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14. ABSTRACT FGI-101-1A6 is a broad spectrum anti-TSG101 monoclonal antibody demonstrating broad in vitro anti-viral activity against several strains of Influenza and HIV. Under this contract, Functional Genetics will complete Phase Ia Human Safety Studies and an efficacy study against HIV in primates. This report describes the status of the program to date as well as outline the activities to be performed in the next period.					
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a. REPORT UU	b. ABSTRACT UU	c. THIS PAGE UU			19b. TELEPHONE NUMBER 240-631-6790

Report Title

Phase I Human Safety Studies of FGI-101-1A6 to Combat HINI Influenza Virus

ABSTRACT

FGI-101-1A6 is a broad spectrum anti-TSG101 monoclonal antibody demonstrating broad in vitro anti-viral activity against several strains of Influenza and HIV. Under this contract, Functional Genetics will complete Phase Ia Human Safety Studies and an efficacy study against HIV in primates. This report describes the status of the program to date as well as outline the activities to be performed in the next period.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received

Paper

TOTAL:

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

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Paper

TOTAL:

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received

Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received

Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received

Paper

TOTAL:

Number of Manuscripts:

Books

Received

Paper

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
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FTE Equivalent:

Total Number:

Names of Post Doctorates

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
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FTE Equivalent:

Total Number:

Names of Faculty Supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
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FTE Equivalent:

Total Number:

Names of Under Graduate students supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
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FTE Equivalent:

Total Number:

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:.....

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:

Names of Personnel receiving masters degrees

<u>NAME</u>
Total Number:

Names of personnel receiving PHDs

<u>NAME</u>
Total Number:

Names of other research staff

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

Functional Genetics, Inc.
Period of Performance November 1, 2010 - March 31, 2013

I. Statement of the Problem Studied:

The tasks performed under the contract were undertaken to determine the safety and efficacy of TSG101 monoclonal antibody FGI-101-1A6. The Phase 1a clinical study in healthy human subjects was designed to understand the safety and tolerability of the antibody and determine the drug's pharmacokinetic parameters. The optional task added under the contract was an efficacy study in a non-human primate model of HIV infection to establish efficacy in enveloped viruses that share a budding mechanism involving TSG101 such as Influenza and Ebola.

II. Summary of the Most Important Results

The following activities were undertaken in the reporting period of August 1, 2011 to March 31, 2013.

- Completion of the Clinical Study Report for the Phase 1a clinical trial in healthy human subjects under clinical protocol FGI-101-CP002.
- Efficacy evaluation of FGI-101-1A6 in an in vivo model of SIV infection.

Completion of the Clinical Study Report for the Phase 1a clinical trial in healthy human subjects under clinical protocol FGI-101-CP002.

The Phase 1a FGI-101-CP002 clinical trial in healthy volunteers included six ascending dose cohorts from a starting single dose of 0.0017 mg/kg to 10 mg/kg. The primary objective of the study was to understand the safety and tolerability of FGI-101-1A6 in healthy volunteers with the secondary objectives being the pharmacokinetic parameters of the drug product. Subjects were enrolled in each cohort sequentially starting with the lowest dose. Guided by the protocol and based on the safety data from the subjects through day 8 of dosing, the Safety Monitoring Committee (SMC) authorized the continuation to the next cohort. Subjects were closely monitored during the first 48 hours post infusion to identify any adverse events and clinical abnormalities. Follow up was continued over the next 60 days at various time intervals to collect blood samples and identify any long term adverse events.

The results of the clinical study indicated that treatment with FGI-101-1A6 was well tolerated by at all dose levels and was not associated with any local irritation. None of the subjects experienced serious adverse events. There were no reports of Grade 4 or 5 adverse events, and 3 subjects experienced Grade 3 adverse events. All 3 subjects experienced Grade 3 lipase increased, with one subject each in the 0.0017, 10.0 mg/kg and Placebo groups.

Pharmacokinetic (PK) analysis showed increased consistency of PK parameters with increased dose levels. Median tmax was 0.7 hrs for the 1.5 mg/kg group, 0.8 hrs for the 5.0 mg/kg group, and 2.2 hrs for the 10.0 mg/kg group and was fairly consistent with the end of infusion (30 minutes) in most subjects. Mean half life was 170-287 hours and appeared to be consistent across doses. The long half life is consistent with previously reported estimates for other monoclonal antibodies. A detailed study report is attached.

Efficacy evaluation of FGI-101-1A6 in an in vivo model of SIV infection.

Non-human primate models of SIV infection have been extensively used to study anti-HIV drug efficacy. In the current study, twelve female Rhesus macaques were infected intravaginally with SIV. Six animals were treated with 25 mg/kg of FGI-101-1A6 weekly for 3 weeks (4 doses total) starting 24 hours prior to virus infection. The remaining 6 monkeys were given a placebo control on the same schedule as antibody treatment. Blood samples were taken weekly just prior to dosing in order to measure virus titer and antibody levels. At the completion of the study all animals were sacrificed and necropsied to collect tissue for viral measurement. Efficacy was determined by comparing the amount of virus found in serum and tissues of the treated animals to those of the placebo control group. Evaluation of the blood and tissue samples for viral load showed no difference between treated and untreated animals. A detailed study report is attached.

Technology Transfer

Final Report
DARPA Contract No. W911NF-11-C-0029
Phase I Human Safety Studies of FGI-101-1A6
To Combat H1N1 Influenza Virus

Functional Genetics, Inc.
Period of Performance November 1, 2010 - March 31, 2013

I. List of Appendices

- a. Appendix 1: Clinical Study Report Synopsis
- b. Appendix 2: *In vivo* Efficacy Report

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The tasks performed under the contract were undertaken to determine the safety and efficacy of TSG101 monoclonal antibody FGI-101-1A6. The Phase 1a clinical study in healthy human subjects was designed to understand the safety and tolerability of the antibody and determine the drug's pharmacokinetic parameters. The optional task added under the contract was an efficacy study in a non-human primate model of HIV infection to establish efficacy in enveloped viruses that share a budding mechanism involving TSG101 such as Influenza and Ebola.

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Completion of the Clinical Study Report for the Phase 1a clinical trial in healthy human subjects under clinical protocol FGI-101-CP002.

The Phase 1a FGI-101-CP002 clinical trial in healthy volunteers included six ascending dose cohorts from a starting single dose of 0.0017 mg/kg to 10 mg/kg. The primary objective of the study was to understand the safety and tolerability of FGI-101-1A6 in healthy volunteers with the secondary objectives being the pharmacokinetic parameters of the drug product. Subjects were enrolled in each cohort sequentially starting with the lowest dose. Guided by the protocol and based on the safety data from the subjects through day 8 of dosing, the Safety Monitoring Committee (SMC) authorized the

continuation to the next cohort. Subjects were closely monitored during the first 48 hours post infusion to identify any adverse events and clinical abnormalities. Follow up was continued over the next 60 days at various time intervals to collect blood samples and identify any long term adverse events.

The results of the clinical study indicated that treatment with FGI-101-1A6 was well tolerated by at all dose levels and was not associated with any local irritation. None of the subjects experienced serious adverse events. There were no reports of Grade 4 or 5 adverse events, and 3 subjects experienced Grade 3 adverse events. All 3 subjects experienced Grade 3 lipase increased, with one subject each in the 0.0017, 10.0 mg/kg and Placebo groups.

Pharmacokinetic (PK) analysis showed increased consistency of PK parameters with increased dose levels. Median t_{max} was 0.7 hrs for the 1.5 mg/kg group, 0.8 hrs for the 5.0 mg/kg group, and 2.2 hrs for the 10.0 mg/kg group and was fairly consistent with the end of infusion (30 minutes) in most subjects. Mean half life was 170-287 hours and appeared to be consistent across doses. The long half life is consistent with previously reported estimates for other monoclonal antibodies.

In summary, pharmacokinetic and safety results from this clinical study support continued clinical investigation of monoclonal antibody FGI-101-1A6. A synopsis of the study attached as Appendix 1.

Efficacy evaluation of FGI-101-1A6 in an in vivo model of SIV infection.

Non-human primate models of SIV infection have been extensively used to study anti-HIV drug efficacy. In the current study, twelve female Rhesus macaques were infected intravaginally with SIV. Six animals were treated with 25 mg/kg of FGI-101-1A6 weekly for 3 weeks (4 doses total) starting 24 hours prior to virus infection. The remaining 6 monkeys were given a placebo control on the same schedule as antibody treatment. Blood samples were taken weekly just prior to dosing in order to measure virus titer and antibody levels. At the completion of the study all animals were sacrificed and necropsied to collect tissue for viral measurement. Efficacy was determined by comparing the amount of virus found in serum and tissues of the treated animals to those of the placebo control group. Evaluation of the blood and tissue samples for viral load showed no difference between treated and untreated animals. A detailed study report is attached as Appendix 2.

Appendix 1

1. SYNOPSIS

Name of Sponsor/Company: Functional Genetics, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: FGI-101-1A6 (fully human monoclonal antibody directed against TSG101)		
Name of Active Ingredient: FGI-101-1A6		
Title of Study: A Phase 1a, Double-Blind, Placebo-Controlled, Single, Ascending Dose Escalation Study to Determine the Pharmacokinetics and Safety of FGI-101-1A6 Administered as an Intravenous Infusion in Sequential Cohorts of Healthy Adult Volunteers		
Investigators: Mohammed Al-Ibrahim, MB, ChB, FACP		
Study centre: SNBL Clinical Pharmacology Center, 800 West Baltimore St., Baltimore, MD 21201		
Publication (reference) None		
Studied period (years): (date of first informed consent): 20 Dec 2010 (date of last completed visit): 12 Jul 2011	Phase of development: Phase 1	
Objectives: Primary: • To evaluate the safety and tolerability of single, escalating doses of FGI-101-1A6 administered as an intravenous (IV) infusion in healthy adult volunteers Secondary: • To evaluate the single dose pharmacokinetics (PK) of FGI-101-1A6 • To evaluate the immunogenicity of FGI-101-1A6 (induction of anti-drug antibodies)		
Methodology: This was a single center, randomized, double-blind, placebo-controlled, single, ascending dose-escalation study to assess the safety, pharmacokinetic (PK) and immunogenicity of single doses of FGI-101-1A6 in healthy adults. Up to 6 dose level cohorts were to be enrolled sequentially; within each dose level cohort, the first 2 subjects were randomized in a 1 to 1 ratio to receive FGI-101-1A6 or placebo and the remaining subjects were randomized in a 5 to 1 ratio to receive FGI-101-1A6 or placebo.		

Name of Sponsor/Company: Functional Genetics, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: FGI-101-1A6 (fully human monoclonal antibody directed against TSG101)	Volume:	
Name of Active Ingredient: FGI-101-1A6	Page:	

Number of subjects (planned and analyzed): For this study, 48 - 60 subjects were planned to be enrolled (up to six cohorts with 8 - 10 subjects for each dose level). In total, 48 subjects (36 treated with FGI-101-1A6 and 12 placebo subjects) were enrolled in the study, received study medication and provided data. All 48 subjects were included in analyses of safety and PK.
Diagnosis and main criteria for inclusion: Healthy adults 18 to 45 years of age with no history of major medical conditions.
Test product, dose and mode of administration, batch number: A single dose of FGI-101-1A6 or placebo (0.9% Sodium Chloride for Injection, USP) was administered by intravenous (IV) infusion with an infusion pump over 30 minutes using an infusion set with an in-line, sterile, non-pyrogenic, low-protein binding filter of pore size 0.22 µm. The dosage form of FGI-101-1A6 is a parenteral solution provided in single-use glass vials. The formulation is 22.7 mg of the active pharmaceutical ingredient per mL in 20 mM histidine, 50 mM glycine, 7.0% trehalose and 0.01% polysorbate-80. The volume of the infused solution remained constant in each cohort (to preserve blinding) by further diluting the drug product as needed with the formulation buffer. Total FGI-101-1A6 per injection (assuming 65 kg) were 0.11 mg, 0.98 mg, 9.80 mg, 98.0 mg, 325 mg, and 650 mg.
Duration of treatment: The study was conducted over 5 months including a 2-month post-infusion period.
Reference therapy, dose and mode of administration, batch number: The placebo used for the study is commercially available 0.9% Sodium Chloride for Injection, USP administered by intravenous (IV) infusion with an infusion pump over 30 minutes using an infusion set with an in-line, sterile, non-pyrogenic, low-protein binding filter of pore size 0.22 µm.

Name of Sponsor/Company: Functional Genetics, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: FGI-101-1A6 (fully human monoclonal antibody directed against TSG101)		
Name of Active Ingredient: FGI-101-1A6		

Criteria for Evaluation: Efficacy: The primary intent of the study was to determine the dose(s) of FGI-101-1A6 to be studied in subsequent trials. The secondary endpoints were to determine the PK of FGI-101-1A6 following single doses as determined by serial measurements of concentration in serum and to evaluate the potential immunogenicity of single doses of FGI-101-1A6 as determined by serial measurements of human anti-FGI-101-1A6 antibody. Safety: Tolerability was assessed based on AEs, physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory tests (hematology, blood chemistries, urinalysis, and creatinine clearance).
Statistical methods: <u>Sample Size Justification</u> The main objectives of this study were to evaluate safety and characterize the PK profile of FGI-101-1A6 in normal healthy adults. Sample size calculations based on primary parameters of interest were not used in determining the number of subjects. The sample size was based on feasibility and consistency with first-time-in-human, Phase 1, single ascending dose study designs. In total, 48 subjects completed the study. Subjects who were discontinued early were not replaced. <u>Pharmacokinetics</u> Descriptive summary statistics including median, mean, geometric mean, standard deviation (SD), range and %CV were reported by dose. Plots of dose normalized C_{max} and AUC(0-∞) were generated to provide a preliminary evaluation of the relationship between dose and exposure. <u>Safety</u> The safety data are presented in individual listings and tabular summaries by dose level. The safety data include all adverse events (AE), vital signs, ECG and physical examination data, and laboratory data.

Name of Sponsor/Company: Functional Genetics, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: FGI-101-1A6 (fully human monoclonal antibody directed against TSG101)	Volume:	
Name of Active Ingredient: FGI-101-1A6	Page:	

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

Complete results of this single, ascending dose Phase 1 study designed to determine the PK of a single dose of FGI-101-1A6 administered as an intravenous infusion in healthy adult volunteers are provided in Appendix 16.1.13.

SAFETY RESULTS:

- Treatment with FGI-101-1A6 was generally well tolerated by subjects in this study.
- No subjects died or experienced an SAE. One subject discontinued the study due to Grade 2 hematuria.
- There were no reports of Grade 4 or 5 TEAEs, and 3 subjects experienced Grade 3 TEAEs. All 3 subjects experienced Grade 3 lipase increases, with one subject each in the 0.0017, 10.0 mg/kg and Placebo groups.

CONCLUSION:

In this study, considerable variability was evident in the concentrations of FGI-101-1A6 across subjects for the lower dose groups (0.0017, 0.015, and 0.15 mg/kg), and PK results for subjects in the higher dose groups were more consistent. For the higher dose groups (1.5 mg/kg, 5.0 mg/kg, and 10.0 mg/kg), mean C_{max} and AUC estimates increased with increasing dose but increases were not dose proportional. Mean half life was 170-287 hours and appeared to be consistent across doses. The long half life is consistent with previously reported estimates for other monoclonal antibodies.

Results of this Phase 1 study indicate that FGI-101-1A6 administered as an intravenous infusion in healthy adult volunteers was well tolerated at all doses, and was not associated with any local irritation. In summary, pharmacokinetic and safety results from this study support continued clinical investigation of FGI-101-1A6.

Date of report: 17 October 2011

Appendix 2

Final Report:

Effect of FGI-101-1A6 on SIV Transmission

Principal Investigator: **Christopher J. Miller**

Institution: **Center for Comparative Medicine
University of California, Davis**

Date of Report: **November 16, 2012**

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h. Lymphoid Tissue SIV GAG vRNA Data

Summary:

The objective of this project was to test the effect of FGI-101-1A6 on vaginal transmission of 5000 50% Tissue Culture Infectious Dose (TCID₅₀) of SIVmac251. Animal experiments started on May 21, 2012 as scheduled. By November 16, 2012, animal experiments had been finished as per protocol, assays were performed on all collected samples, data was compiled and results prepared for this report. All procedures were followed as per protocol with no changes. All data has been kept confidential. There were no significant differences between the groups in plasma and lymphoid tissue vRNA.

A. Objective: To evaluate the effect on vaginal SIV transmission by infusing animals with FGI-101-1A6 (mAb) or Placebo

B. Progress to date: The study was completed on November 16, 2012

C. Results

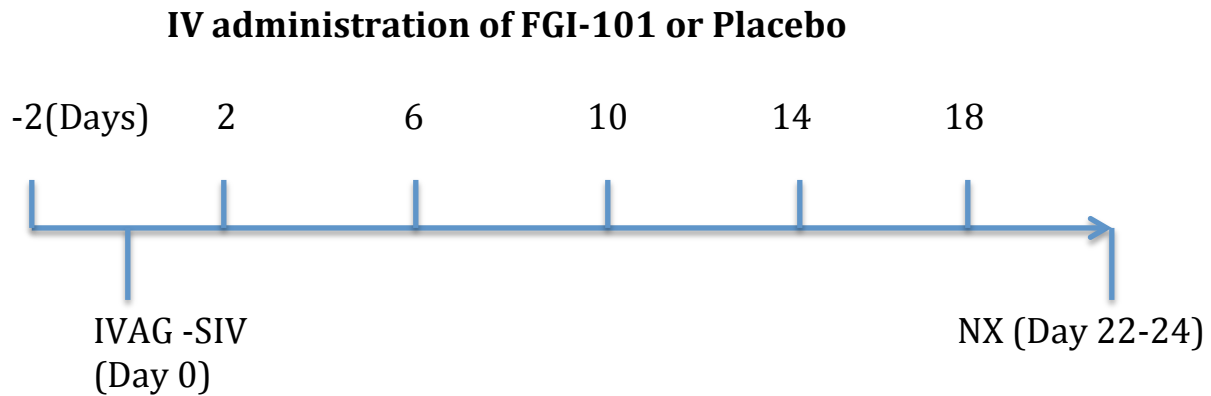
a. Experimental design

1. Animals: 12 adult, normal cycling, female rhesus macaques
2. Groups: 2 treatment groups, each subdivided into two groups. One group received FGI-1-1-1A6 (Experimental Group A), the other received the Placebo (Control Group B)
3. Treatment: Animals were infused IV with either FGI-101-1A6 or Placebo, on Days -2, 2, 6, 10, 14 and 18 post SIV inoculation.
4. Inoculation: Animals were inoculated intravaginally with a 5000 TCID₅₀ of SIVmac251 48 hours after first mAb infusion.
5. Follow up: The animals were followed for 22-24 days post SIV inoculation.
6. Procedures:
 - i. Blood Collection: Blood was collected on Days -2, 0, 1, 2, 6, 10, 14, 18 and at necropsy.
 - ii. Necropsy: Animals were sacrificed 22 to 24 days following SIV inoculation.

b. Study Endpoints

1. Plasma Viral RNA (quantitative RT-PCR assay)
2. Tissue Viral RNA (quantitative RT-PCR assay)

c. Timeline of Project



d. Experimental Group Information

1. Animals Enrolled: 12 adult normal cycling female rhesus macaques
2. Two Groups: A (mAb treated) & B (Placebo treated)
3. Subdivided: A1, A2, B1, B2
4. Experimental Start Date: A1- 06/16/12
A2- 09/08/12
B1- 06/16/12
B2- 09/08/12

e. Monoclonal Antibody Information:

FGI-101-1A6: Initial Stock (Lots 387-01-001 and 387-01-002)-
20mg/ml in a buffer containing 20mM Histidine, 50mM L-glycine, 7%
Trehalose, 0.01% Polysorbate 80.

Placebo: Lot 387-02-001, 20mg/ml

Monoclonal Antibody was given to each animal, in the Experimental
Group A, at a concentration of 25mg/kg in a total volume of 10mls,
using the placebo as the diluent.

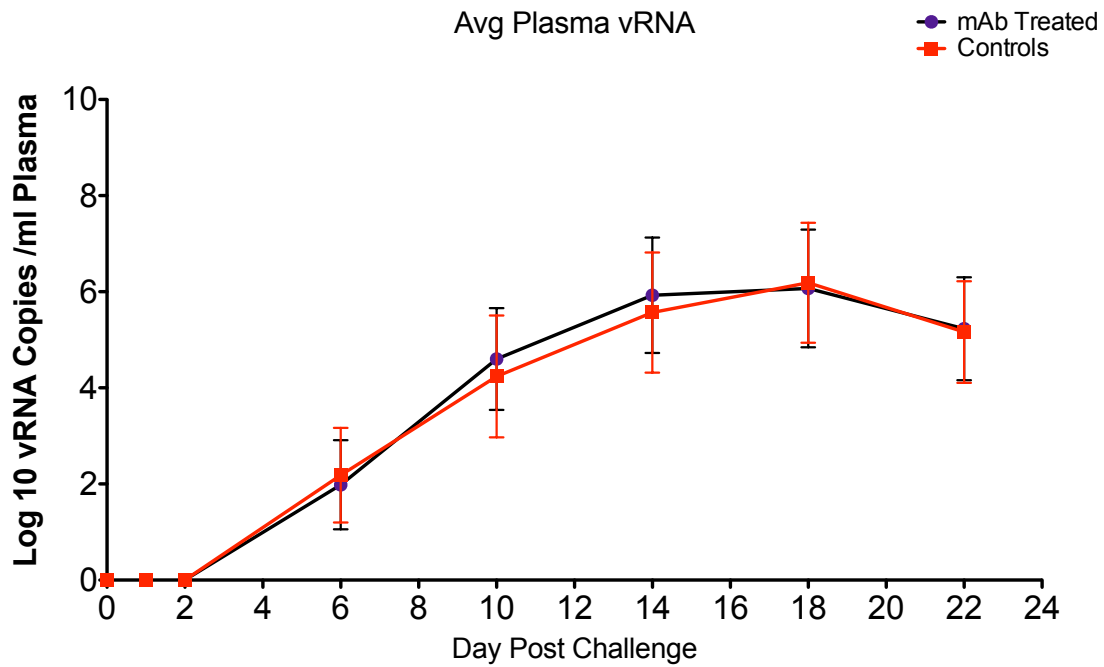
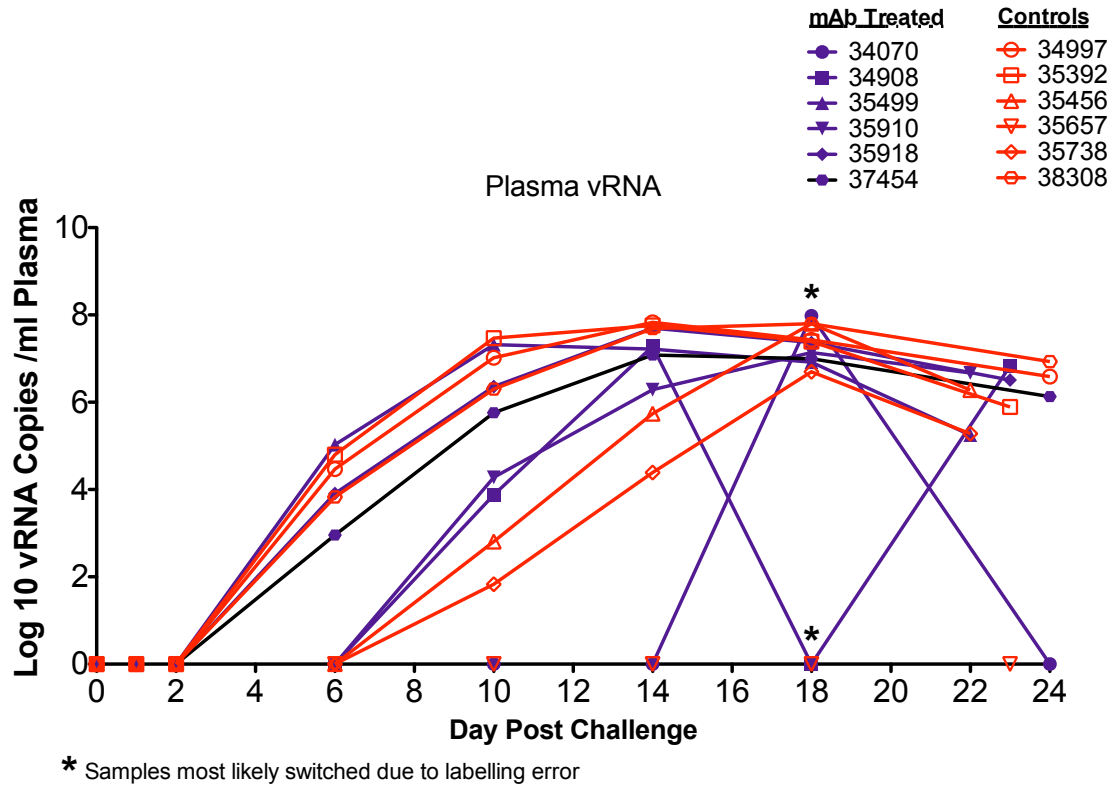
For Control Group B, 10mls of the Placebo was given at each time point.

Group	Treatment	Dates
A1	FGI-101-1A6	6/16, 6/20, 6/24, 6/28, 7/2, 7/6/12
A2	FGI-101-1A6	6/16, 6/20, 6/24, 6/28, 7/2, 7/6/12
B1	Placebo	6/16, 6/20, 6/24, 6/28, 7/2, 7/6/12
B2	Placebo	6/16, 6/20, 6/24, 6/28, 7/2, 7/6/12

f. Animal Information:

Animal #	Age (at NX)	Group	Treatment
34070	10y2mo	A1	FGI-101-1A6
34908	9y3mo	A1	FGI-101-1A6
35499	8y3mo	A1	FGI-101-1A6
35910	8y4mo	A2	FGI-101-1A6
35918	8y4mo	A2	FGI-101-1A6
37454	6y5mo	A2	FGI-101-1A6
34997	9y2mo	B1	Placebo
35392	8y4mo	B1	Placebo
35456	8y3mo	B1	Placebo
35657	8y5mo	B2	Placebo
35738	8y5mo	B2	Placebo
38308	5y5mo	B2	Placebo

g. Plasma SIV GAG vRNA Data

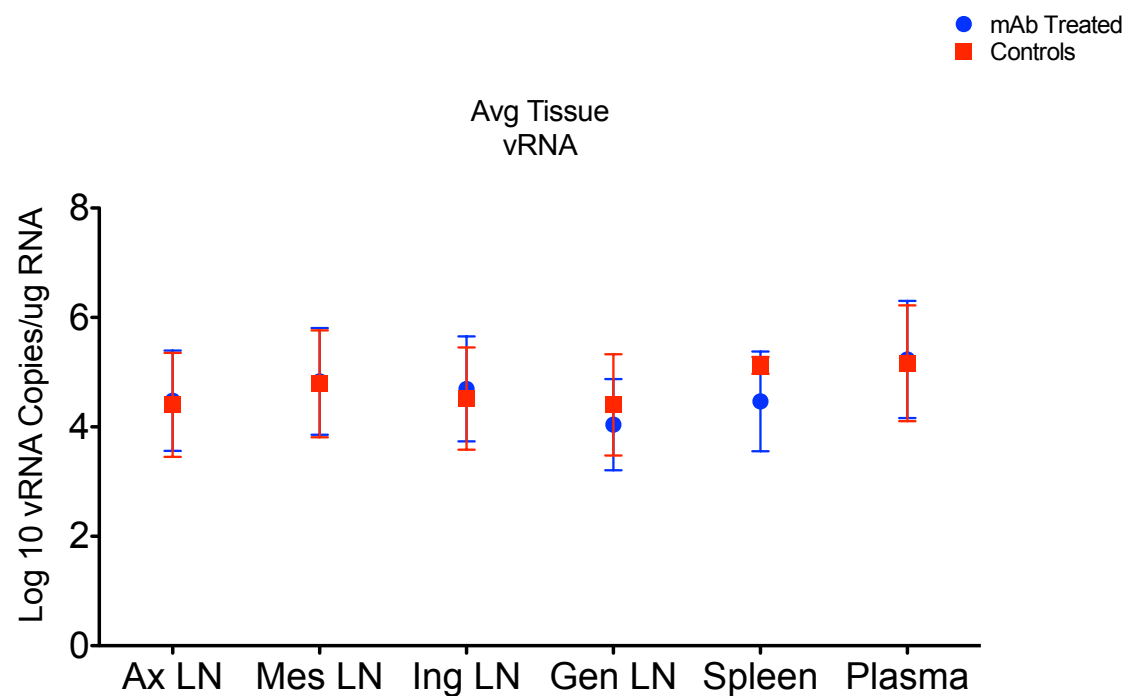
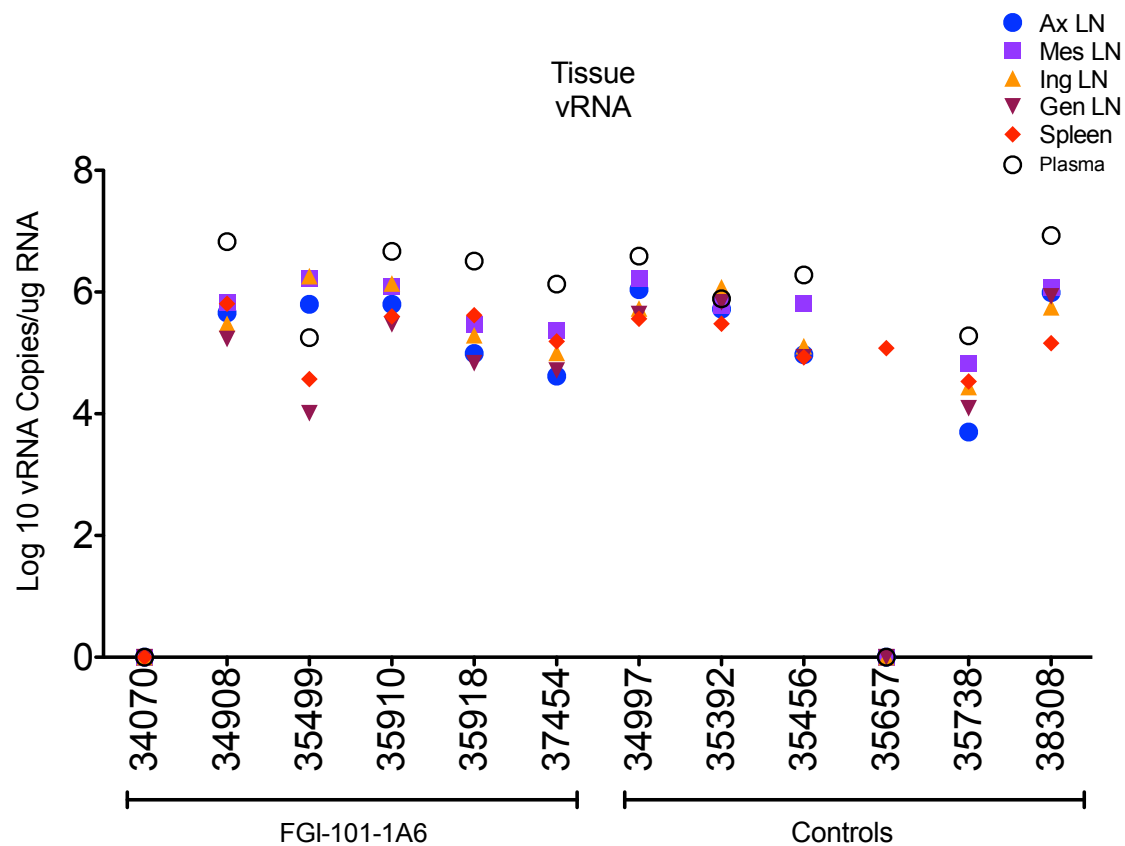


Plasma Log₁₀ vRNA

Animal #		Day	PC						
Group A-FGI-101-1A6		0	1	2	6	10	14	18	NX
34070	Group1	Neg	Neg	Neg	Neg	Neg	Neg	7.98	Neg
34908		Neg	Neg	Neg	Neg	3.88	7.28	Neg	6.83
35499		Neg	Neg	Neg	5.03	7.32	7.22	6.92	5.25
35910	Group2	Neg	Neg	Neg	Neg	4.28	6.29	7.14	6.67
35918		Neg	Neg	Neg	3.91	6.36	7.7	7.37	6.51
37454		Neg	Neg	Neg	2.96	5.76	7.08	7	6.13
Group B-Placebo (Controls)									
34997	Group1	Neg	Neg	Neg	4.47	7.02	7.83	7.43	6.59
35392		Neg	Neg	Neg	4.8	7.47	7.76	7.39	5.89
35456		Neg	Neg	Neg	Neg	2.81	5.74	7.8	6.28
35657	Group2	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
35738		Neg	Neg	Neg	Neg	1.83	4.39	6.7	5.28
38308		Neg	Neg	Neg	3.83	6.3	7.69	7.8	6.93

Note-Values in red most likely switched due to labeling error. We are still calling 34070 negative and 34908 positive.

h. Lymphoid Tissue SIV GAG vRNA Data



Tissue Log₁₀ vRNA

Animal #		Ax LN	Mes LN	Ing LN	Gen LN	Spleen	Plasma
Group A-FGI-101-1A6							
34070	Group 1	Neg	Neg	Neg	Neg	Neg	Neg
34908		5.66	5.83	5.48	5.23	5.81	6.83
35499		5.8	6.23	6.26	4.01	4.57	5.25
35910	Group 2	5.8	6.1	6.14	5.47	5.6	6.67
35918		4.99	5.46	5.29	4.83	5.62	6.51
37454		4.62	5.37	5	4.71	5.19	6.13
Group B-Placebo (Controls)							
34997	Group 1	6.04	6.22	5.73	5.64	5.56	6.59
35392		5.72	5.78	6.08	5.83	5.48	5.89
35456		4.97	5.81	5.11	4.93	4.93	6.28
35657	Group 2	Neg	Neg	Neg	Neg	5.08	Neg
35738		3.7	4.83	4.44	4.09	4.53	5.28
38308		5.99	6.08	5.75	5.93	5.16	6.93