PharmaLegacy

Preclinical Specialty Pharmacology Services

EXPECT MORE FROM PHARMACOLOGY:

Non-Human Primate Models for Immunological Research

At PharmaLegacy we endeavor to help you find the next therapy for patients with immune mediated diseases. Immune mediated inflammatory diseases are mostly complex with many contributing signaling pathways, processes, environmental influences, genetics and other factors. Thus, you need a pre-clinical model system that captures as much of the complexity as possible to determine the potential of your therapy for patients.

Non-human primates (NHP) share significant homology with humans allowing cross reactivity with biologic, cell and gene-based therapies. This permits testing of your treatment without the need to generate a costly rodent surrogate. Additionally, your therapies physiological and histological effects are more likely to be faithfully recapitulated compared to rodent systems.

Let PharmaLegacy help you design and execute the best study for your novel treatment. Together we can ensure your study will capture all the critical endpoints you need to understand your therapies' value to patients.

In this document, we'll show you a small sample of our many immune NHP models obtain from our more than 300 clients, including many leading pharmaceutical companies, who have learned they can expect more from PharmaLegacy.

PHARMALEGACY & NON-HUMAN PRIMATES

Primate research has always been a cornerstone of PhamaLegacy's offerings, and we have the facilities, models, accreditations, and operating procedures to ensure we deliver the highest quality data for even the most demanding studies.

- On-site capacity for up to 350 non-human primates
- Partnerships with three premium non-human primate centers having capacity for 30,000 monkeys (Cynomolgus and Rhesus)
- Many validated immune disease models
- AAALAC accredited
- FDA-compliant quality assurance system

PharmaLegacy has Non-Human Primate Models covering many disease areas, including:

- Rheumatoid Arthritis
- Lung Inflammation
- Inflammatory Bowel Disease (IBD)
- Delayed Type Hypersensitivity (DTH)
- Experimental Autoimmune Encephalomyelitis (EAE)
- Asthma
- LPS-Induced Systemic Infection
- Chemotherapy Induced Mucositis
- Many more + bespoke models available upon request

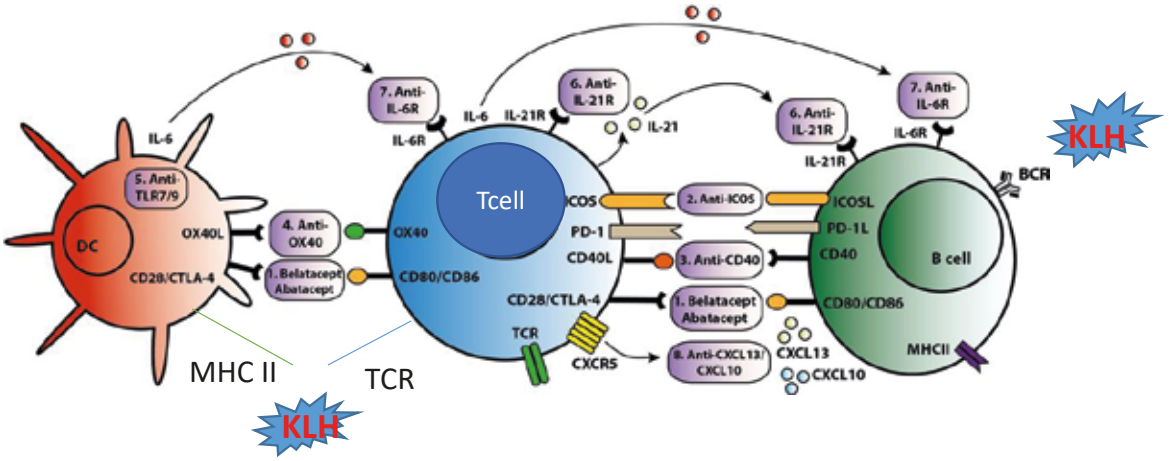
A sample of our NHP immune models include:

- Keyhole limpet hemocyanin (KLH)-induced T cell dependent antibody response (TDAR) model
- Tetanus toxoid (TTx)-induced delayed type hypersensitivity (DTH) model
- Chemotherapy (Irinotecan)-induced mucositis model
- Intrabronchial LPS-induced acute lung injury (ALI) model
- Pharmacodynamic testing models

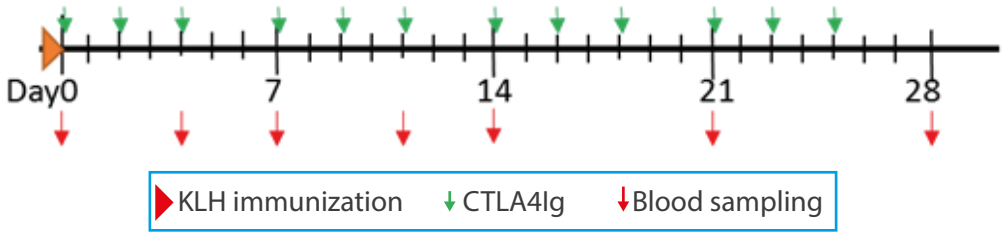
DON'T SEE A MODEL YOU WANT? **ASK US!**

Sample Model #1: Keyhole Limpet Hemocyanin (KLH)-Induced T Cell-Dependent Antibody Response (TDAR).

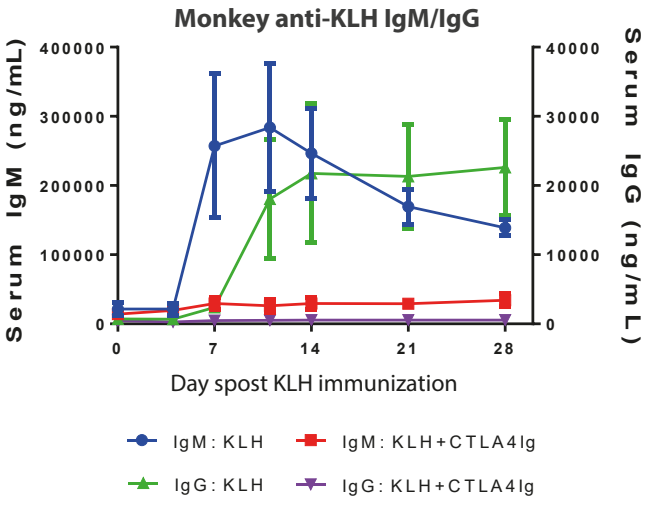
T cell-dependent antibody response (TDAR) is a comprehensive immune function assay evaluating various aspects of immune responses including antigen presentation, T/B cell activation, antibody production and class switching. It's a great model for testing your therapeutic effects on adaptive immunity. Additionally, it's endorsed by regulatory agencies as a "default" immune function test for evaluating immunotoxicity. TDAR in NHP closely matches that in humans.



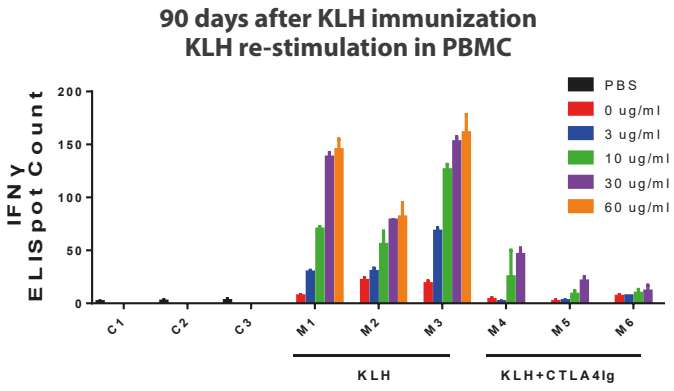
Schematic diagram



CTLA4Ig results treatment results in decrease KLH antibody production



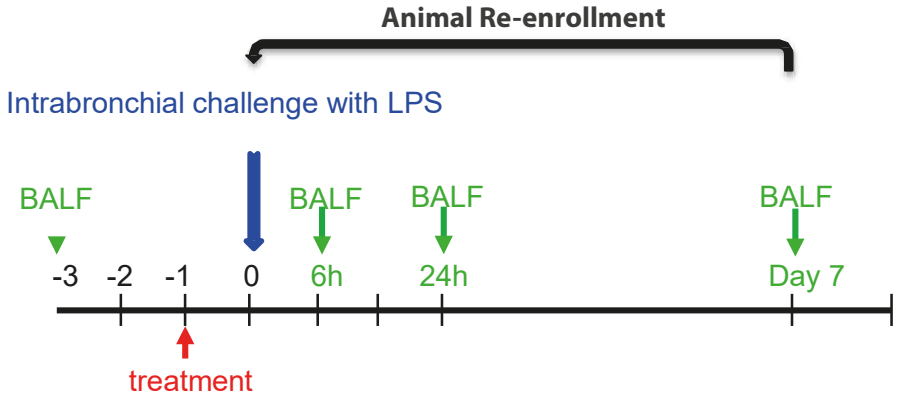
CTLA4Ig treatment reduces T cell recall response to KLH



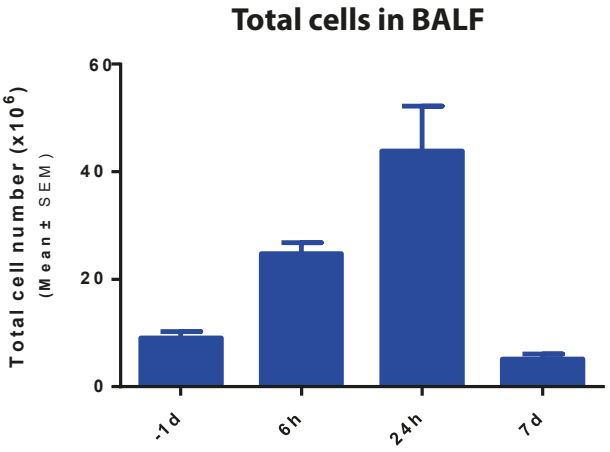
Sample Model #2:
Lipopolysaccharide-Induced Lung Inflammation

Lipopolysaccharide (LPS) driven TRL4 inflammation induces a large cascade of intra-cellular signaling resulting in cytokine production and neutrophil recruitment. Because of LPS's broad pro-inflammatory effects, it is a useful model system to test novel therapies effects on innate immunity demonstrated here by inhibition seen with a varied set of mechanisms: B1R antagonist, steroids, and PDE4 inhibitor. Additionally, animals revert to normal after one week allowing for a cross over study design that can match future clinical studies in humans.

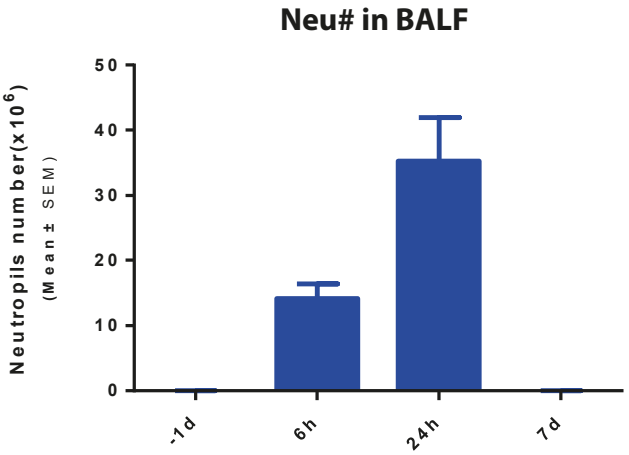
Schematic diagram



Time course of LPS induced Neutrophilia

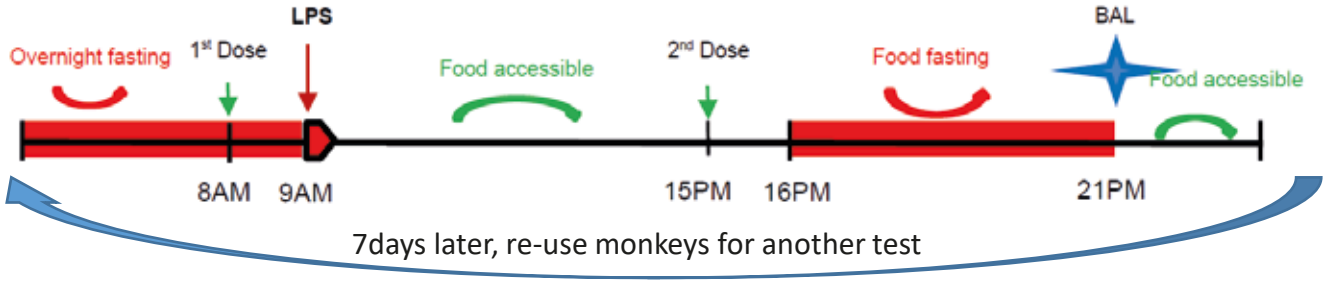


Time post intrabronchial challenge with aerosol LPS

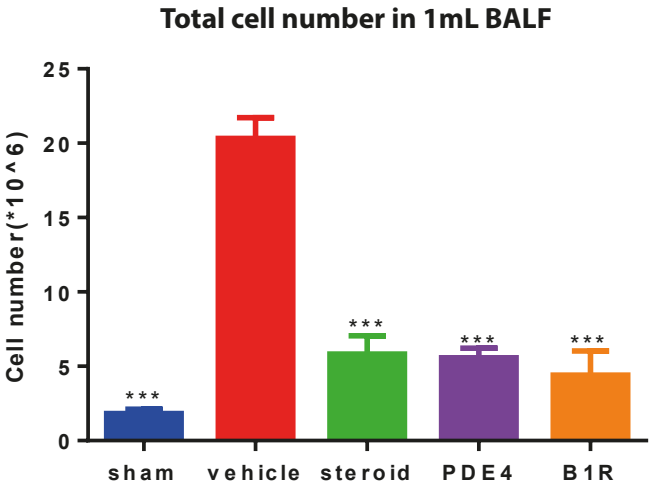


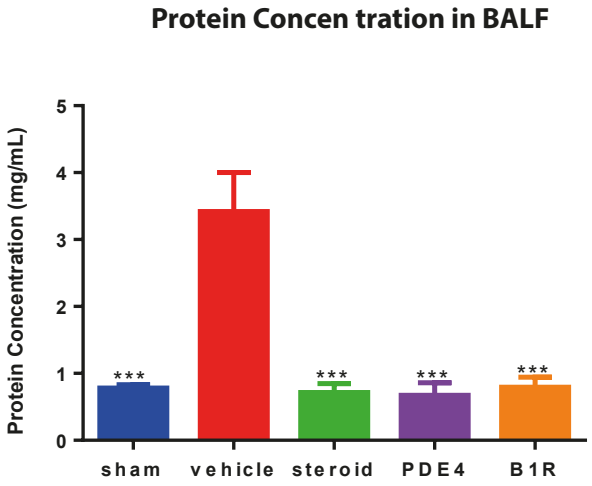
Time post intrabronchial challenge with aerosol LPS

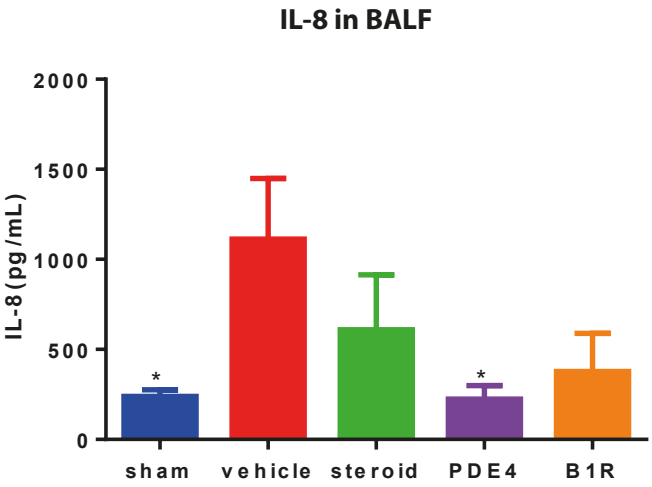
Cross-over design allows re-testing animals



Case study with cross-over design



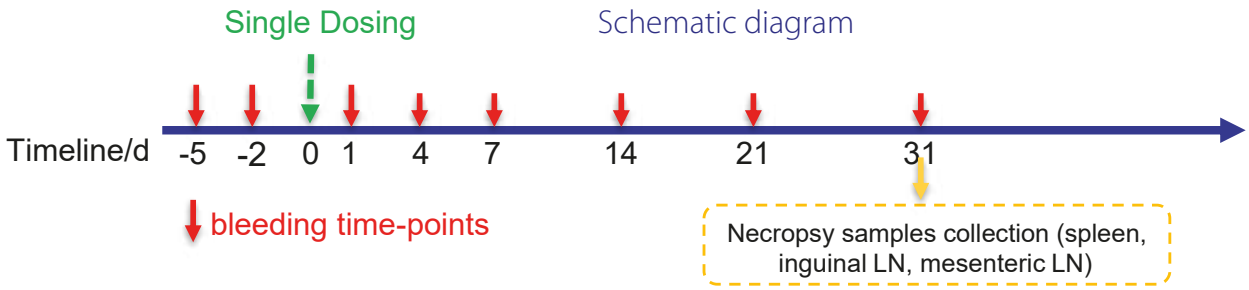


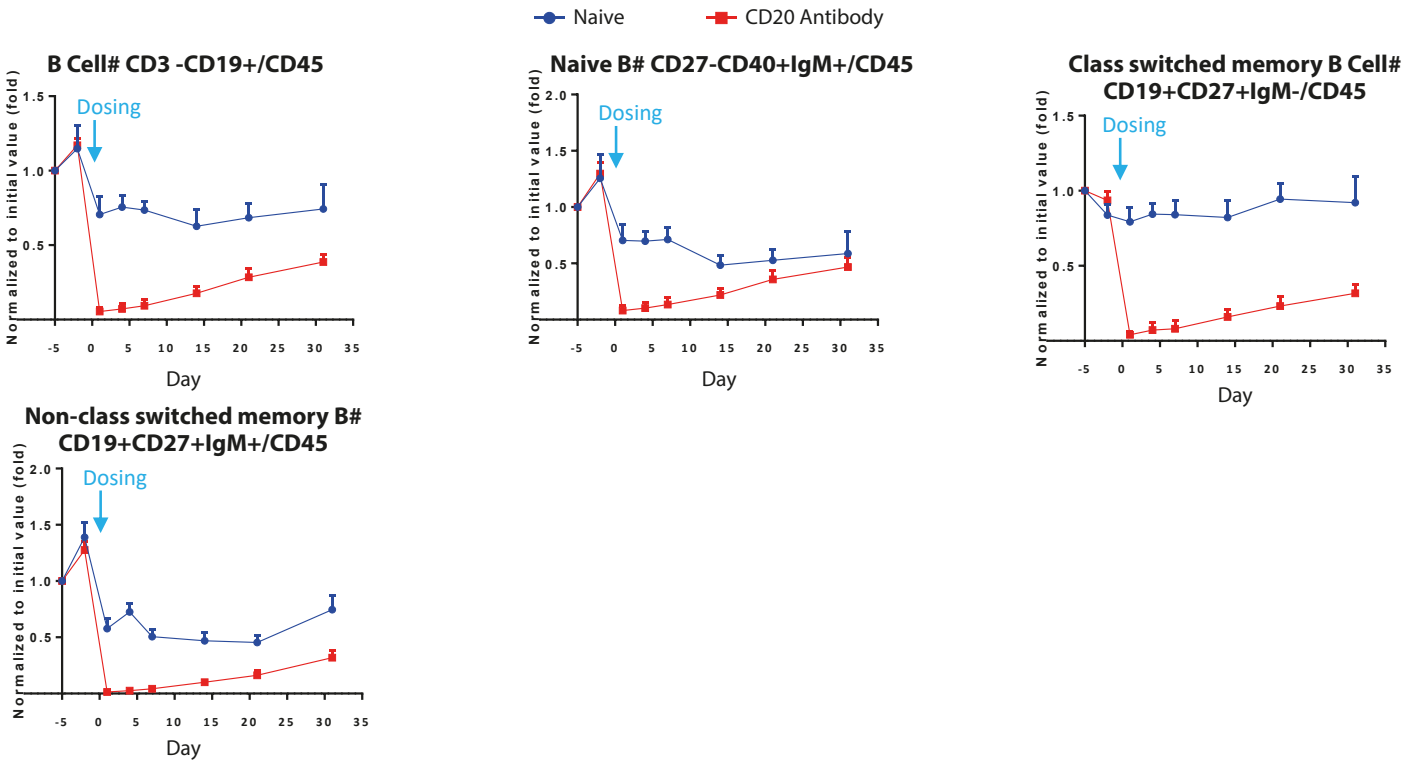


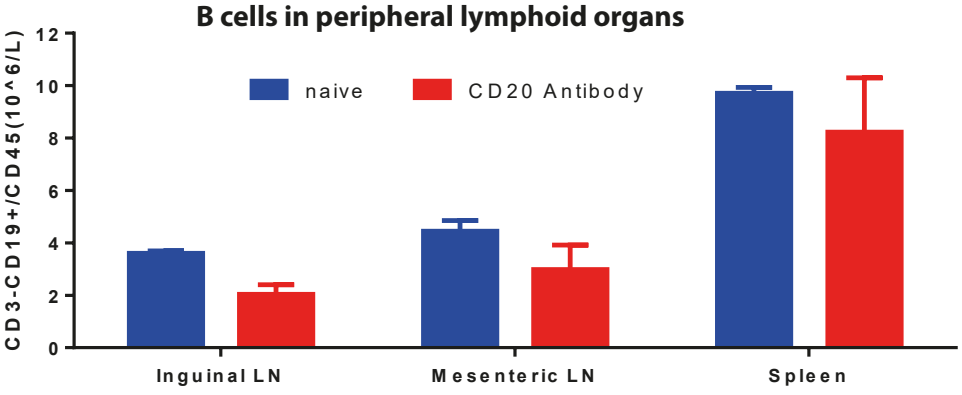
At 12 h post LPS challenge, BAL cells were significantly elevated ($p < 0.05$) over baseline (LPS: 20 x 106 vs naive: 2 x 106) which was mainly due to an accumulation of neutrophils (LPS: 80% vs naive: 1.5 %). BALF protein was significantly increased ($p < 0.05$) 12 h after LPS challenge (LPS: 3 mg/ml vs naive: 0.9 mg/ml). Of all the cytokines measured, only BALF IL-8 was significantly increased ($p < 0.05$) 12 h after LPS challenge (LPS: 1100 pg/ml vs naive: 200 pg/ml). The number of neutrophils and other inflammatory parameters returned to baseline level one week after LPS challenge. All treatments, B1R antagonist, PDE4 inhibitor and dexamethasone, significantly reduced ($p < 0.05$) LPS-induced BAL neutrophilia (~80% inhibition) and BALF protein (~90% inhibition). The B1R-antagonist inhibited BALF IL-8 by 50 %, dexamethasone by 80% and the PDE4 inhibitor by 100%.

Sample Model #3: PD Testing: anti-CD20 duration and onset of B cells depletion

PD testing is critical for the success of any novel therapy and is used to determine predicted efficacious doses for both preclinical models and patients. Here, we show the incomplete efficacy of an anti-CD20 antibody at B cell depletion. Although B cells were depleted in the peripheral blood, they remained largely intact in tissues and this suggests an insufficient dose. This is one example of many different PD models PharmaLegacy can conduct to further your drug discovery program.

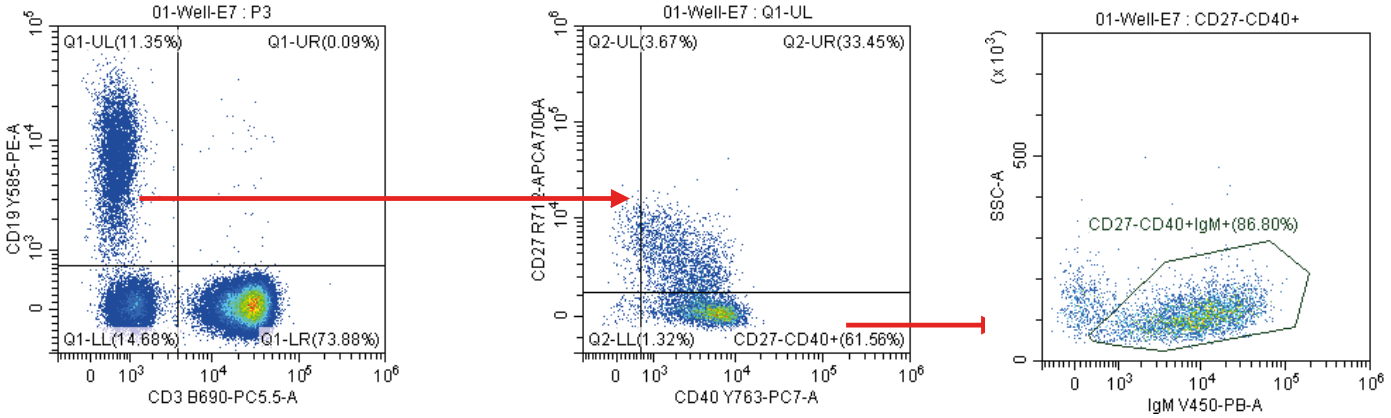






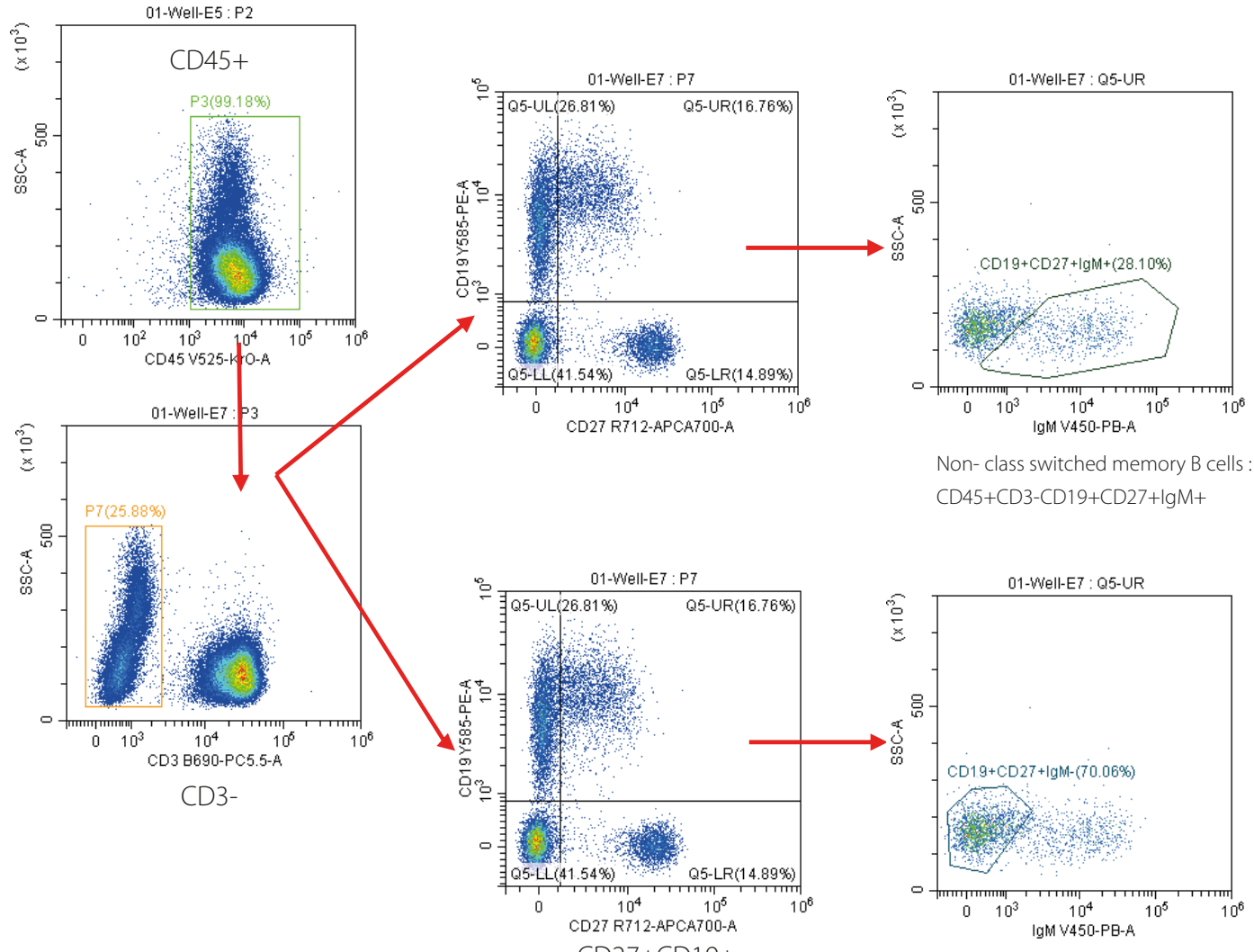
This suggests the dose of anti-CD20 was suboptimal

Gating strategy



CD3-CD19+

Native B cells:
CD45+CD3-CD19+CD27-CD40+IgM+



Non- class switched memory B cells :
CD45+CD3-CD19+CD27+IgM+

Class switched memory B cells :
CD45+CD3-CD19+CD27+IgM-

Sample Model #4: Tetanus Toxoid (TTx)-Induced Delayed Type Hypersensitivity (DTH)

DTH is a classic model of Type IV hypersensitivity reactions driven by an antigen-specific T cell response resulting in inflammation and tissue injury. In preclinical studies, DTH models are widely used for the evaluation of novel immunosuppressive and immunomodulatory agents, as well as in vaccine development.

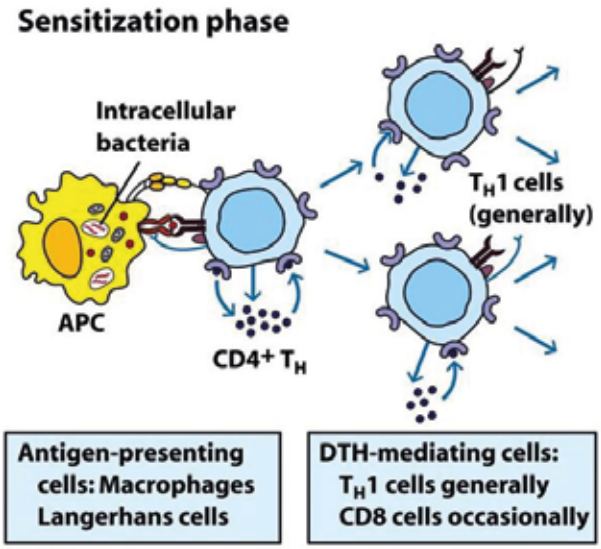


Figure 15-17a
Kuby IMMUNOLOGY, Sixth Edition

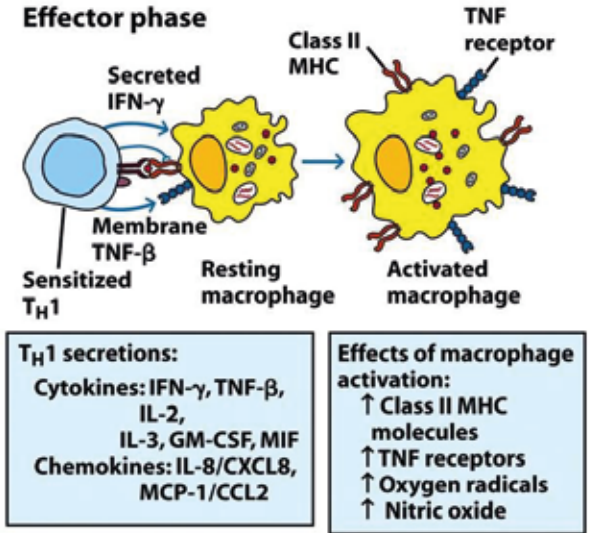
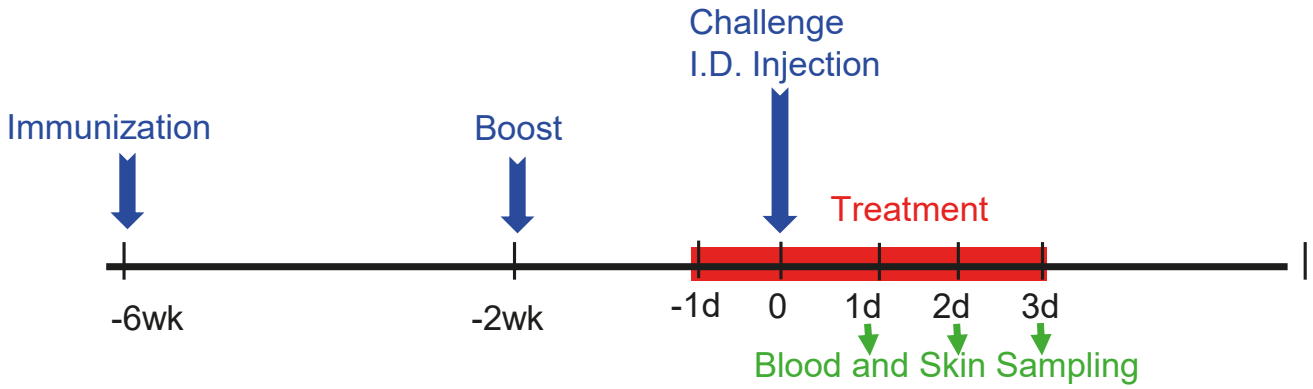
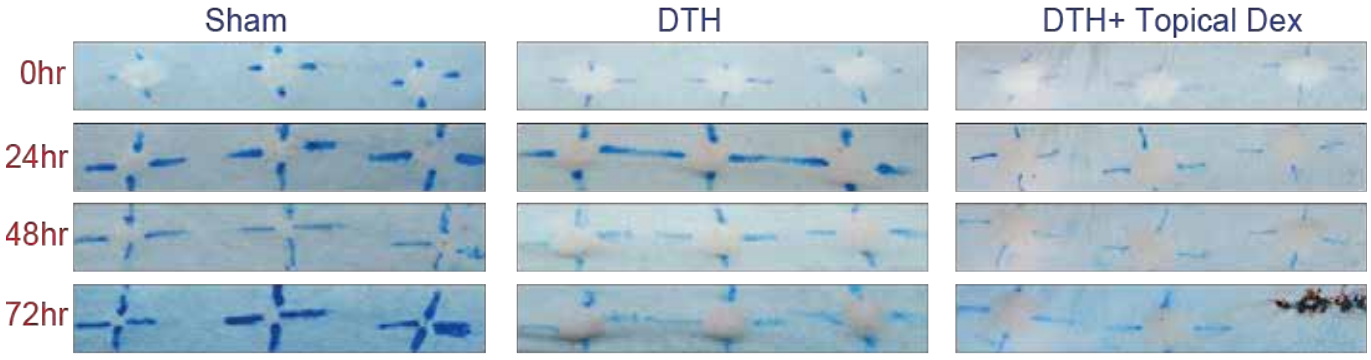
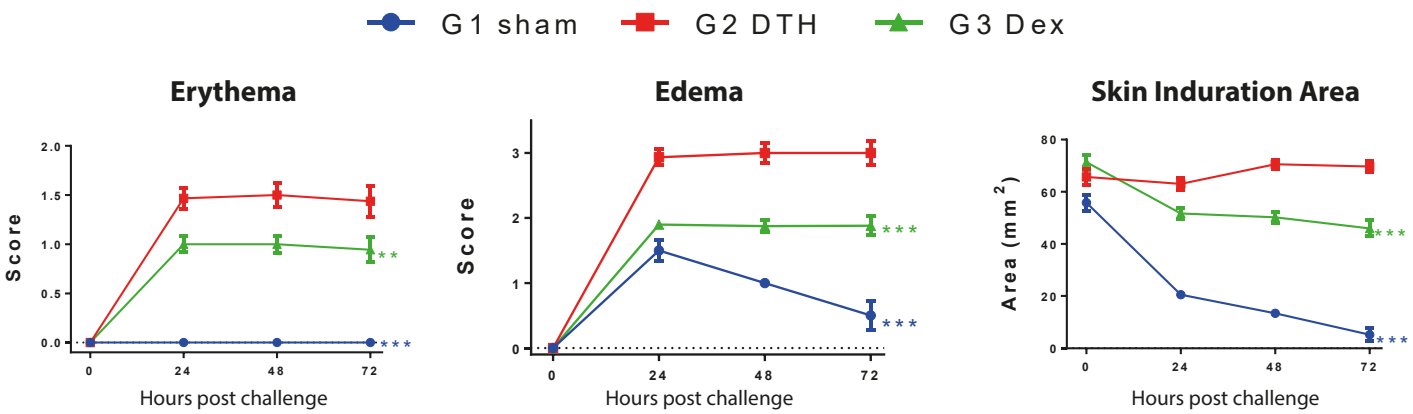


Figure 15-17b
Kuby IMMUNOLOGY, Sixth Edition

Schematic diagram

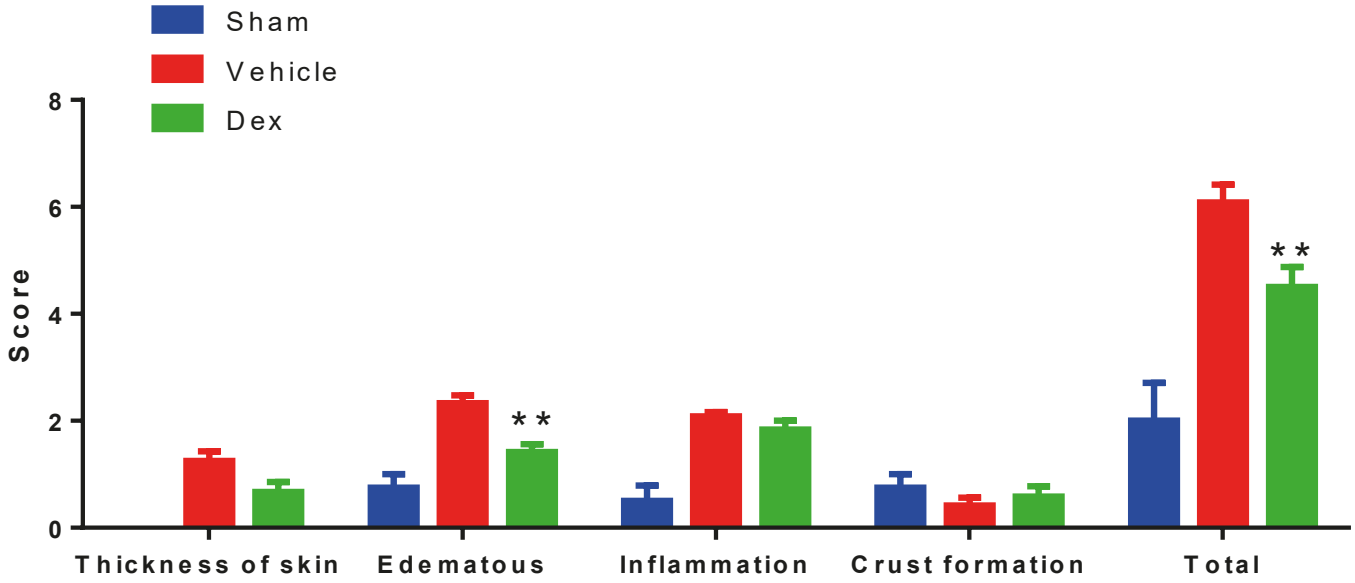






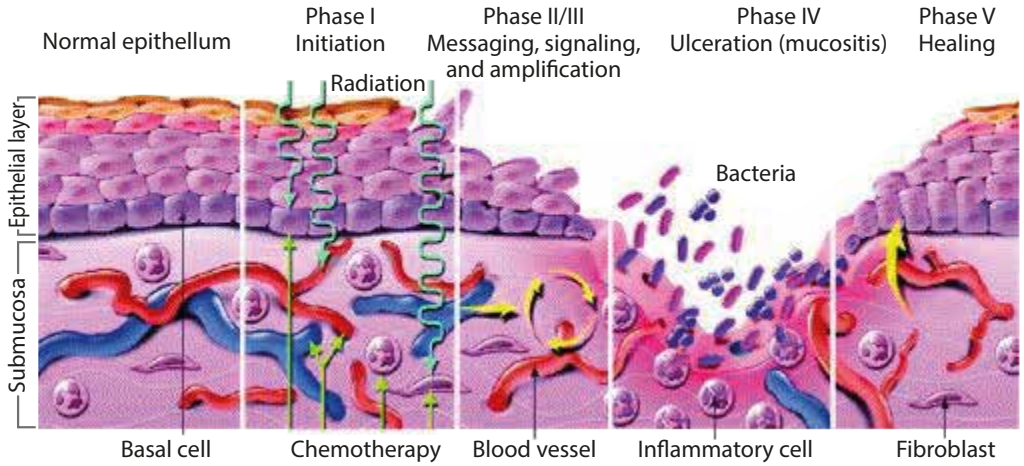
*p<0.05 compared vs vehicle group (Repeated Measures ANOVA)

Score	Erythema	Edema	Induration Area
1	very slight, barely perceptible	very slight, barely perceptible	A=length x width
2	slight	slight with area edges well-defined by definite raising	
3	moderate	moderate with approximately 1-mm of raising	
4	severe erythema to slight eschar formation	severe with more than 1- mm of raising and extension beyond area of exposure	

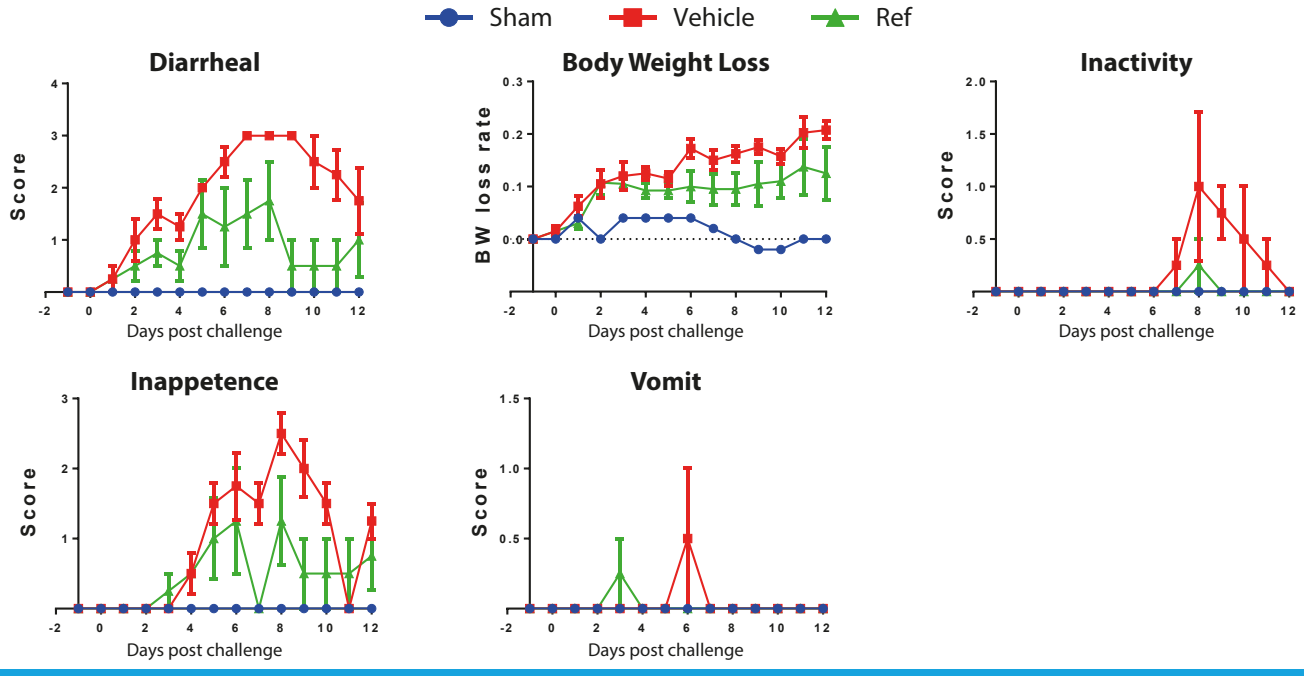


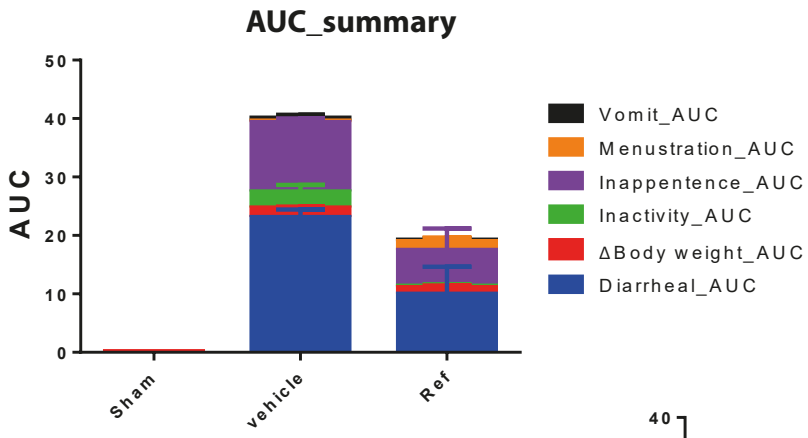
Sample Model #5:
Irinotecan Induced Mucositis

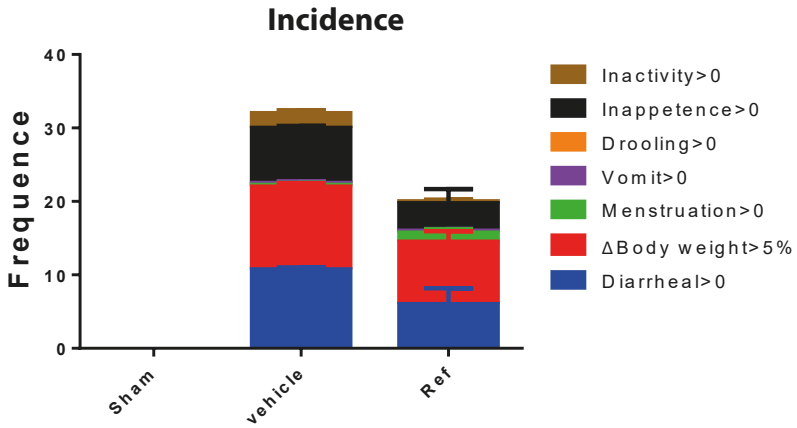
Oral and gastrointestinal mucositis is a common dose-limiting side effect of both radiation and chemotherapies in cancer patients. These oncology treatments cause death of the rapidly-dividing cells in mucous membrane leading to disruption in barrier function, ulcerative lesions, and in severe cases bacteremia. In this case study, Irinotecan, a chemotherapy used in the treatment of colon cancer and small cell lung cancer was used to induce mucositis. Beyond its utility as a mucositis model, the damage caused to the GI mucosal layer also makes it useful for testing some novel IBD therapies.



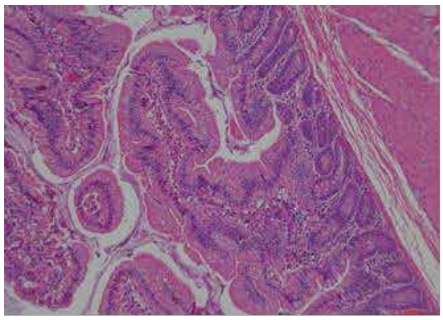
Schematic diagram



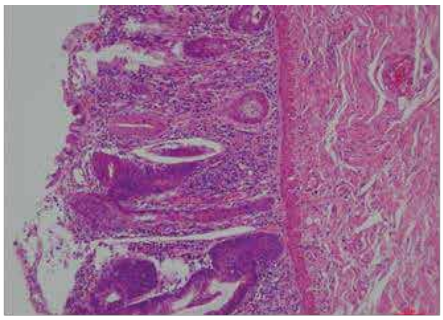




Sham



Vehicle



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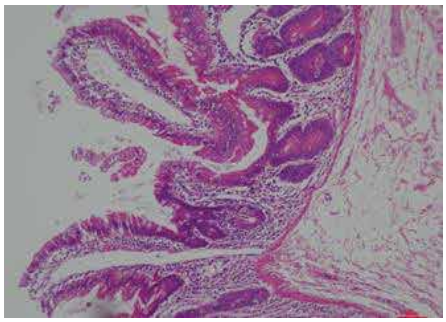

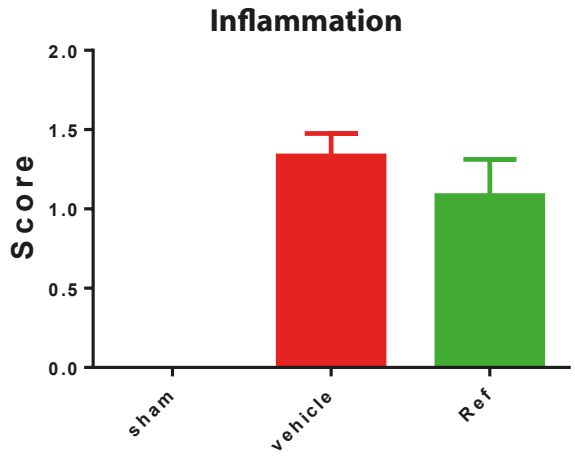

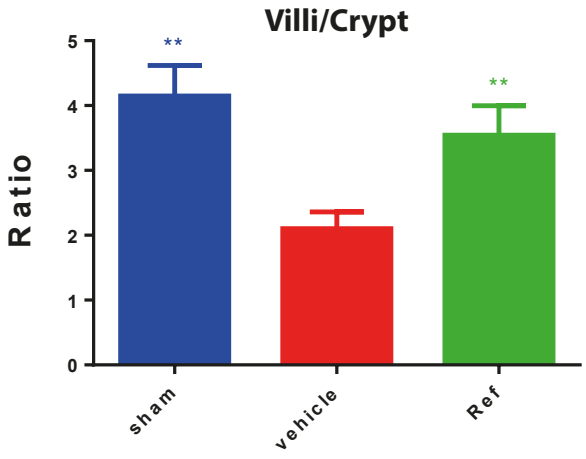

Being Correct is Everything

To advance a compound from discovery to clinical, or to halt its development, is a huge and costly decision. For the benefit of you and your company, and for the well-being of patients in need of treatment, that decision needs to be based on correct information.

PharmaLegacy has more capability to provide rich, correct answers to pharmacological questions due to our huge repository of in vivo models, the rich experience of our company and scientists, our intense focus on pharmacology, and our proprietary technological platforms.

There's a lot on the line. Let PharmaLegacy get the correct answers.

Quick Facts:

- Over 300 validated animal models of disease spanning over 40 di¬fferent diseases
- Scientific staff¬ average over 15 years of pharmacology experience
- FDA Part 11 compliant
- 45,000 ft2 facility with 22,000 ft2 of SPF and conventional vivarium to house 10,000 rodents and large animals
- Capacity to run 200 animal studies concurrently while strictly following AAALAC and ILAC guidelines
- Research data is electronically managed by BioBook (IDBS, UK)
- Web-based live video streaming allows remote monitoring of operations from any location worldwide
- Operations structured for maximum protection of clients' work and intellectual property
- 24/7 access to PharmaLegacy representatives
- More than 200 FDA / CFDA IND filings

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