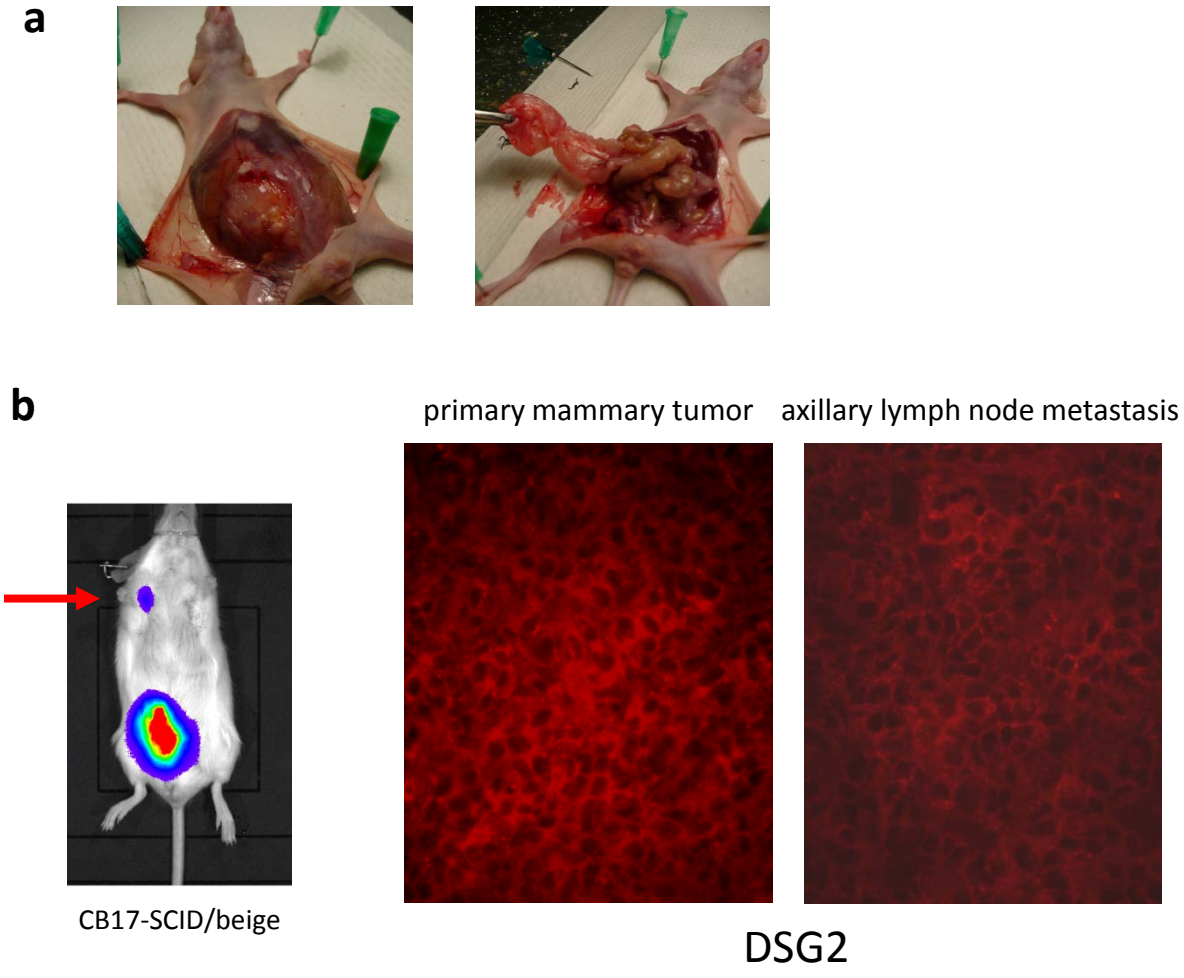
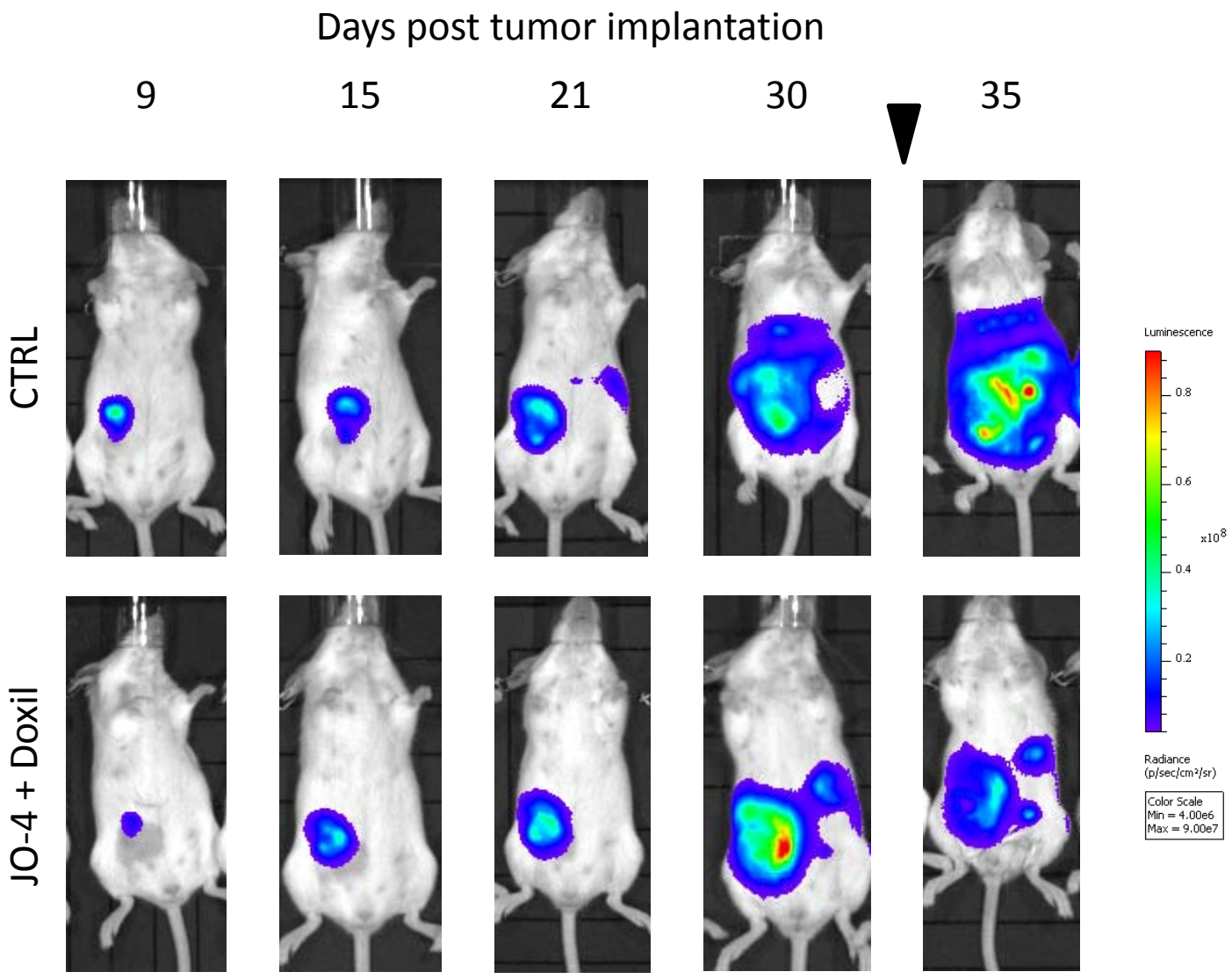


Suppl. Fig.1 Mouse model with invasive cancer and spontaneous metastases. Mammary fat pad tumor derived from MDA-MB-231-luc-D3H2LN were established. **a)** The primary tumor invades and penetrates the peritoneum. **b)** primary tumors were removed when they reached a volume of ~200mm and before they became attached to the peritoneum. 5 weeks later axillary metastases were observed by *in vivo* luciferase imaging. The image also shows residual primary tumor that re-grew. Right panel: DSG2 immunofluorescence analysis of sections from the primary tumor and axillary lymph node metastases. DSG2 appears in red in cell membranes. The images are representative for the other animals.



Suppl. Fig.2 Monitoring of therapeutic effect of JO-4+Doxil by *in vivo* imaging. Shown are a representative control untreated (CTRL, top) and treated animal (bottom). Treatment was started at day 31.

Accession # 12-165
Submission Date 26 July 2012

University of Washington
National Primate Research Center

DIAGNOSTIC LABORATORY NECROPSY REPORT

Requester DR Investigator Lieber Animal ID # A10271
Species Mfl Requester's Phone

Date of Death July 26, 2012 Date of Necropsy July 26, 2012 Time 8:30am Pathologist AB

Nutritional Condition: ☒ Adequate ☐ Marginal ☐ Poor ☐ Obese

Other Tests Required: ☐ Sero ☐ Micro ☐ Parasit ☐ Other

Other Diagnostic Samples

Type of report: ☒ Final _31 Aug 2012_ ☒ Preliminary 27 July 2012 ☐ Amended

Clinical History: this animal was assigned to the "Safety studies with a companion therapeutic for chemotherapy drugs and monoclonal antibodies to treat cancer" protocol. There was a transient mild leukocytosis and neutrophilia on July 24th and mild elevation in ALT and AST on July 25-26.

Gross Description: a 4.81 year old, 5.54 kg, male M. fascicularis is submitted in good nutritional and post mortem condition. No external lesions or gross lesions are seen.

Gross Diagnosis(es): None

Histological Findings:
Gastro-intestinal tract: there is moderate to occasionally severe, lymphocytic plasmacytic and mildly eosinophilic inflammation, extending from the stomach into the large intestine. Plasma cells often predominate. There are multifocal hyperplastic lymphoid aggregates in the deep mucosa and submucosa, coalescing in the ileum. There are mixed bacteria in the lumen, and rare ciliates. Villi are blunted in the duodenum and appear more robust in the jejunum. Low numbers of small lymphocytes extend into the mucosal epithelium within villi to mid mucosa.

Sections from the brain, cerebellum, brain stem, eye, lymph nodes (mesenteric (slide 4) and submandibular (slide 5), diffuse mild to moderate reactive hyperplasia), left and right adrenal glands, left and right kidneys (few sloughed renal tubular epithelial cells), urinary bladder, lung (normal peribronchial and perivascular lymphoid tissue, occasional mild respiratory epithelial hyperplasia), left and right testes, seminal vesicle, prostate gland, thymus, bone marrow core and cytology / impression smear (mild myeloid hyperplasia with orderly maturation and adequate erythroid and megakaryocytic cells and iron stores), trachea (mild, multifocal submucosal lymphoid hyperplasia), liver and gall bladder (minimal lymphocytic, plasmacytic, neutrophilic and eosinophilic cholangiohepatitis), spleen (mild lymphoid follicular hyperplasia, mild to moderate mixed extramedullary hematopoiesis), heart (moderate myofiber anisokaryosis), aorta, skeletal muscle, skin, esophagus and pancreas are examined and no histologic changes seen with the exception of those stated.

Final Principal Diagnosis(es):

1. Gastroenterocolitis, diffuse, moderate to severe, lymphocytic, plasmacytic and mildly eosinophilic.

Cause of Death: Experimental euthanasia.

Histology Comments: histologic examination is consistent with gastroenterocolitis, changes which are commonly seen within the colony. The etiology of these changes are likely multifactorial. Interpret with antemortem physical exam findings to evaluate clinical significance. The transient leukocytosis / neutrophilia may have been due to stress, as it was mild and resolved quickly. Other minor histologic changes as stated are unlikely to have been clinically significant.

Pathologist_____AB_____

University of Washington
National Primate Research Center

Accession # 12-166
Submission Date July 26, 2012

DIAGNOSTIC LABORATORY NECROPSY REPORT

Requester DR Investigator Lieber Animal ID # A10272
Species Mfl Requester's Phone _____

Date of Death July 26, 2012 Date of Necropsy July 26, 2012 Time 9:30am Pathologist AB

Nutritional Condition: ☒ Adequate ☐ Marginal ☐ Poor ☐ Obese

Other Tests Required: ☐ Sero ☐ Micro ☐ Parasit ☐ Other _____

Other Diagnostic Samples _____

Type of report: ☒ Final 31 Aug 2012 ☒ Preliminary July 27, 2012 ☐ Amended _____

Clinical History: this animal was assigned to the "Safety studies with a companion therapeutic for chemotherapy drugs and monoclonal antibodies to treat cancer" protocol. The hematology data shows leukocytosis and neutrophilia July 23-26, with monocytosis in the 26th, and mild elevation in AST on July 24 and 26.

Gross Description: a 5 year old, 6.96 kg, male M. fascicularis is submitted in good nutritional and post mortem condition. No external lesions are seen. Internal organs are grossly normal.

Gross Diagnosis(es): None

Gross comments: No gross lesions are seen. Microscopic examination is pending.

Histological Findings:
Brain stem: there is multifocal, mild perivascular acute hemorrhage within the brain stem, unassociated with inflammation or gliosis, interpreted to be most consistent with an agonal change.

Lung: there is multifocal, minimal to mild interstitial, mixed and neutrophilic pneumonia with scattered syncytial cells, mild alveolar edema and mild type II pneumocyte hyperplasia. Alveoli in these areas contain small amounts of foamy macrophages or are obscured by collapsed interstitium. Peribronchial and perivascular lymphoid aggregates appear to be normal.

Left and right testes: there are low numbers of multinucleated cells within the seminiferous tubules, along with sloughed tubular cells. Spermatogenesis appear to be progressing in some tubules and is arrested or sparse in others. The epididymis contains dense clusters of spermatids in some tubules and other are sparse.

Seminal vesicles: tubules contain lakes of eosinophilic proteinaceous material and oval basophilic structures (spermatid heads). There are overall low numbers of spermatids.

Prostate gland: There are rare small aggregates of lymphocytes and plasma cells with fewer neutrophils within the interstitial connective tissue. Small lymphocytes occasionally extend into the tubular

epithelium. The tubular lumens are predominantly empty or contain small amounts of protein material, cell debris and sloughed epithelial cells.

Spleen: lymphoid follicles appear to be of normal size, with occasional mild hyperplasia. The splenic stroma is congested with abundant extramedullary hematopoiesis, especially of myeloid cells progressing to numerous mature neutrophils.

Bone marrow: there is moderate to occasionally marked myeloid hyperplasia, progressing to mature neutrophils and eosinophils. Erythroid cells appear adequate and are maturing, and adequate megakaryocytes are present. Iron is sparse.

Gastro-intestinal tract: there is diffuse, moderate to occasionally marked lymphocytic, plasmacytic inflammation within the stomach, small and large intestines. Fewer eosinophils and neutrophils are seen. Villi are blunted. There are multifocal hyperplastic lymphoid aggregates and follicles in the deep mucosa to submucosa. Mixed bacteria and ingesta are present in the lumen.

Sections from the cerebrum, cerebellum, pituitary gland, eye, inguinal (slide 5), mesenteric (slide 6) and submandibular (slide 7) lymph nodes (mild to moderate lymphoid follicular hyperplasia with focal tattoo ink (inguinal node)), left and right adrenal glands, left and right kidneys (rare, mild interstitial lymphocytic, plasmacytic nephitis and rare tubular epithelial cell degeneration and luminal proteinaceous material), liver (mild lymphocytic, plasmacytic periportal cholangiohepatitis, mild centrilobular hepatocellular vacuolization), urinary bladder, heart (mild anisokaryosis), thymus, pancreas, trachea, esophagus, aorta, thyroid and parathyroid gland, aorta, skin, skeletal muscle and examined and no abnormalities found with the exception of those minor stated changes described above.

Final Principal Diagnosis(es):

1. Multifocal, minimal to mild interstitial pneumonia, with mild alveolar histiocytosis; lung.
2. Multifocal reduced spermatogenesis; testes.
3. Splenic extramedullary hematopoiesis with myeloid predominance.
4. Myeloid hyperplasia, moderate to marked: bone marrow.
5. Gastroenterocolitis, diffuse, moderate to marked, chronic to mixed, with villous blunting.

Cause of Death: Experimental euthanasia.

Histology Comments: There is evidence of myeloid hyperplasia with the bone marrow (cytology and fixed tissue) and spleen. This may be associated with an inflammatory stimulis and is consistent with the leukocytosis / neutrophilia seen in the hematology data, with WBC count of 25,440 on July 24th. Stress may be playing a role in the leukocytosis (but is not typically associated with myeloid hyperplasia). No infectious agents are seen within the examined tissue sections. There is diffuse gastro-enterocolitis, which may be contributing to an inflammatory response. Testicular maturation may vary in animals of the age range of 3 to 5 years of age, and the variability in spermatogenesis may be at least partially due to age / immaturity.

Pathologist_____AB_____

University of Washington
National Primate Research Center

Accession # 14-139
Submission Date 14 July 2014

DIAGNOSTIC LABORATORY NECROPSY REPORT

Requester DM Investigator AL Animal ID # A11293
Species Mf Requester's Phone

Date of Death 14 Jul 2014 Date of Necropsy 14 Jul 2014 Time 4:50 pm Pathologist AB

Nutritional Condition: ☒ Adequate ☐ Marginal ☐ Poor ☐ Obese

Other Tests Required: ☐ Sero ☐ Micro ☐ Parasit ☐ Other

Other Diagnostic Samples

Type of report: ☒ Final 30 Jul 2014 ☒ Preliminary 14 July 2014 ☐ Amended

Clinical History: this animal was assigned to the "toxicology studies with adenovirus proteins in NHPs" protocol. No clinical abnormalities are noted. Current CBC and chemistry panel appear unremarkable.

Gross Description: this 5 year, 11 month old, 6.2 kg intact male cynomolgous macaque is presented in good nutritional and post mortem condition. The right cheek pouch is distended by spongy bedding material; the pouch appears normal after removal of the material. No other significant external lesions are observed, and all body systems, including the musculoskeletal, nervous, cardiovascular, respiratory, digestive, urogenital, endocrine, lymphatic and integumentary systems appear grossly unremarkable.

Gross Diagnosis(es):
1. Unremarkable gross exam

Gross Comments:

There were no significant gross lesions. Histology is pending. Touch imprints of bone marrow were prepared in necropsy and are stained with Wrights giemsa.

Histological Findings:
Lungs: sections from two lobes contain multifocal bronchiolar and alveolar aggregates of macrophages, multinucleated cells, and neutrophilis, sometimes filling smaller air spaces. There is occasional amphophilic to fibrous foreign material surrounded by or within the multinucleated cells. Minimal fibroplasia is present in the surrounding connective tissue. Sections from three lobes display multifocal, mild to moderate perivascular and peribronchiolar lymphohistiocytic aggregates and pneumoconiosis with occasional alveolar histiocytic cells.

Gastrointestinal tract: there is multifocal to diffuse, moderate to severe lymphocytic, plasmacytic and eosinophilic mucosal inflammation, with multifocal, scattered moderately hyperplastic lymphoid follicles, especially in the stomach, ileum, cecum and colon. Plasma cells display multifocal Mott cell

differentiation. Villi are diffusely blunted within the duodenum and more mildly blunted in the jejunum. The colonic mucosa is diffusely edematous.

Sections of brain, cerebellum, brainstem, pituitary gland, eye and lacrimal glands, spleen (normal lymphoid activity, moderate, mixed myeloid and erythroid hematopoiesis), lymph nodes (axillary, inguinal, hilar (mild lymphoid hyperplasia, sinus histiocytosis with occasional pigmented macrophages), liver (mild centrilobular hepatocellular atrophy and minimal periportal lymphohistiocytic inflammation), gall bladder, heart (few/minimal random perivascular lymphohistiocytic cells (normal background)), aorta, kidneys (minimal parietal epithelial hyperplasia), urinary bladder, trachea, esophagus, pancreas, salivary gland, thyroid glands, adrenal glands, tongue, skeletal muscle, testicle (occasional mildly reduced spermatogenesis), epididymis (normal amounts of spermatids), seminal vesicle, prostate gland, skin (thigh and ventral abdomen with mammary gland – few dermal individual pigmented macrophages) and bone marrow histology and cytology (normal megakaryocytic, myeloid and erythroid numbers and maturation, approximately 2:1 M:E, adequate iron stores) are unremarkable besides stated minor changes.

Final Principal Diagnosis(es):

1. Pneumonia, multifocal / patchy (two lobes), mild to moderate, macrophagic and neutrophilic, with intra- and extra-cellular foreign material.
2. Gastroenterocolitis, multifocal to diffuse, moderate to severe, mixed with villous blunting and fusion and multifocal lymphoid hyperplasia.

Cause of Death: Experimental euthanasia.

Histology Comments: the inflammatory foci in the lungs are seen in two lobes and were unlikely to have been detectable clinically. The foreign material is seen in macrophages in bronchioles and adjacent alveoli and most likely represents aspirated ingesta or other material, unrelated to the experimental protocol. Gastroenterocolitis is commonly observed in the colony, and development of this lesion is most likely multifactorial, with potential factors including nutritional, stress or possibly food intolerances or allergies. Other minor changes are interpreted to be nonspecific background or incidental findings.

Pathologist_____AB_____

University of Washington
National Primate Research Center

Accession # 14-138
Submission Date 14 July 2014

DIAGNOSTIC LABORATORY NECROPSY REPORT

Requester DM Investigator AL Animal ID # A11288
Species Mfl Requester's Phone

Date of Death 14 Jul 2014 Date of Necropsy 14 Jul 2014 Time 3:40pm Pathologist AB

Nutritional Condition: ☒ Adequate ☐ Marginal ☐ Poor ☐ Obese

Other Tests Required: ☐ Sero ☐ Micro ☐ Parasit ☐ Other

Other Diagnostic Samples

Type of report: ☒ Final 29 Jul 2014 ☒ Preliminary 14 July 2014 ☐ Amended

Clinical History: this animal was assigned to the "toxicology studies with adenovirus proteins in NHPs" protocol. Daily clinical observations indicate normal activity, appetite and normal stools. CBC shows mild lymphocytosis (nonspecific reactivity to a number of possible antigens), and chemistry panel is unremarkable.

Gross Description: this 5 year old, 5.6 kg intact male cynomolgous macaque is presented euthanized in good post mortem and nutritional (adequate muscling and adipose stores) condition. No significant external lesions are observed, and all body systems, including the musculoskeletal, nervous, cardiovascular, respiratory, digestive, urogenital, endocrine, lymphatic and integumentary systems appear grossly unremarkable.

Gross Diagnosis(es):

1. Unremarkable gross exam

Gross Comments:
There were no significant gross lesions. Histology is pending. Touch imprints of bone marrow were prepared in necropsy and are stained with Wrights giemsa.

Histological Findings:
Gastrointestinal tract: there is multifocal to diffuse, moderate lymphocytic, plasmacytic inflammation within the mucosa with scattered hyperplastic lymphoid follicles, especially in the stomach, ileum and cecum. Plasma cells predominate in the stomach and small intestine, with scattered Mott cell differentiation. Fewer eosinophils are observed proximally and are present in approximately equal amounts to the mononuclear cells in the colon. Villi are robust (jejunum) to occasionally mildly blunted (duodenum).

Sections of brain, cerebellum, brainstem, pituitary gland, proximal cervical spinal cord, eye and lacrimal glands (few periductal lymphocytes), spleen (robust follicular activity, moderate mixed myeloid and erythroid hematopoiesis), lymph nodes (axillary (mild lymphoid hyperplasia with sinus histiocytes and few pigmented macrophages (skin tattoo ink)), inguinal, hilar), liver (mild centrilobular hepatocellular atrophy

and mild periportal lymphohistiocytic inflammation), gall bladder, heart (few/minimal random perivascular and focal subvalvular small lymphocytes (normal background)), aorta, kidneys (mild, multifocal glomerular endothelial and parietal epithelial hyperplasia, focal/single glomerular fibrin thrombus, and focal corticomedullary lymphohistiocytic infiltrates), urinary bladder, lungs (mild perivascular, peribronchial and peribronchiolar lymphohistiocytic aggregates and minimal pneumoconiosis), trachea, esophagus, pancreas, salivary gland (mild, multifocal lymphohistiocytic aggregates), thyroid glands, parathyroid glands, tongue, skeletal muscle, testicle (occasional mildly reduced spermatogenesis), epididymis (normal amounts of spermatids), seminal vesicle, prostate gland, skin (thigh and ventral abdomen with mammary gland) and bone marrow histology and cytology (normal megakaryocytic, myeloid and erythroid numbers and maturation, approximately 2-3:1 M:E, adequate iron stores) are unremarkable besides stated minor changes.

Final Principal Diagnosis(es):

1. Gastroenterocolitis, multifocal to diffuse, moderate, mixed with mild villous blunting (duodenum) and lymphoid hyperplasia.

Cause of Death: Experimental euthanasia.

Histology Comments: gastroenterocolitis is commonly seen in the colony and etiologies are likely multifactorial, and stress, nutritional/food intolerances, or allergies are possibly playing a role. A few seminiferous tubules in each testis display reduced spermatogenesis, which may be due to normal variation in hormonal levels (FSH, LH, testosterone) or response to such hormones. Normal amounts of mature spermatids are present in the epididymis.

Pathologist_____AB_____