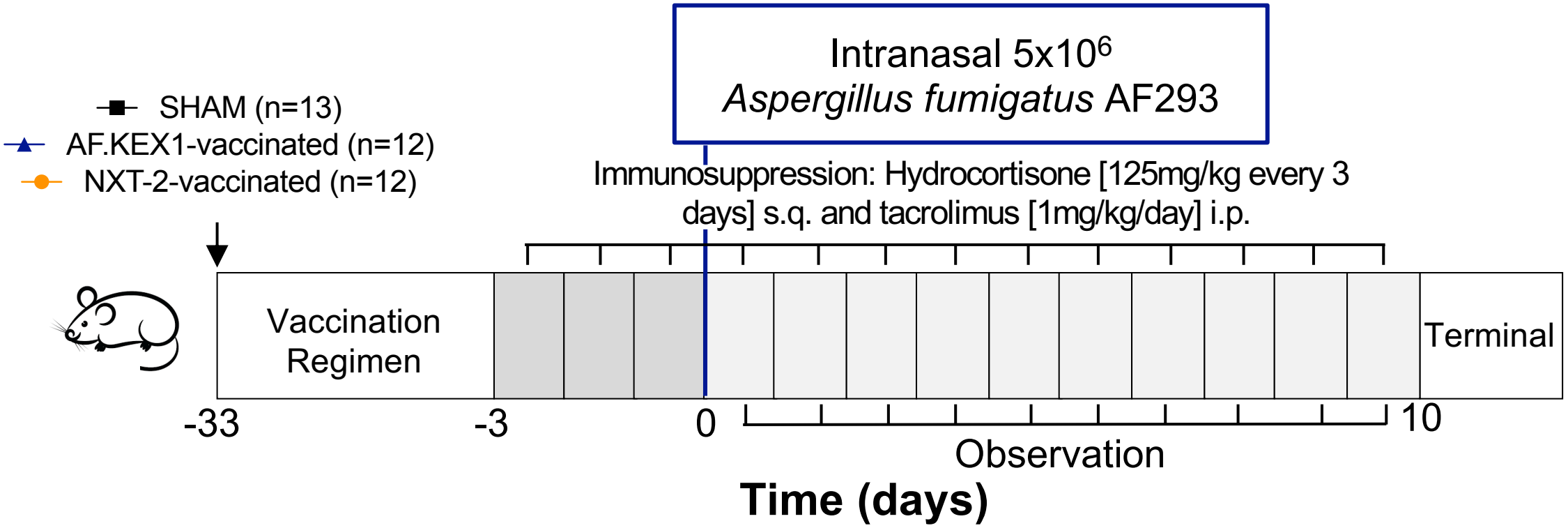
1. **Invasive Pulmonary Aspergillosis** in murine model of drug-induced immunosuppression

2. **Invasive Candidiasis** in murine model of drug-induced immunosuppression

3. ***Pneumocystis* pneumonia** in non-human primate model of HIV-induce immunosuppression

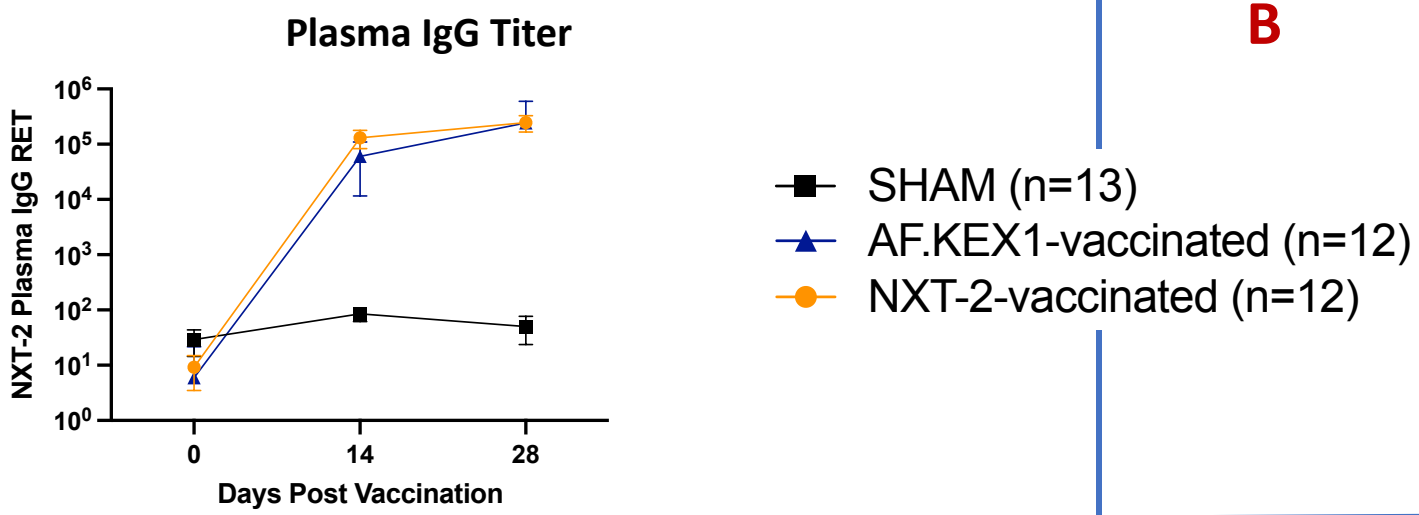
Rayens E, et al. (2022). Immunogenicity and protective efficacy of a pan-fungal vaccine in preclinical models of aspergillosis, candidiasis, and pneumocystosis. PNAS Nexus.

NXT-2 vaccination reduces Invasive Pulmonary Aspergillosis in immunosuppressed murine model



NXT-2 vaccination reduces Invasive Pulmonary Aspergillosis morbidity and mortality in an immunosuppressed murine model.

A



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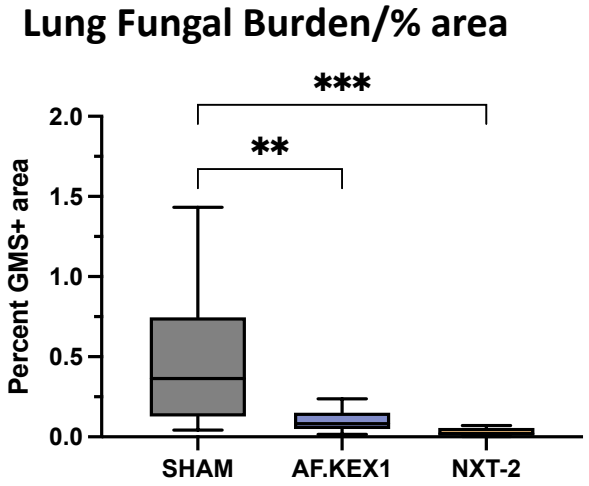

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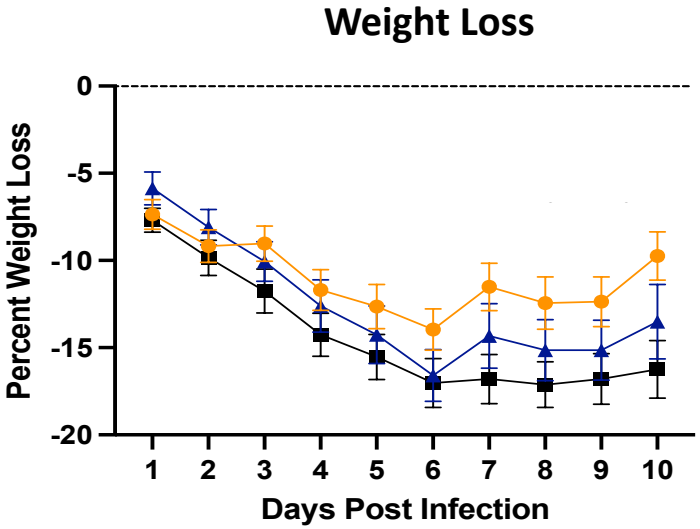

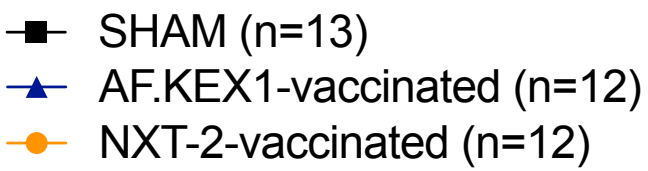

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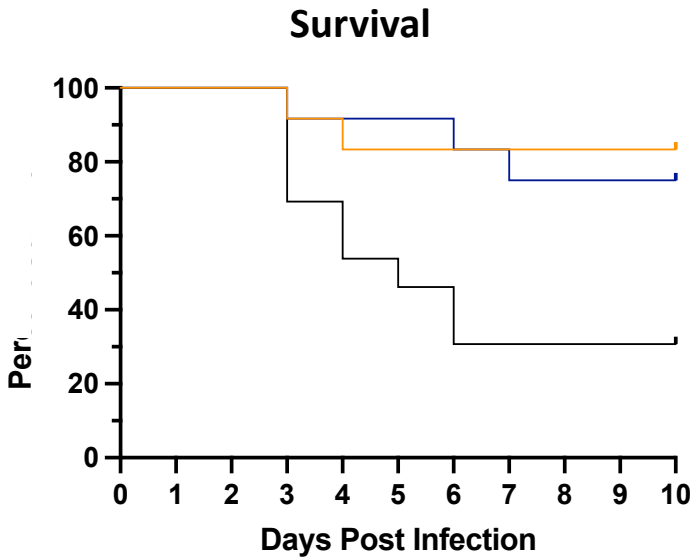
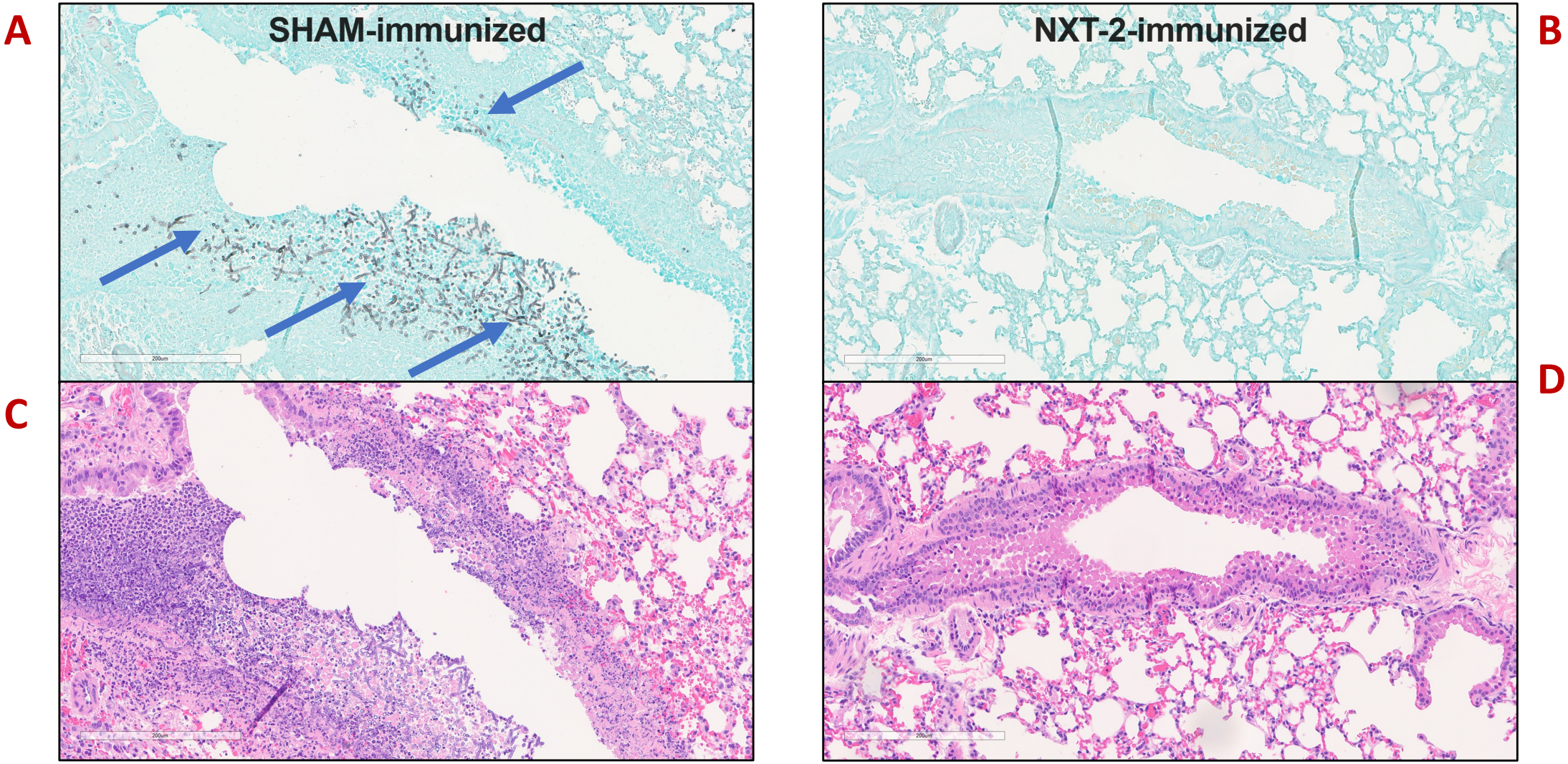
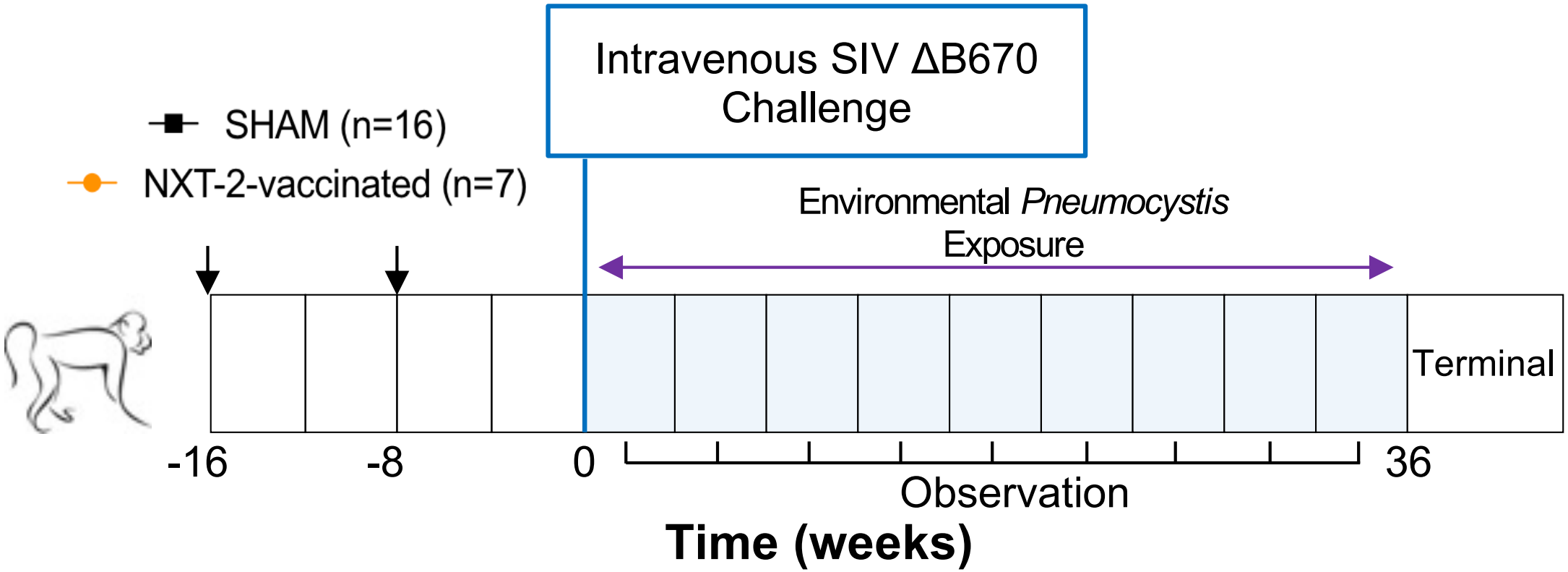


NXT-2 vaccination reduces Invasive Pulmonary Aspergillosis morbidity and mortality in an immunosuppressed murine model.



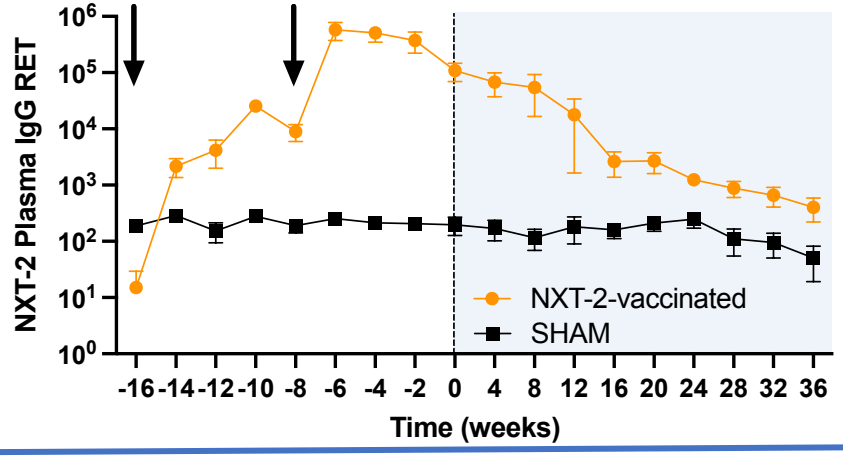
NXT-2 vaccination reduces frequency of ***Pneumocystis pneumonia and colonization*** in a non-human primate model of HIV/AIDS-immunosuppression



NXT-2 vaccination reduces frequency of ***Pneumocystis pneumonia*** in a non-human primate model of HIV/AIDS-immunosuppression

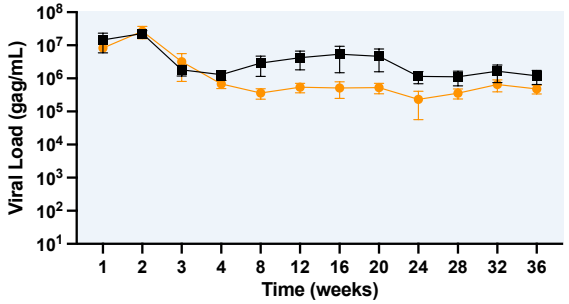
A

Plasma IgG Titer

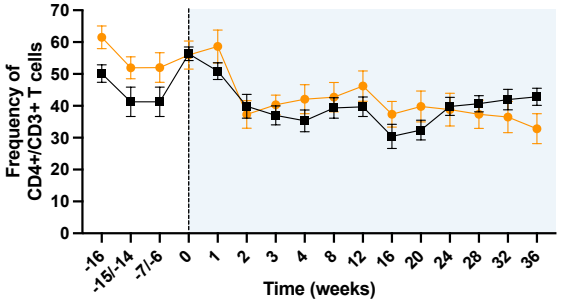


B

SIV Viral Load

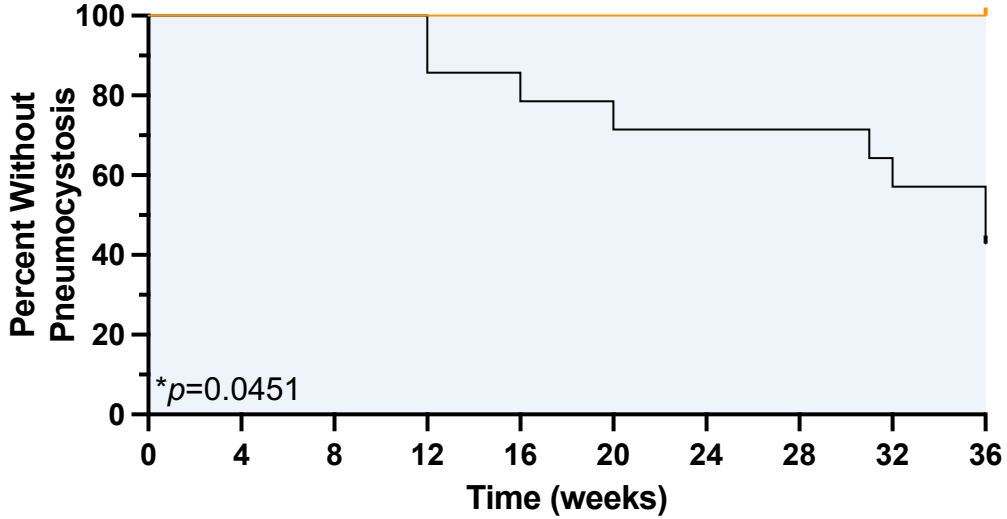


CD4+ T cells



C

Percentage without pneumocystosis



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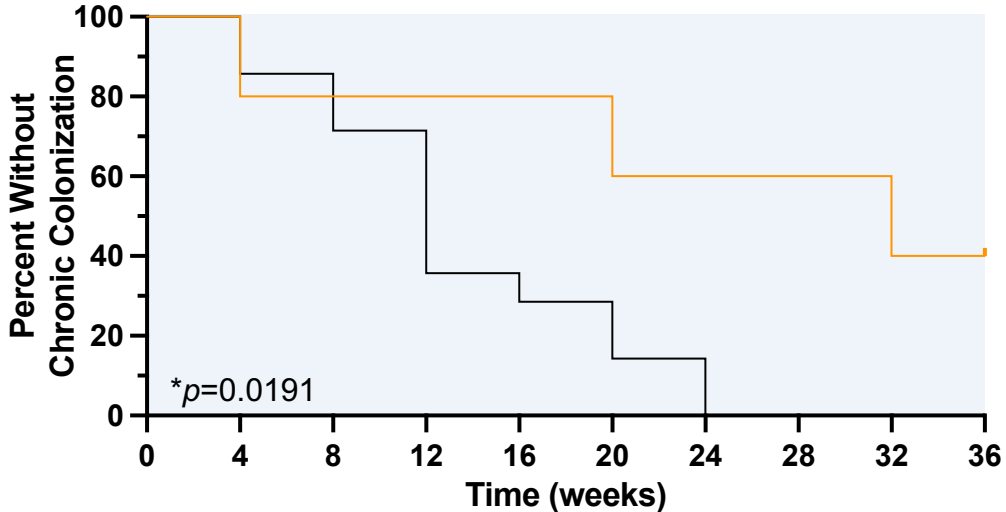
Percentage without *Pneumocystis* colonization



MECHANISM OF ACTION:

Anti- NXT-2 Antibodies Promote Opsonic-Phagocytic Killing of *Candida albicans and Aspergillus fumigatus*

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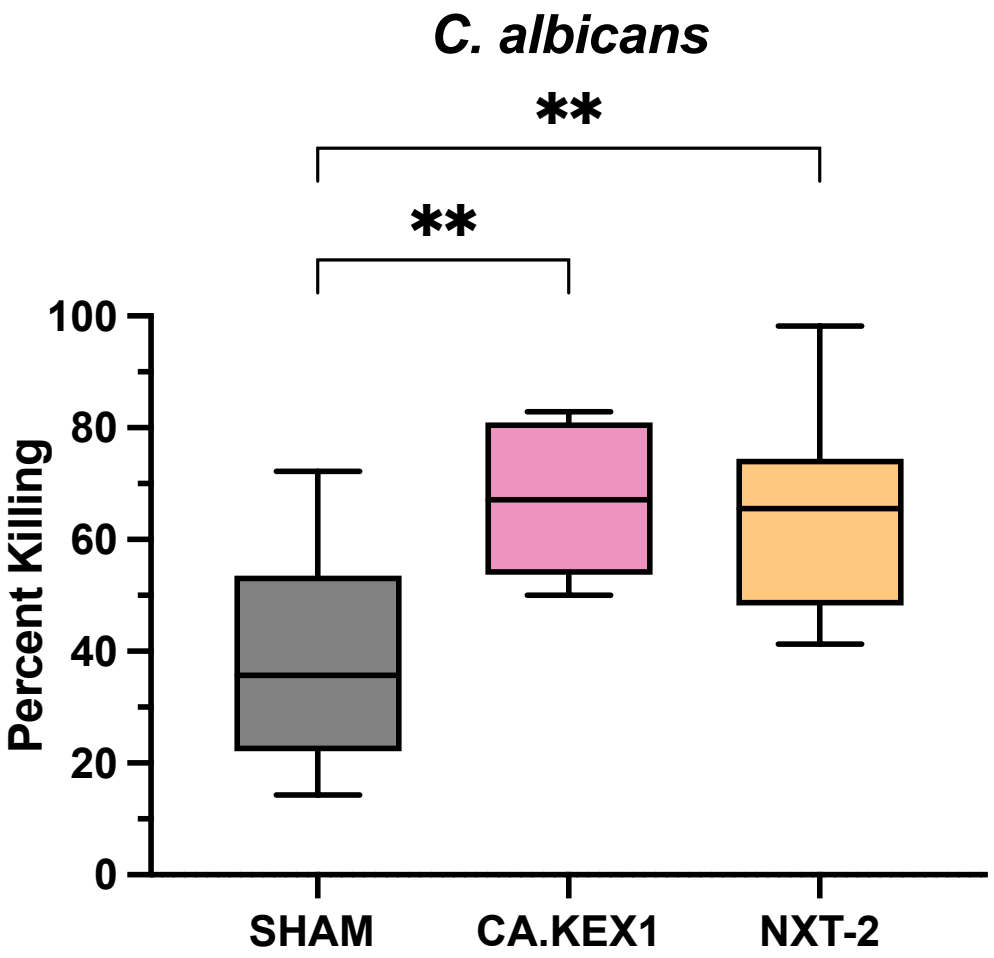

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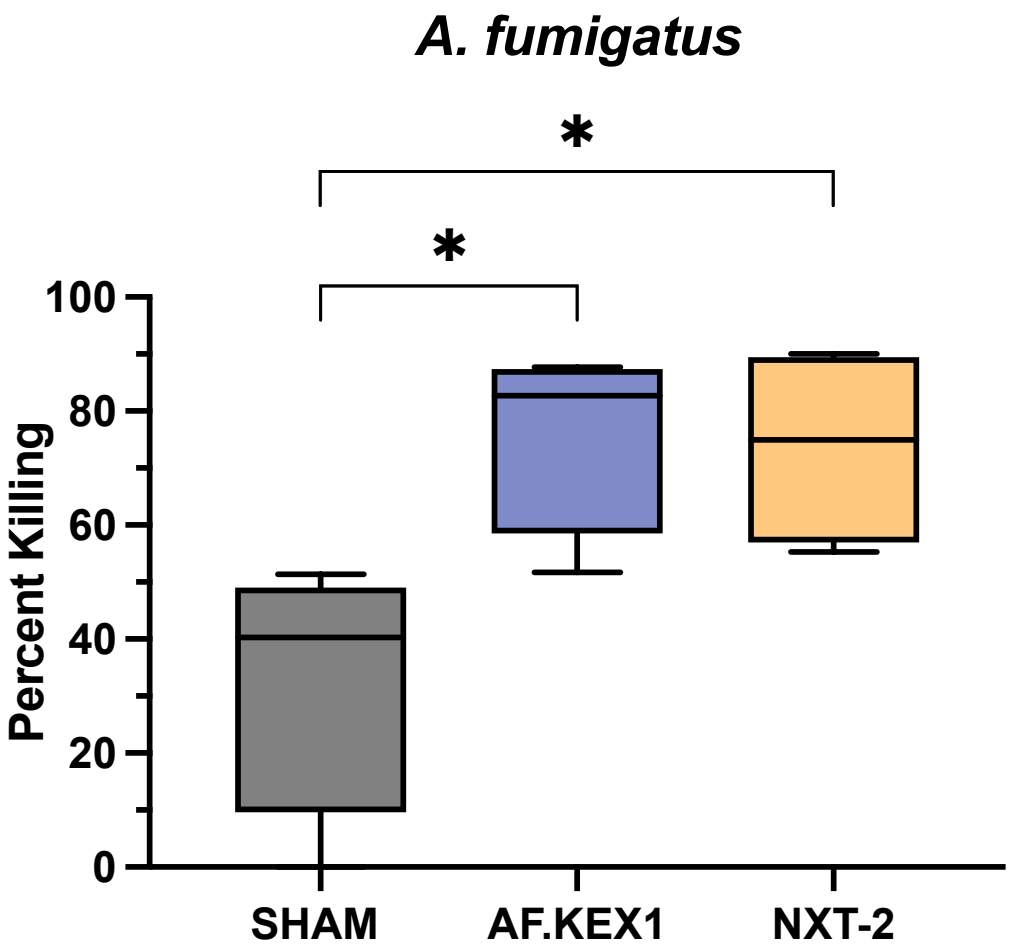
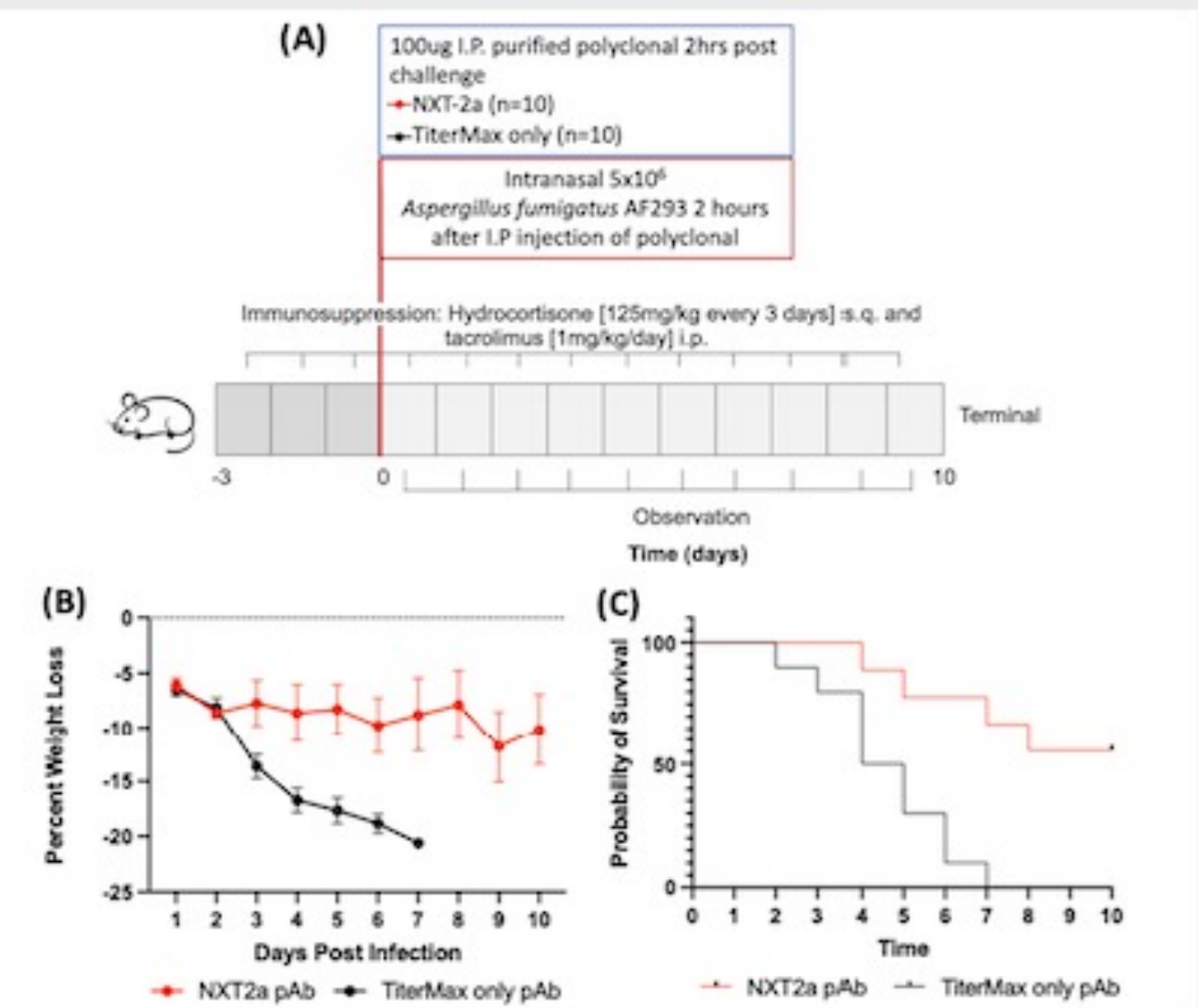


MECHANISM OF ACTION:

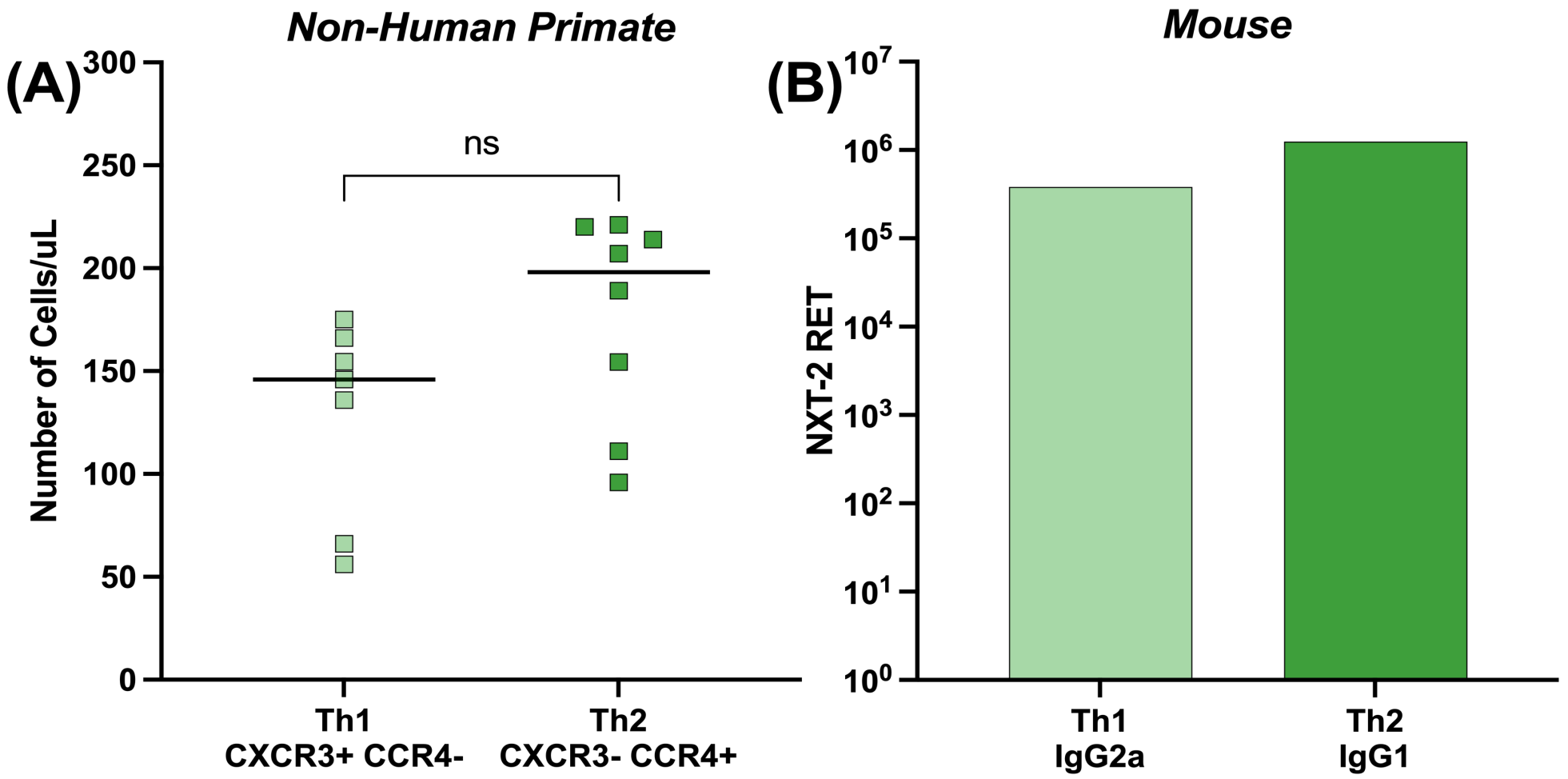
.**Prophylactic treatment with NXT-2 polyclonal IgG reduces the morbidity and mortality of aspergillosis immunosuppressed murine model.**



Immunosuppressed mice receiving NXT-2 IgG had less weight loss (panel B) significantly protected compared to animals receiving IgG controls (*P-0.0012 Mantel-Cox) (panel C)

MECHANISM OF ACTION:

Immunization of mice and non-human primates elicits mixed Th1/Th2 responses



Summary of Preclinical NXT-2 Vaccine Results

- Vaccination with NXT-2 generates a robust, durable antibody response that is cross-reactive with multiple fungal pathogens.
- NXT-2 vaccination significantly reduces morbidity and mortality in immunosuppressed pre-clinical murine and primate models
- Vaccine-induced antibodies promote fungal killing and inhibit biofilm formation
- Vaccine-induced antibodies passively protect against pulmonary aspergillosis in immunocompromised murine model.

NXT-2 offers novel, single vaccine strategy to patient populations at risk of the most clinically important, invasive fungal infections

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University of Georgia

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Brandi Celia-Sanchez
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