PRESCOS: YOUR PARTNER FOR PRECLINICAL R&D

Company Overview January 2011

PRESCOS
Preclinical Research &
Scientific Consulting Services

The PRESCOS Offering

- Introduction and Company Background
- The Service Offering
- PK and Pharmacology Services
- Advanced and Customized Statistical Solutions
- Summary

PRESCOS
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Introduction and Company Background

PRESCOS
Preclinical Research &
Scientific Consulting Services

PRESCOS: Quality Preclinical Contract and Expert Consulting Services

PRESCOS: Customized Planning, Execution and Analysis Solutions

- PRESCOS assists the pharmaceutical and biotechnology industries by offering quality contract research and expert consultancy services to its clients
- PRESCOS was founded out of the conviction that high quality preclinical pharmacology studies are essential for the efficient, economical and successful development of pharmaceutical drugs
- PRESCOS firmly believes that state-of-the-art quality solutions need to be applied to all stages of pharmacological studies, including the planning and conduct of studies, and the analysis of study results
- PRESCOS enables these requirements by applying “lessons learnt” from clinical studies to preclinical development

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Company Background: The Management Team

PRESCOS Offers a Wealth of Expertise in Preclinical and Clinical Drug Development and Contract Research

- Joachim Vollmar, CEO - Co-founder of PRA International, a global Clinical Research Organization, and of ICDC, an independent Expert Consultancy. Brings 40+ years of experience in preclinical and clinical drug development with 100+ peer-reviewed scientific publications
- Thomas Moll, PhD, COO – Biotech R&D executive with 20+ years experience in basic and applied research and preclinical drug development . Extensive experience in the design and execution of IND enabling preclinical R&D programs, as well as individual pharmacology and safety studies

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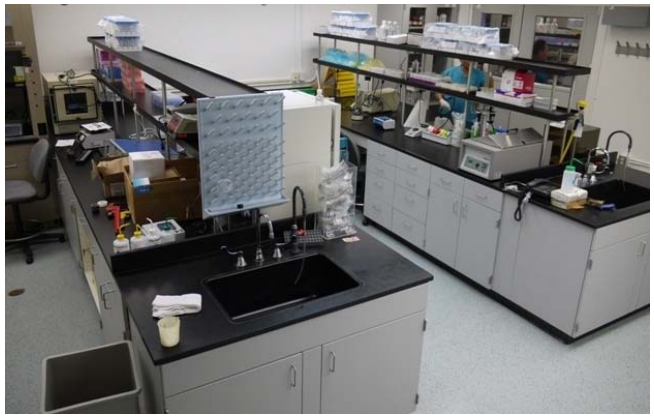
Company Background: Facilities and Staff

PRESCOS is Located in the Heart of San Diego's Biotech Area

- PRESCOS is located in the Torrey Pines area of San Diego, near major universities, research institutes, pharmaceutical and biotech companies
- The company's 5100 sf facility is located in a secure, controlled-access campus environment
- The PRESCOS facility comprises fully equipped mouse and rat vivarium spaces, procedure rooms, and analytical laboratories.



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Company Background: Facilities and Staff – cont.

PRESCOS is Well Positioned to Offer Quality Contract Services

- Attending veterinarian is an active AAALAC council emeriti, and Senior Director of the Scripps Research Institute (SRI) Institutional Animal Program
- Capabilities include housing for immune competent and immune compromised rodents
- All animals are housed in microisolator cage systems
- Well-trained and experienced staff

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The Service Offering

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PRESCOS: A Preclinical CRO and Expert Consultancy Service

PRESCOS Offers Customized Solutions for your R&D Outsourcing Needs

- Pharmacology Services
  - Pre-clinical in vivo and in vitro pharmacology studies
  - Planning, execution, and analysis of single experimental studies as well as of comprehensive pharmacology programs

- Consulting Services
  - Pre-clinical in vivo and in vitro pharmacology study design and analysis
  - Study and program evaluations, including technical and scientific due diligences
  - Preparation of IND enabling R&D development plans, taking leads from discovery to the IND

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Quality Track for Customized Solutions

Fully Integrated Planning, Conduct, Analysis and Reporting Processes

- Detailed planning meetings with client to determine client's needs, and to develop optimized study protocols
- Use of advanced statistical tools for study protocol generation and study initiation (e.g. cutting edge power analysis / sample size determination, state-of-the-art randomization procedures including stratification variables)
- Continuous communication during ongoing studies
- Established QC and QA procedures
- Comprehensive and integrated data management and analysis solutions using DMARS, the PRESCOS proprietary data management, analysis and randomization system
- On-time delivery of study reports

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Drug Screening and Evaluation

PRESCOS Offers Rodent PK Studies as well as Rodent In Vitro and In Vivo Pharmacology Models of Disease

- Rat and Mouse PK studies
  - Single dose PK studies
  - Repeat dose PK studies
- In vitro pharmacological studies
  - Cell proliferation and toxicity assays
  - Human cancer cell models
- In vivo pharmacological studies
  - Cancer models in immune compromised, irradiated and immune competent rodents
  - Autoimmune disease models
  - Asthma models (Airway Hyperreactivity Models)
  - Inflammation models
  - Additional models, including models for wound healing, alopecia areata, hepatic fibrosis (CCl4-induced in mice)

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Routes of Administration

PRESCOS Offers the Following Routes of Administration:

- Oral (PO) administration
- Dermal (Dermal Patches, Topical Applications)
- Intravenous (IV)
- Subcutaneous (SC)
- Intradermal (ID)
- Intraperitoneal (IP)
- Intramuscular (IM)
- Intratracheal (IT)
- Intranasal (IN)
- Continuous Infusion
- Intravitreous (in rats)

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Terminal Procedures

PRESCOS Offers the Following Terminal Procedures:

- Whole blood, serum and plasma collection (also in-life)
- Cerebrospinal fluid collection
- Bone marrow collection
- Tissue and organ collection
- Harvesting of tumors
- Processing and preservation of collected fluids, cells, tissues and organs
- Ex vivo analytical services

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PK and Pharmacology Services

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Pharmacokinetic Studies

Evaluation of Pharmacokinetic Parameters Following Single Dosing, Repeat Dosing or e.g. Timed Perfusion

- PK Studies in mice and rats
- Evaluation of biologics and small molecule drugs
- Conduct of GLP toxicology enabling studies
- Determination of serum PK parameters such as C_{max}, T_{max}, $T_{1/2}$, AUC and drug clearance
- Study protocols are custom developed on the basis of compound(s), route of administration, dosing regimen

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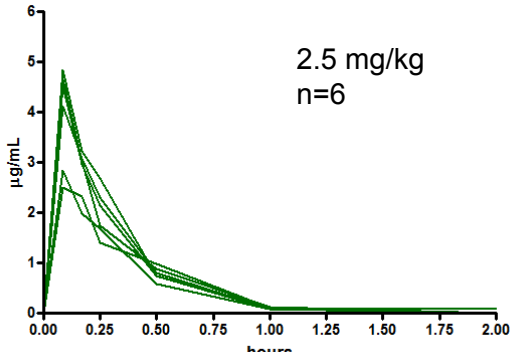
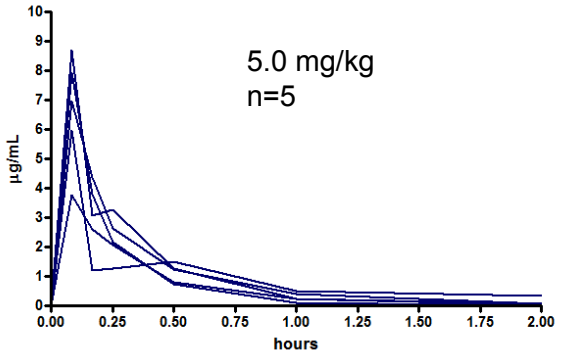
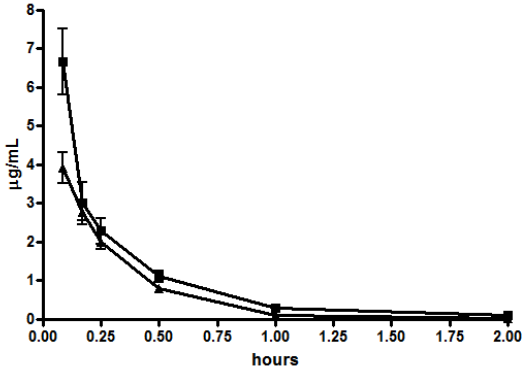
Pharmacokinetics of Omeprazole After IV Administration in Male Wistar Rats

Plasma Omeprazole concentration after single IV bolus administration







Omeprazole	AUC* [µg h/ml]	$T_{1/2}$* [h]	T_{max}* [h]	C_{max}* [µg/ml]
IV 2.5 mg/kg	1.06/0.06	0.06/0.001	0.09/0.004	4.35/0.06
IV 5.0 mg/kg	1.88/0.16	0.05/0.008	0.07/0.01	10.8/0.16

* Numbers given are Mean/SEM

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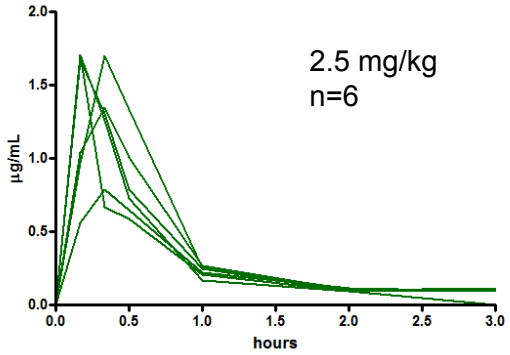
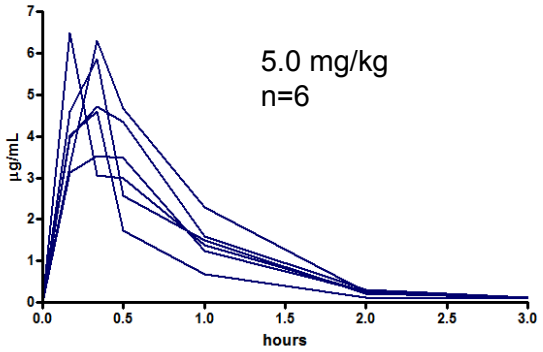
Pharmacokinetics of Omeprazole After PO Administration in Male Wistar Rats

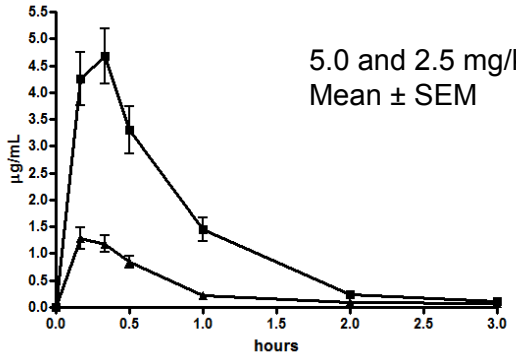
Plasma Omeprazole concentration after single PO administration



2.5 mg/kg
n=6



5.0 mg/kg
n=6



5.0 and 2.5 mg/kg
Mean ± SEM

Omeprazole	AUC* [µg h/mL]	$T_{1/2}$* [h]	T_{max}* [h]	C_{max}* [µg/mL]
PO 2.5 mg/kg	1.00/0.066	0.14/0.018	0.23/0.033	1.77/0.25
PO 5.0 mg/kg	3.96/0.34	0.16/0.017	0.26/0.03	5.78/0.75

* Numbers given are Mean/SEM

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In Vitro Cancer Models

In Vitro Assays to Help Determine the Efficacy, Mechanism of Action, and Toxicity of Compounds

- Cell proliferation and cellular toxicity assays
- Soft agar colony formation assay
- Apoptosis assays

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In Vivo Cancer Models

In Vivo Cancer Models to Help Determine the Efficacy, Mechanism of Action, and Toxicity of Compounds

- Human cancer xenografts in immunodeficient (athymic nude, scid) mice
  - Breast (MDA-MB231, MDA-MB468, MCF-7, BT-474, SKBR3)
  - Prostate (PC-3, DU-145)
  - Lung (A549, H460, H146)
  - Stomach (N87)
  - Colon (Colo-205, DLD-1, HT29)
  - Liver (HepG2)
  - Pancreas (Mia-Paca, Panc1)
  - Leukemia (HL-60, Hut78, K562, Raji (Ramos))
- Tumor models in irradiated mice

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In Vivo Cancer Models – cont.

In Vivo Cancer Models to Help Determine the Efficacy, Mechanism of Action, and Toxicity of Compounds

- Spontaneous and Syngeneic Tumors in Mice and Rats (e.g. for immunotherapeutics)
  - Mouse prostate (spontaneous; TRAMP mice)
  - Mouse melanoma (B16F10)
  - Mouse colon (CT26)
  - Mouse lung (M109)
  - Rat gliosarcoma (9L)

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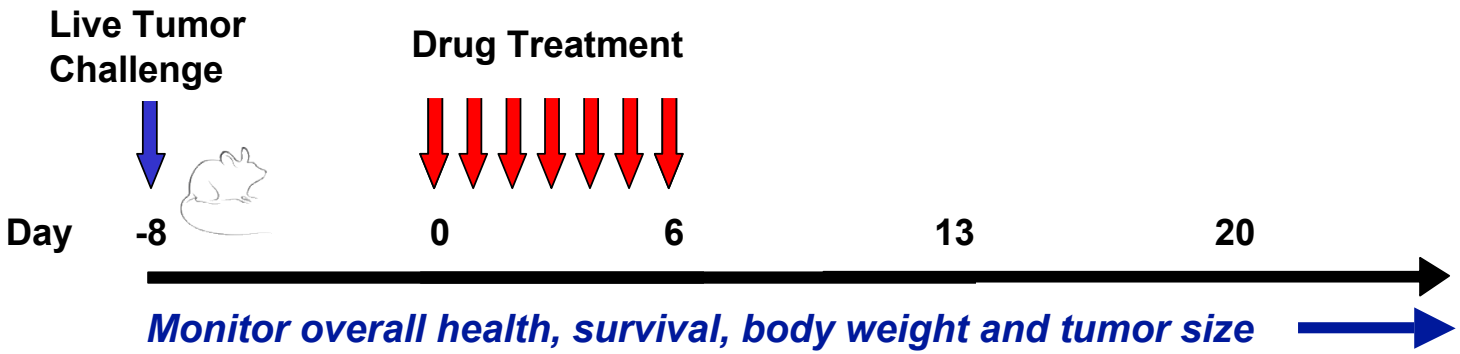
In Vivo Cancer Model: Example of a Study Design



Live challenge: 5×10^5 M109 cells, s.c.
Treatments delivered i.p.

Gp	Treatment regimen
A	Vehicle control (DMSO 1:10 in PBS), qd × 7
B	16 mg/kg compound X, qd × 7
C	8 mg/kg compound X, qd × 7
D	4 mg/kg compound X, qd × 7

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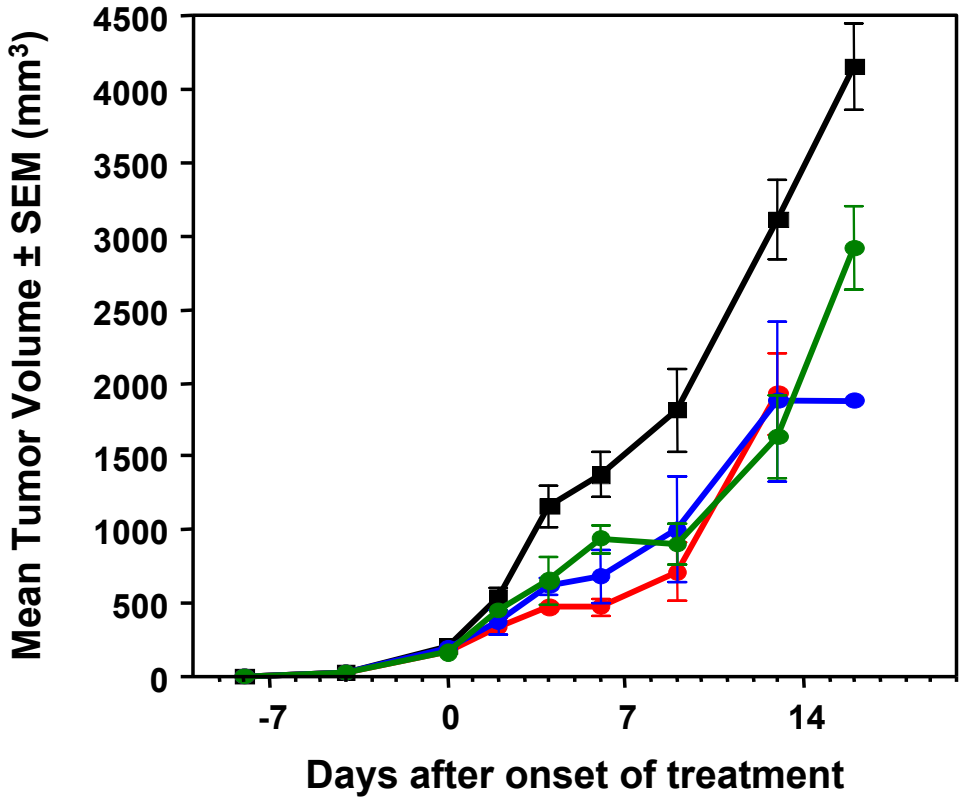
Drug Treatment LimitsThe Growth of M109 Lung Carcinoma During Therapy



DMSO Vehicle
16 mg/kg compound X
8 mg/kg compound X
4 mg/kg compound X

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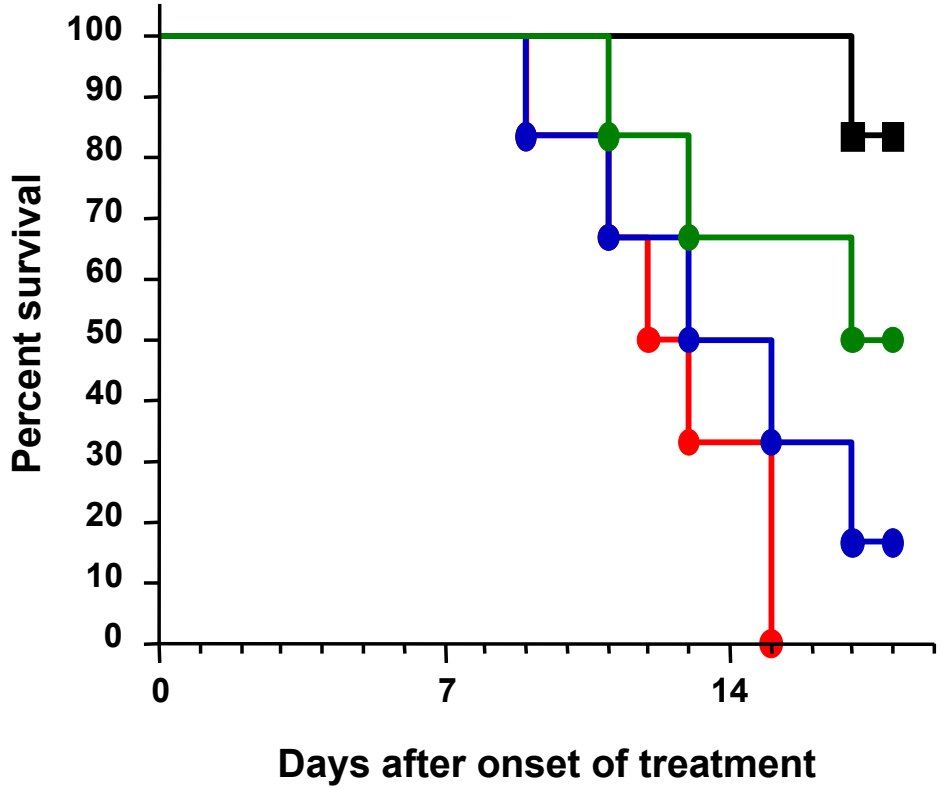
Drug Treatment is Toxic and Leads to Dose Dependent Animal Mortality



DMSO Vehicle

16 mg/kg compound X

8 mg/kg compound X

4 mg/kg compound X

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Autoimmune Disease Models

PRESCOS Offers Rodent Models for a Variety of Autoimmune Diseases

- Rheumatoid Arthritis
  - Collagen-Induced Arthritis (CIA) in mouse and rat
  - Collagen Antibody Induced Arthritis (CAIA) in the mouse
  - Streptococcal cell wall induced arthritis in the rat
- Multiple Sclerosis
  - Experimental autoimmune encephalomyelitis (EAE) models in mouse and rat, including
    - PLP-induced EAE in SJL/J mice
    - MOG-induced EAE in C57BL/6 mice
    - MBP-induced EAE in Lewis rats
- Uveitis
  - Mouse (C57BL/6) and rat (Lewis) uveitis using interphotoreceptor retinoid binding protein (IRBP) derived peptides for disease induction.

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Autoimmune Disease Models – cont.

- Systemic Lupus Erythematosus (SLE)
  - Several mouse models of the disease are available at PRESCOS. These include the MRL/lpr mouse model, as well the NZW and/or NZW/NZB F1 mouse models of SLE
- Diabetes
  - Streptozotocin-induced diabetes in mice and rats
  - Diabetes in NOD mice
- Idiopathic Pulmonary Fibrosis (IPF)
  - Bleomycin-induced pulmonary fibrosis in mice (C57BL/6; or ICR)
- Scleroderma
  - Bleomycin-induced dermal scleroderma
  - Murine sclerodermatous graft versus host disease (skin and lung fibrosis)
- Primary Biliary Cirrhosis (PBC)
  - PBC model in NOD.c3c4 mice

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Collagen-Induced Arthritis in Mice: Example of a Study Design

21 days

Sensitization:
Collagen ID in CFA

Boost:
Collagen IP or ID In IFA

Treatment with compound and controls; Prophylactic or therapeutic treatment protocols

Monitoring of overall health, survival, body weight, as well as disease scoring

Disease scoring criteria:
joint swelling, erythema, edema, ankylosis develops with variable onset after boost; disease severity is scored on a scale 0-4 per limb (16 maximum)

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CIA: Example of Disease Scoring and Disease Progression

Mouse:	1	2	3	4	5	6	7	8
Treatment:	Cnt	Cnt	Cnt	Cnt	Trt	Trt	Trt	Trt
Day 1:	1 1 0 0	0 0 1 1	1 0 0 0	0 0 0 1	0 0 0 1	0 0 0 1	0 0 0 1	0 0 0 1
Day 2:	2 2 0 0	0 0 2 2	2 0 1 0	0 0 0 1	0 0 0 1	0 0 0 1	0 0 1 1	0 0 1 1
Day 3:	3 3 0 2	0 0 2 2	2 0 1 0	0 0 0 1	0 0 0 1	0 0 0 1	0 0 1 1	0 0 1 1
Day 4:	3 3 1 3	0 0 2 2	3 0 1 0	0 0 0 1	0 0 0 1	0 0 2 1	0 0 1 1	0 0 2 1
Day 5:	3 3 1 3	0 0 3 2	3 0 1 0	0 0 0 1	0 0 0 1	0 0 3 1	0 0 2 1	0 0 3 1
Day 6:	3 3 1 3	1 1 3 2	3 0 1 2	0 0 0 1	0 0 0 1	0 0 3 1	0 0 3 1	0 0 3 1
Day 7:	3 3 1 3	1 2 3 2	3 0 1 2	0 0 0 1	0 0 0 1	0 0 3 1	0 0 3 1	0 0 3 1
Day 8:	4 3 1 3	1 2 3 2	4 0 1 2	0 0 0 1	0 0 0 1	0 1 3 1	0 0 3 1	0 0 3 1
Day 9:	4 4 1 3	0 3 3 2	4 0 1 3	0 0 0 1	0 0 0 1	0 1 3 1	0 0 3 1	0 0 3 1
Day 10:	4 4 1 3	0 3 3 2	4 0 2 3	0 0 0 0	0 0 0 1	0 2 3 1	0 0 3 1	0 0 4 1
Day 11:	4 4 1 3	0 3 3 2	4 1 2 4	0 0 0 0	0 0 0 1	0 3 4 1	0 0 4 1	0 0 4 0
Day 12:	4 4 1 3	0 4 3 2	4 1 2 4	0 0 0 0	0 0 0 1	0 4 4 1	0 0 4 1	0 0 4 0

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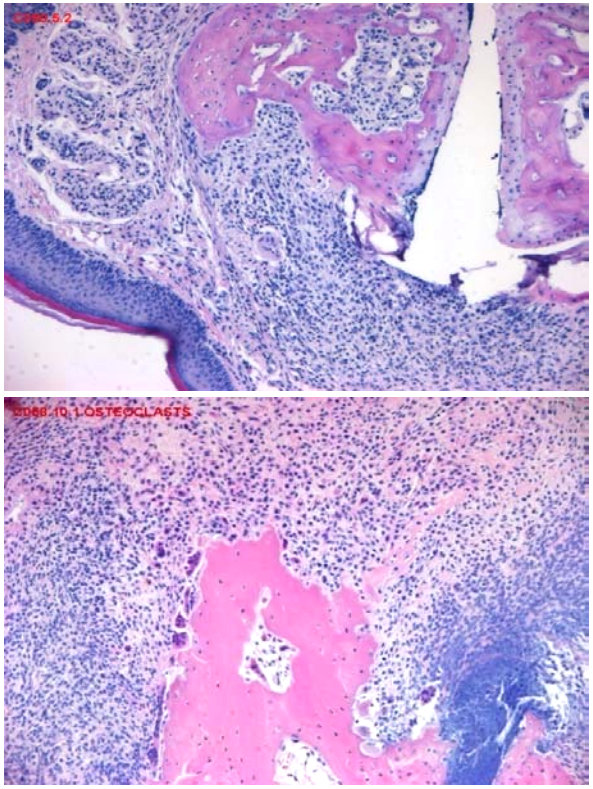
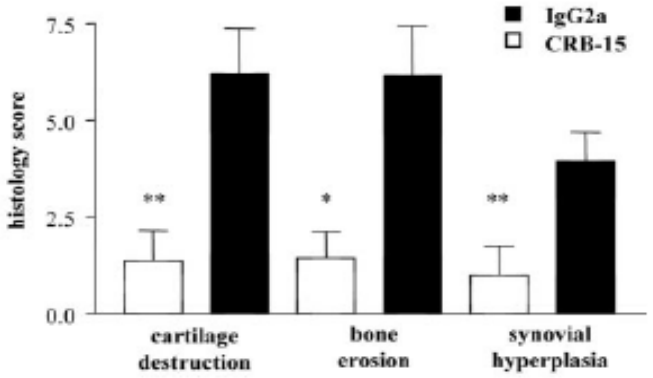
CIA: Histopathology and Pathological Scoring





Ferrari-Lacraz et al. (2004) JI, 173:5818

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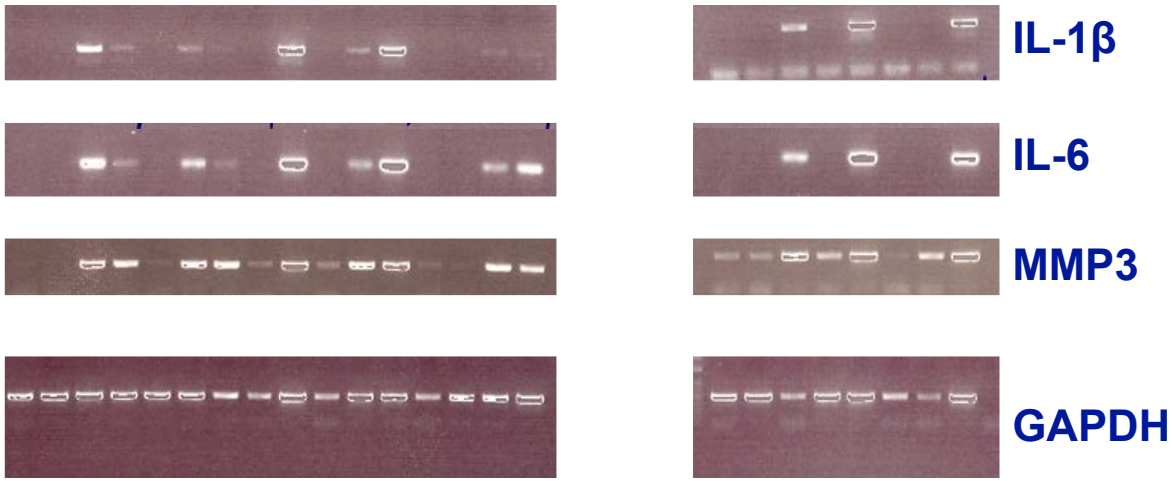
CIA: Gene Expression Analysis

Clinical Scores (on a scale from 0 to 4 per limb):
0 0 4 2 0 3 3 1 4 0 2 3 0 0 3 1 0 0 2 1 3 0 1 3



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EAE in Mice: Example of a Study Design

Immunize s.c. with PLP (200µg) in CFA + 100ng PT, i.v.

Monitoring of overall health, survival, body weight, as well as disease scoring

0 1 2 3 4 5 6 7 8 9 10 11 12

Days

Customized treatment protocol with compound and controls

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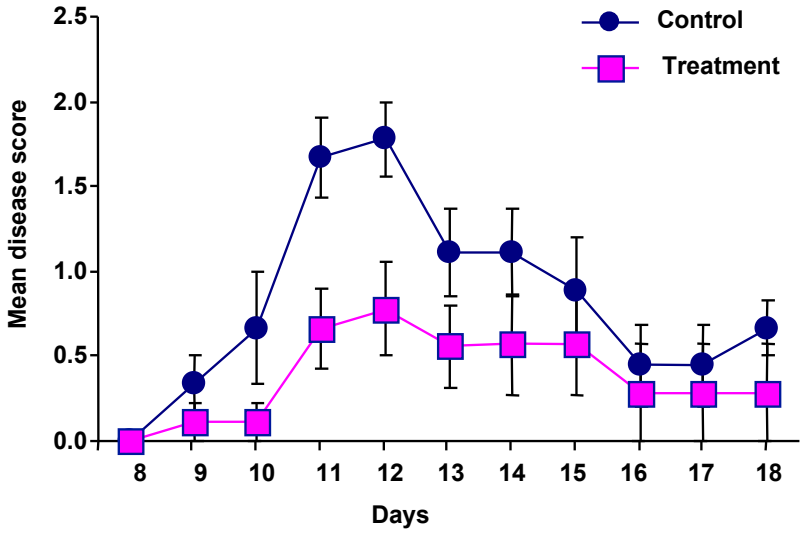
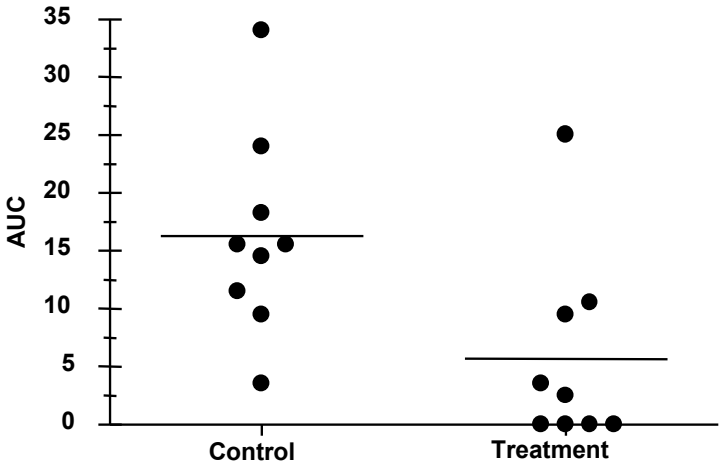
EAE: Monitoring of Disease





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Inflammation and Asthma Models

PRESCOS Offers a Variety of Rodent Models of Inflammation, Including a Mouse Airway Hyperreactivity Asthma Model

- Asthma
  - Mouse ovalbumin-induced airway hyperreactivity model (AHR)
- Chronic Obstructive Pulmonary Disease (COPD)
  - Elastase-induced COPD
  - Smoke inhalation induced COPD
- Inflammatory Bowel Disease (IBD)
  - Dextran Sulfate (DSS) induced gastrointestinal inflammation
  - Oxazolone and Trinitrobenzene Sulfonic Acid (TNBS) induced colitis
- Bacterial antigen induced inflammatory responses in mice and rats
- Irritant-induced contact hypersensitivity (CHS) and delayed-type hypersensitivity (DTH) inflammation models
- Mouse airpouch model (leukocyte migration)

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Allergen (OVA)-induced Airway Hyperreactivity in Mice: Example of a Study Design

Days 0 and 14: Immunize IP with OVA in Alum

Days 32, 33, and 34: IN challenge with OVA, vehicle

0 3 6 9 12 15 18 21 24 27 30 33 35 Days

Control treatment (positive control)

Monitoring of overall health, survival, body weight

Terminal assays for lung histopathology, BALF cell counts, IgE

Customized treatment protocol with compound and controls

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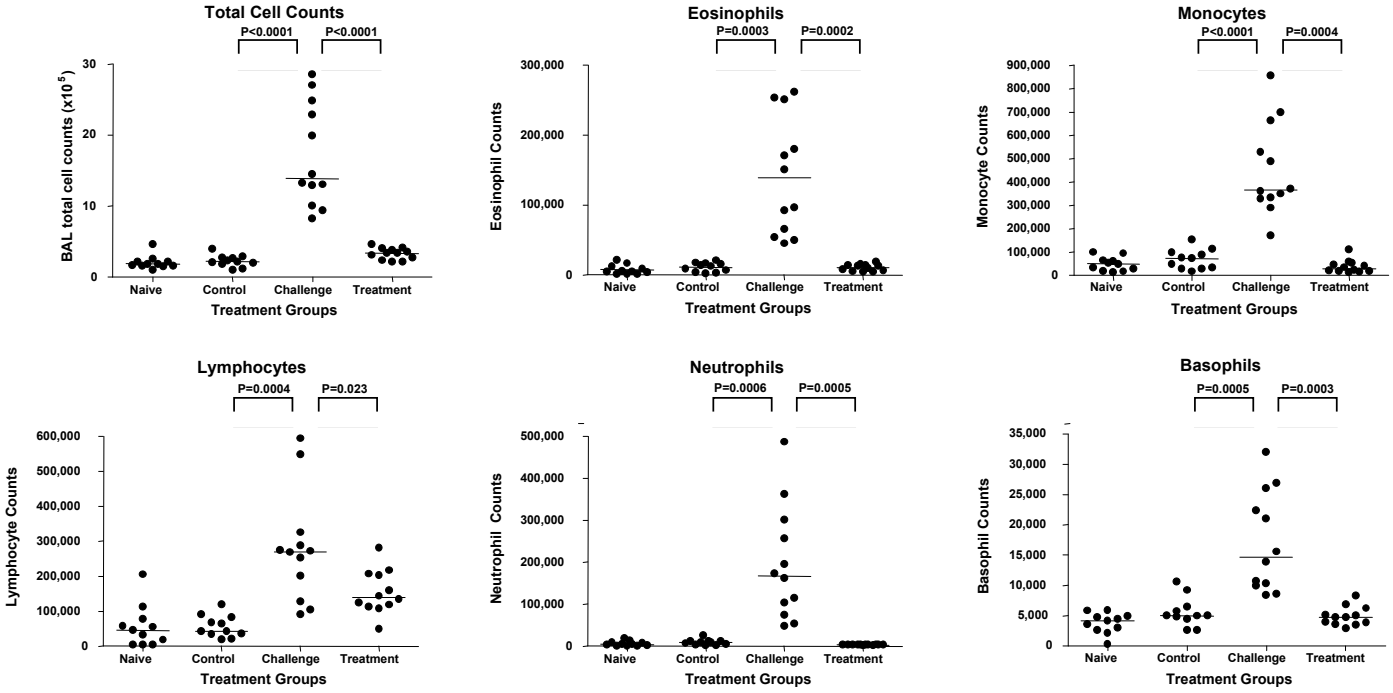
AHR: Leukocyte Counts in Bronchoalveolar Lavage Fluid



Naïve (n=11): Naïve mice, untreated; Control (n=11): Immunized with OVA
Challenge (n=12): Immunized with OVA, challenged with OVA, treated with vehicle
Treatment (n=12): Immunized with OVA, challenged with OVA, treated with dexamethasone

p values were calculated using a Welch-t-test. Similar results were obtained using a modified Wilcoxon test.

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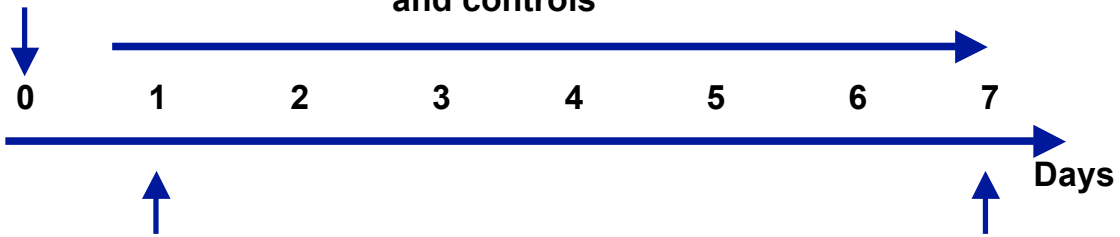
Elastase-Induced COPD in Mice: Example of a Study Design

Day 0: Intranasal administration of porcine pancreatic elastase

Customized treatment protocol with compound and controls



Terminal assays for lung histopathology, BALF cell counts

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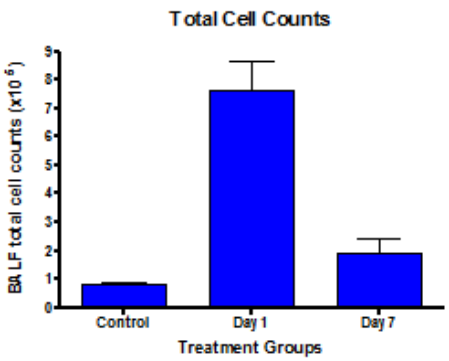
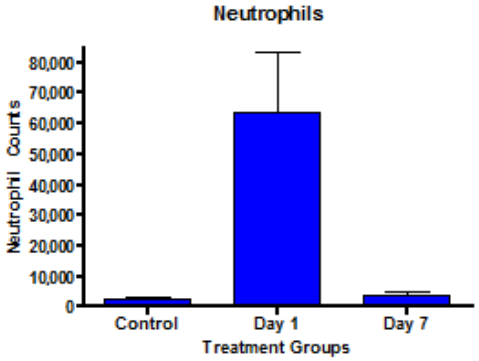
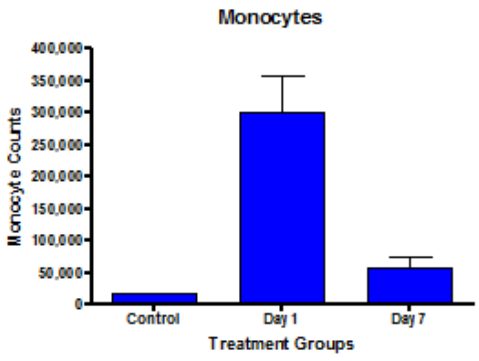
Elastase-Induced COPD: Leukocyte Counts in Bronchoalveolar Lavage Fluid (BALF)







Acute lung injury was induced by IN administration of elastase or saline (control) and BALF collected from one half of the lung after 1 day and after 7 days, respectively. Values given are mean ± SEM.

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Advanced and Customized Statistical Solutions

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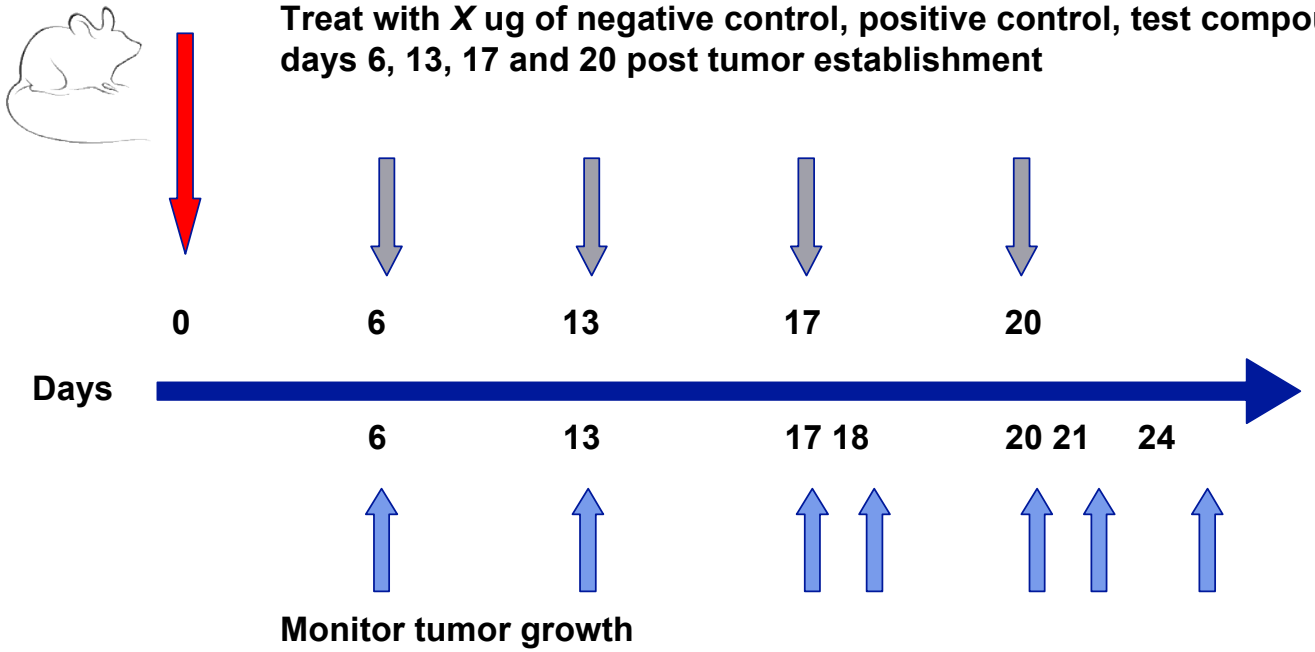
Treatment of Mouse Thymoma (EL4) in Immuno-competent Mice

Inject mice with 5x10^5 EL4 cells (SC)
to establish tumor



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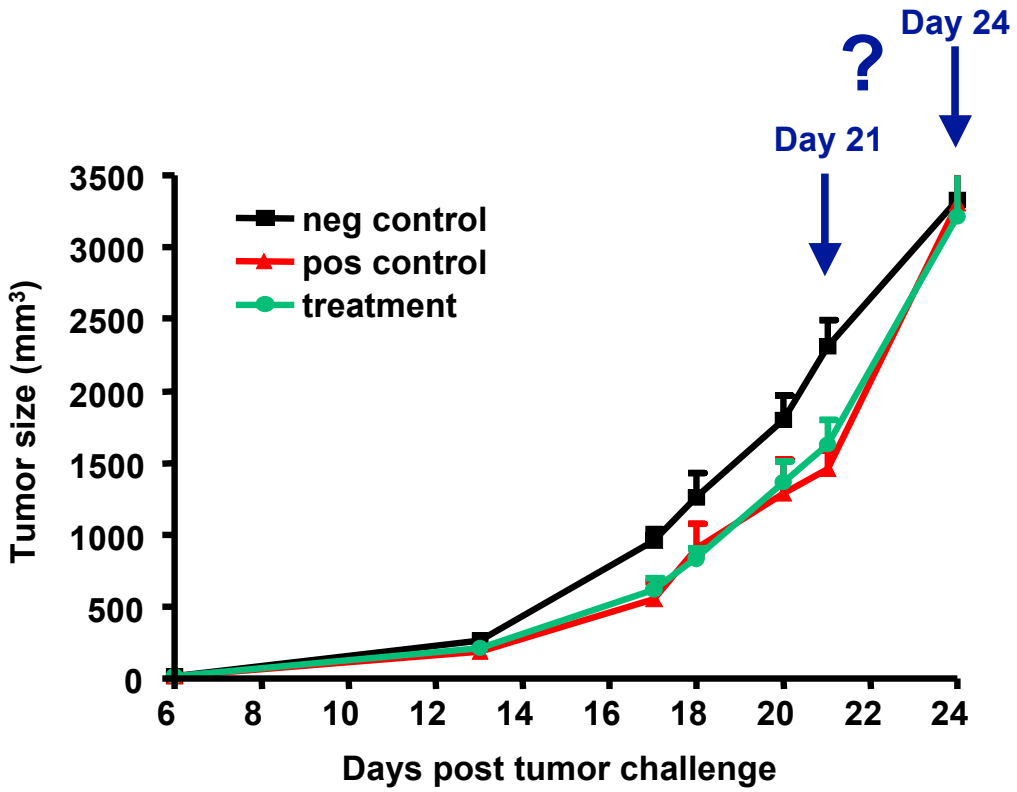
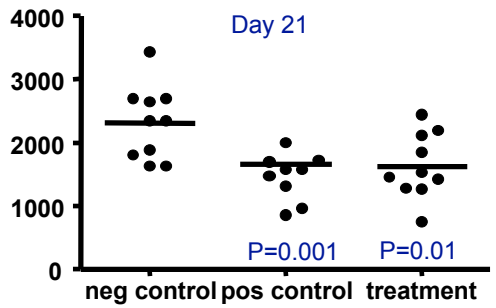
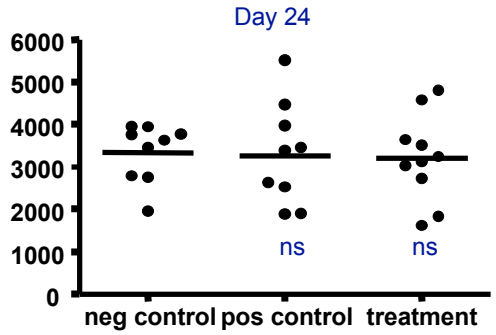
EL4 Thymoma is a Fast Growing Mouse Tumor







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Statistical Evaluation: Limitations of Study Case

PRESCOS Offers Model-Driven and Customized Statistical Analysis Solutions

- Due to physiological limitations and IACUC regulations tumor size is limited, potentially biasing study results at later time points (and/or animals with large tumor volumes)
- Standard t-test or ANOVA analyses do not allow an appropriate statistical evaluation over the study duration
- Many standard analysis programs do not determine confidence intervals

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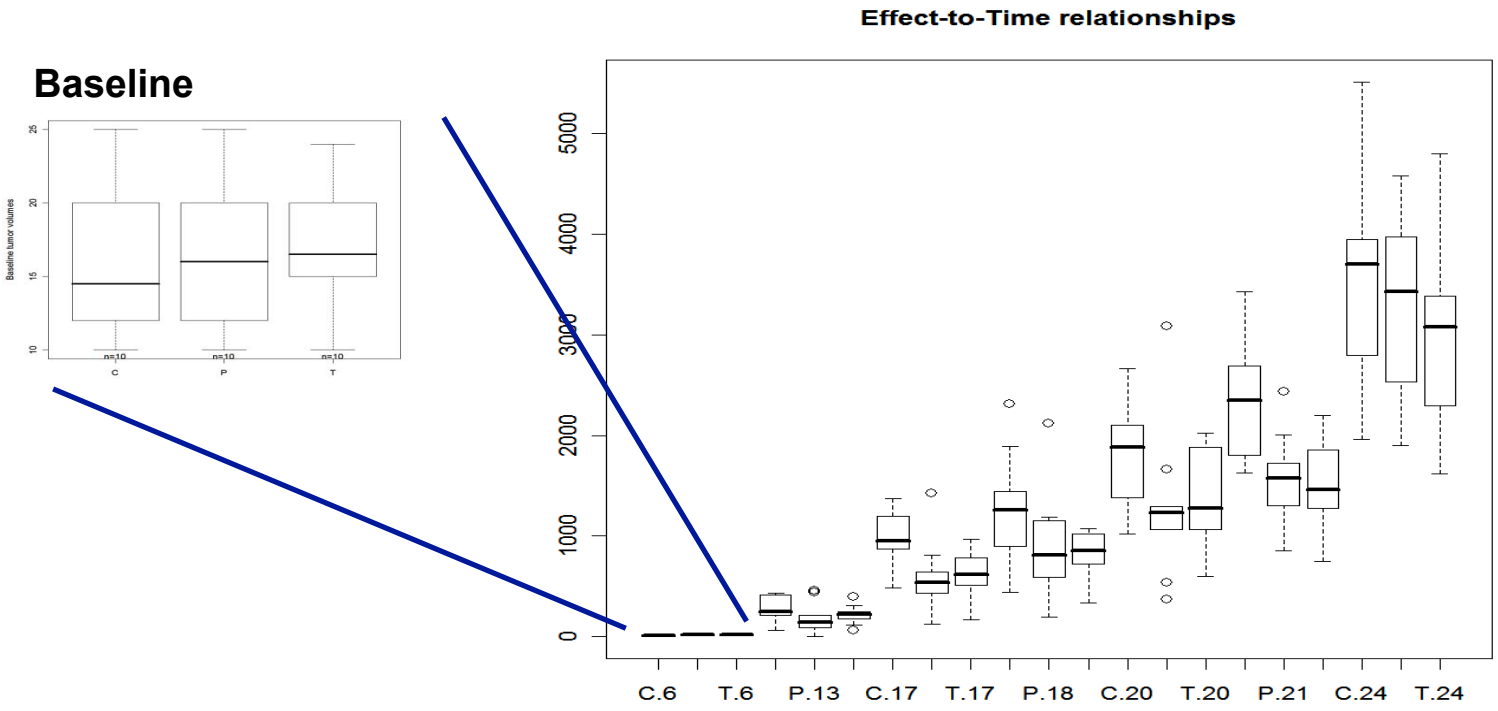
Statistical Evaluation: Limitations of Study Case – cont.



Time dependence of tumor volumes; experimental studies often show significant variability for individual data points

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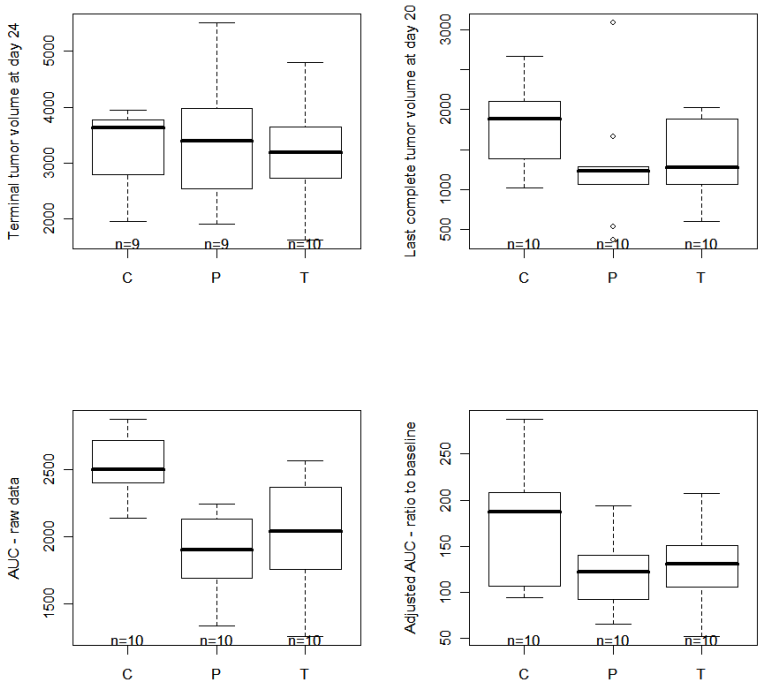
Statistical Evaluation: Limitations of Study Case – cont.



For background on statistical methodology see:
Hothorn (2006) DIJ, 40:229

AUC and baseline corrected AUC variance analysis incorporate data variance and allow inclusion of study endpoint (Day 24 analysis included)

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Statistical Evaluation: Limitations of Study Case – cont.

Comparison	Eff in %	Two-sided confidence interval In %
Positive Control / Negative Control	**75**	[66; 85]
Treatment/ Negative Control	**82**	[70; 94]
Treatment/ Positive Control	**108**	[91; 128]

Efficacy estimates and their two-sided 95% confidence intervals for mortality adjusted AUC

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Summary

PRESCOS
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PRESCOS: Quality and Science Driven Research and Preclinical Development Solutions

PRESCOS combines extensive expertise in preclinical pharmacology and statistics to offer quality custom solutions and expert consulting services to its clients:

- PRESCOS can offer support at all stages of preclinical research and development, and offers services at all scales, from individual compound test studies to comprehensive preclinical pharmacology programs
- PRESCOS also offers preclinical study design and analysis services, conducts study and program evaluations, including technical and scientific due diligences - and has the capability to prepare IND enabling R&D development plans, taking leads from discovery to IND filing

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Thank you very much for your consideration, we very much look forward to working with you!

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