CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: MIP
ASP Number: Redacted by agreement
Date of Scientific Review: 5/5/20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: _Redacted by agreement_____

Scientific Review Chairperson Signature: Redacted by agreement

Date: 05-18-20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: PB
ASP Number: Redacted by agreement
Date of Scientific Review: 05/05/20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: _ Redacted by agreement _____

Scientific Review Chairperson Signature: Redacted by agreement

Date: 05/10/20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: VB
ASP Number: Redacted by agreement
Date of Scientific Review: 04-02-20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement

Redacted by agreement

Scientific Review Chairperson Signature: _____

Date: 04-03-20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: Vaccine Branch, CCR, NCI
ASP Number: Redacted by agreement
Date of Scientific Review: 08-11-20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement

Scientific Review Chairperson Signature: Redacted by agreement

Date: 10/2/20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: VB
ASP Number: Redacted by agreement
Date of Scientific Review: 05/5/20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement

Scientific Review Chairperson Signature: Redacted by agreement Date: 06/01/20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: Vaccine Branch, CCR
ASP Number: Redacted by agreement
Date of Scientific Review: 04-02-20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement

Scientific Review Chairperson Signature: Redacted by agreement

Date: 04-14-20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: Vaccine Branch, CCR
ASP Number Redacted by agreement
Date of Scientific Review: 04-02-20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: __Redacted by agreement_____

Scientific Review Chairperson Signature: _ Redacted by agreement _____

Date: ____04-14-20_____

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: Vaccine Branch, CCR
ASP Number: Redacted by agreement
Date of Scientific Review: 08-11-20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement

Scientific Review Chairperson Signature: Redacted by agreement

Date: 09-15-20

CCR NHP Animal Study Protocol Prospective Scientific Review

Investigator: Redacted by agreement
Lab/Branch: VB
ASP Number Redacted by agreement
Date of Scientific Review: 05/15/20

	Response	Comments
Are the study objectives clearly stated and scientific meritorious?	[X] Yes [ ] No	
Are the studies likely to provide knowledge that will improve human and/or animal health?	[X] Yes [ ] No	
Individual studies are designed/powered in such a way as to provide meaningful answers/definitive endpoints for the hypotheses posed?	[X] Yes [ ] No	
The use of NHPs in the proposed research are well justified.	[X] Yes [ ] No	
Recommendation for concept approval	[X] Yes [ ] No	

Scientific Review Chairperson Name: Redacted by agreement _____

Scientific Review Chairperson Signature: Redacted by agreement

Date: 05/22/20

AIDS and Cancer Virus Program NHP Study Scientific Review Form

Date: 10/22/2020

Study Title: Evaluating TLR7 agonist-mediated enhancement of antibody-induced depletion of SIV reservoirs within tissues; **Modification: Add IL-15 Evaluation**

IACUC Number Redacted by agreement

Scientific Justification:

Recent data generated by our collaborators at Redacted by agreement using antibodies with different specificities than the anti-CD4 antibody to be used for this study have suggested that IL-15 administration may enhance antibody-mediated cell depletion in vivo in macaques. Thus, use of IL-15, with which we have extensive experience in macaques, is highly relevant and appropriate for Redacted by agreement which seeks to evaluate enhancement of antibody-mediated depletion of target cells in tissues approach to reduced viral reservoirs in the setting of SIV/HIV infection.

☒Yes ☐No	The proposed research is scientifically significant.
☒Yes ☐No	The proposed research is expected to provide knowledge that will improve human and/or animal health.
☒Yes ☐No	The proposed experiments are well designed to address the study objectives.
☒Yes ☐No	The proposed nonhuman primate species is the appropriate experimental model for the study.
☒Yes ☐No	The number of nonhuman primates requested for use in the study is appropriate.

By signing below, review Chairperson indicates that at least two of three review committee members attest this is a scientifically meritorious study that is ready for ACUC review:

Redacted by agreement 10-26-2020 Redacted by agreement

Review Chairperson Signature, Date *Printed Name*

AIDS and Cancer Virus Program NHP Study Scientific Review Form

Date: 8/5/2020

Study Title: Origin and characterization of HIV/SIV in semen

IACUC Number Redacted by agreement

Scientific Justification:

The majority of new HIV infections result from sexual interactions with infected individuals. Semen is the main vector for viral transmission globally, however, little is known regarding the anatomic origin and form of the virus in semen. In a recent collaborative study addressing this question, we demonstrated that various male genital tract (MGT) organs are involved in the release of virus into semen. However, because this study used a viral swarm, the depth of viral sequencing was limited, therefore the power to conclude the relative contributions of various MGT organs to semen was unclear. Furthermore, the previous study used animals in chronic infection with a diverse but closely relative viral genomes, which complicated the phylogenetic analysis and did not model the most relevant phase of viral transmission. Here we plan to overcome these deficiencies by using a barcoded virus and study primary infection when transmission is most likely to occur. The barcoded virus model allows us to determine the origin of the virus present in the semen by comparing the identity and proportion of the molecularly barcoded clonotype present in the semen (plasma and cells) to the population present in MGT organs, blood (PBMCs and plasma), and lymphoid tissues (LN, GUT, spleen). Additionally, for the first time, our state-of the-art RNAscope assay will be used to detect, identify, and characterize the seminal cells harboring vRNA and/or vDNA, as well as in the various tissues. Finally, by using a highly sensitive viral load assay, we will be able to determine the relative contribution of various anatomic sites within the MGT to cell-free virus in semen and infected seminal cells.
This study will provide novel characterization of the virus at the origin of sexual transmission and will contribute critical new insights to inform novel strategies to prevent the spread of HIV.

☒Yes ☐No	The Animal Study Proposal is designed to develop knowledge with the potential to improve human and/or animal health and well-being.
☒Yes ☐No	The study objectives are clearly stated and scientifically meritorious.
☒Yes ☐No	The experimental methods are reasonable and well justified.
☒Yes ☐No	There is a clear and rational explanation for using NHPs.
☒Yes ☐No	The number of animals required is well-justified and sufficient to achieve the study objectives.

By signing below, reviewer indicates that this is a scientifically meritorious study that is ready for ACUC review:

Redacted by agreement

Redacted by agreement

Reviewer Signature, Date *Printed Name*

AIDS and Cancer Virus Program NHP Study Scientific Review Form

Date: 8/5/2020

Study Title: Origin and characterization of HIV/SIV in semen

IACUC Number: Redacted by agreement

Scientific Justification:

The majority of new HIV infections result from sexual interactions with infected individuals. Semen is the main vector for viral transmission globally, however, little is known regarding the anatomic origin and form of the virus in semen. In a recent collaborative study addressing this question, we demonstrated that various male genital tract (MGT) organs are involved in the release of virus into semen. However, because this study used a viral swarm, the depth of viral sequencing was limited, therefore the power to conclude the relative contributions of various MGT organs to semen was unclear. Furthermore, the previous study used animals in chronic infection with a diverse but closely relative viral genomes, which complicated the phylogenetic analysis and did not model the most relevant phase of viral transmission. Here we plan to overcome these deficiencies by using a barcoded virus and study primary infection when transmission is most likely to occur. The barcoded virus model allows us to determine the origin of the virus present in the semen by comparing the identity and proportion of the molecularly barcoded clonotype present in the semen (plasma and cells) to the population present in MGT organs, blood (PBMCs and plasma), and lymphoid tissues (LN, GUT, spleen). Additionally, for the first time, our state-of the-art RNAscope assay will be used to detect, identify, and characterize the seminal cells harboring vRNA and/or vDNA, as well as in the various tissues. Finally, by using a highly sensitive viral load assay, we will be able to determine the relative contribution of various anatomic sites within the MGT to cell-free virus in semen and infected seminal cells.
This study will provide novel characterization of the virus at the origin of sexual transmission and will contribute critical new insights to inform novel strategies to prevent the spread of HIV.

☒Yes ☐No	The Animal Study Proposal is designed to develop knowledge with the potential to improve human and/or animal health and well-being.
☒Yes ☐No	The study objectives are clearly stated and scientifically meritorious.
☒Yes ☐No	The experimental methods are reasonable and well justified.
☒Yes ☐No	There is a clear and rational explanation for using NHPs.
☒Yes ☐No	The number of animals required is well-justified and sufficient to achieve the study objectives.

By signing below, reviewer indicates that this is a scientifically meritorious study that is ready for ACUC review:

Redacted by agreement

Redacted by agreement 5 AUG 2020

Reviewer Signature, Date *Printed Name*

AIDS and Cancer Virus Program NHP Study Scientific Review Form

Date: 8/5/2020

Study Title: Origin and characterization of HIV/SIV in semen

IACUC Number: Redacted by agreement

Scientific Justification:

The majority of new HIV infections result from sexual interactions with infected individuals. Semen is the main vector for viral transmission globally, however, little is known regarding the anatomic origin and form of the virus in semen. In a recent collaborative study addressing this question, we demonstrated that various male genital tract (MGT) organs are involved in the release of virus into semen. However, because this study used a viral swarm, the depth of viral sequencing was limited, therefore the power to conclude the relative contributions of various MGT organs to semen was unclear. Furthermore, the previous study used animals in chronic infection with a diverse but closely relative viral genomes, which complicated the phylogenetic analysis and did not model the most relevant phase of viral transmission. Here we plan to overcome these deficiencies by using a barcoded virus and study primary infection when transmission is most likely to occur. The barcoded virus model allows us to determine the origin of the virus present in the semen by comparing the identity and proportion of the molecularly barcoded clonotype present in the semen (plasma and cells) to the population present in MGT organs, blood (PBMCs and plasma), and lymphoid tissues (LN, GUT, spleen). Additionally, for the first time, our state-of the-art RNAscope assay will be used to detect, identify, and characterize the seminal cells harboring vRNA and/or vDNA, as well as in the various tissues. Finally, by using a highly sensitive viral load assay, we will be able to determine the relative contribution of various anatomic sites within the MGT to cell-free virus in semen and infected seminal cells.
This study will provide novel characterization of the virus at the origin of sexual transmission and will contribute critical new insights to inform novel strategies to prevent the spread of HIV.

☒Yes ☐No	The Animal Study Proposal is designed to develop knowledge with the potential to improve human and/or animal health and well-being.
☒Yes ☐No	The study objectives are clearly stated and scientifically meritorious.
☒Yes ☐No	The experimental methods are reasonable and well justified.
☒Yes ☐No	There is a clear and rational explanation for using NHPs.
☒Yes ☐No	The number of animals required is well-justified and sufficient to achieve the study objectives.

By signing below, reviewer indicates that this is a scientifically meritorious study that is ready for ACUC review:

Redacted by agreement

Reviewer Signature, Date

Redacted by agreement

Printed Name

AIDS and Cancer Virus Program NHP Study Scientific Review Form

Date: 12/4/2020

Study Title: Evaluation of an IFNAR decoy

IACUC Number: Redacted by agreement

Scientific Justification:

Type I interferons (IFN-I) are cytokines produced early after viral infection and are involved in the regulation of both innate and adaptive immune responses. All type I IFNs bind to a common receptor, IFNAR, and trigger downstream transcription of a variety of IFN stimulated genes (ISGs). IFN-I signaling can induce an antiviral state, based on the expression of a specific set of ISGs referred to as restriction factors, that can inhibit viral replication at multiple points of the replication cycle. While this antiviral response is beneficial in the setting of many viral infections, during HIV and SIV infection IFN-I signaling can be a double edged sword. Aside from restriction factors, other ISGs can further enhance IFN-1 signaling and this positive feedback loop is a main driver of immune activation, one of the strongest predictors of HIV/SIV disease progression to AIDS. Chronic IFN-I signaling is associated with enhanced CD4 T cell depletion and immune suppression, characterized by reduced antigen-specific T cells responses, reduced T cell proliferation, and increased CD8 T cell exhaustion. Taken together, these findings have raised considerable interest in the potential of therapeutics to enhance or block IFN-I signaling at different stages of infection to maximize antiviral effects early in infection and reduce immune activation during chronic stages.

Our collaborators, Redacted by agreement have developed an IFNAR decoy molecule that may reduce IFN-I signaling by competing with endogenous, cell membrane bound IFNAR for binding of IFN-Is. While the safety and tolerability of this molecule has been evaluated in cynomologous macaques, it has not been tested in rhesus macaques or pigtail macaques, the most commonly used species for nonhuman primate models of HIV infection. Importantly, its activity has not be evaluated in any nonhuman primate species. This study is designed to assess the safety, tolerability, and activity of the IFNAR decoy to inhibit ISG expression in rhesus macaques and pigtail macaques. The study will be conducted in two groups. Uninfected rhesus macaques will first receive a TLR7/8 agonist, which has been shown to induce transient IFN expression and subsequent downstream ISG expression in rhesus macaques. After collecting blood samples to confirm IFN and ISG expression following TLR7/8 agonist administration, animals will receive a second course of TLR7/8 agonist along with the IFNAR decoy to assess the impact on IFN and ISG expression. A second group consisting of stHIV infected pigtail macaques will receive the IFNAR decoy during chronic, untreated infection to evalute the impact of the IFNAR decoy on IFN and ISG expression induced by

pathogenic infection. This pilot study will provide valuable data regarding the capacity of the IFNAR decoy to modulate IFN responses and its potential as a therapeutic drug during HIV infection.

☒Yes ☐No	The proposed research is scientifically significant.
☒Yes ☐No	The proposed research is expected to provide knowledge that will improve human and/or animal health.
☒Yes ☐No	The proposed experiments are well designed to address the study objectives.
☒Yes ☐No	The proposed nonhuman primate species is the appropriate experimental model for the study.
☒Yes ☐No	The number of nonhuman primates requested for use in the study is appropriate.

By signing below, review Chairperson indicates that at least two of three review committee members attest this is a scientifically meritorious study that is ready for ACUC review:

Redacted by agreement

Review Chairperson Signature, Date

Redacted by agreement

Printed Name