Diagnostics of Invasive Aspergillosis: From Experimental Models to Clinical Evaluation

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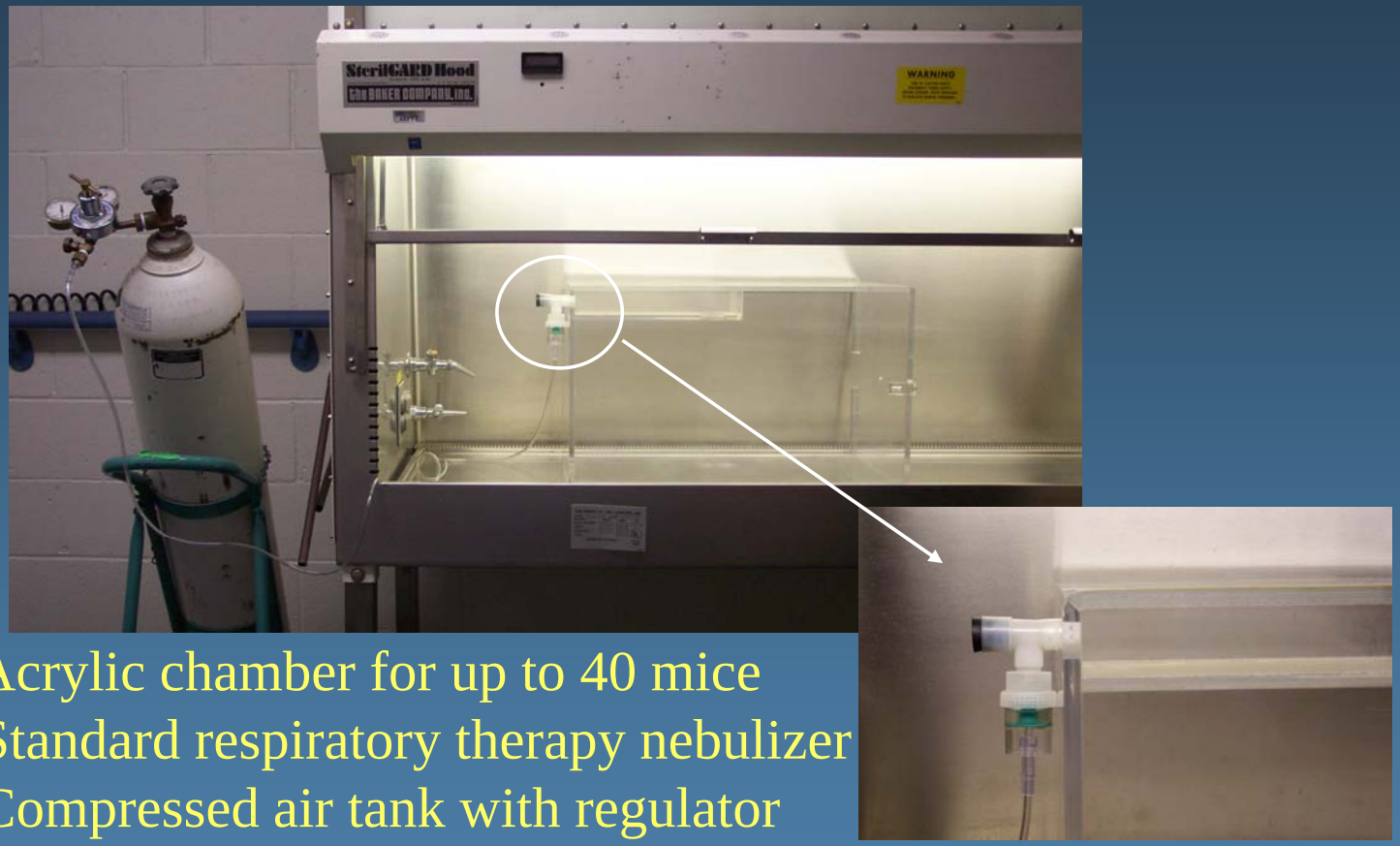
Inhalation Chamber Apparatus for Aspergillosis



- Acrylic chamber for up to 40 mice
- Standard respiratory therapy nebulizer
- Compressed air tank with regulator

Sheppard. AAC 2004;48:1908

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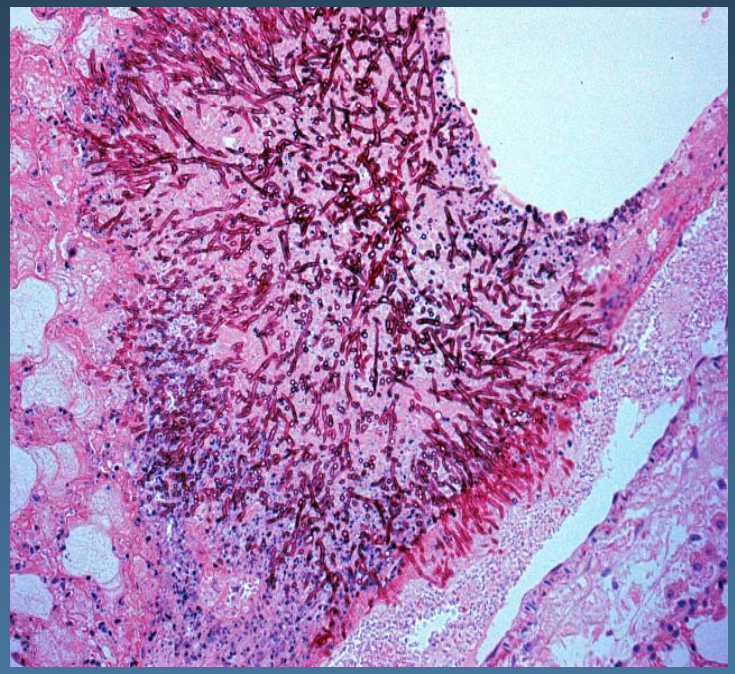
Inhalational Models Advantages

- Relatively low inoculum (~1000 conidia) delivered to alveoli
- Recapitulates human disease
- Reproducible outcome between different experiments and laboratories
- Late mortality
  - Allows multiple time point sampling without survivor bias
- Mortality complete by 14 days



Sheppard. AAC 2004;48:1908
Sheppard. AAC 2006;50:3501

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Key Question: Model Refinement/Diagnostic Targets

Neutropenic vs. Non-neutropenic Model

- Neutropenic:
  - Cyclophosphamide at 250 mg/kg SC on day -2 and 200 mg/kg SC on day +3 of infection
  - Cortisone acetate at 5 mg/mouse SC on days -2 and +3 of infection
- Non-neutropenic:
  - Cortisone acetate at 10 mg/mouse SC on days -4, -2, 0, +2, +4 of infection
- Ceftazidime IP while immunosuppressed

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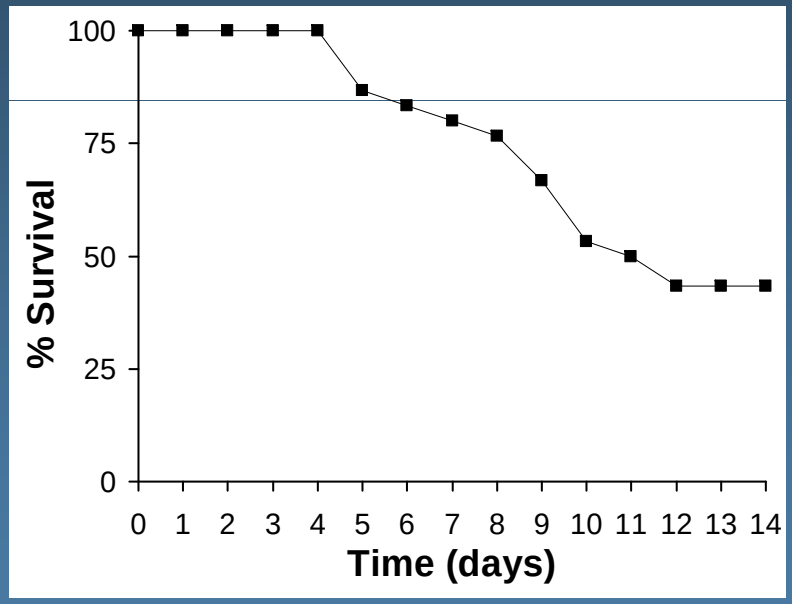
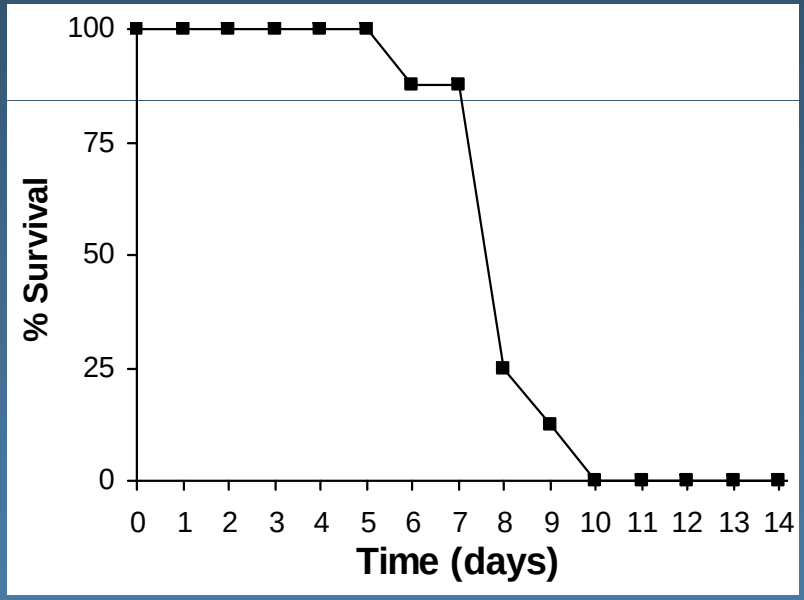
Effects of Different Types of Immunosuppression on Mouse Survival

Neutropenic
(Cortisone Acetate
+ Cyclophosphamide)



Non-neutropenic
(Cortisone Acetate)



Spikes. JID 2008;197:479

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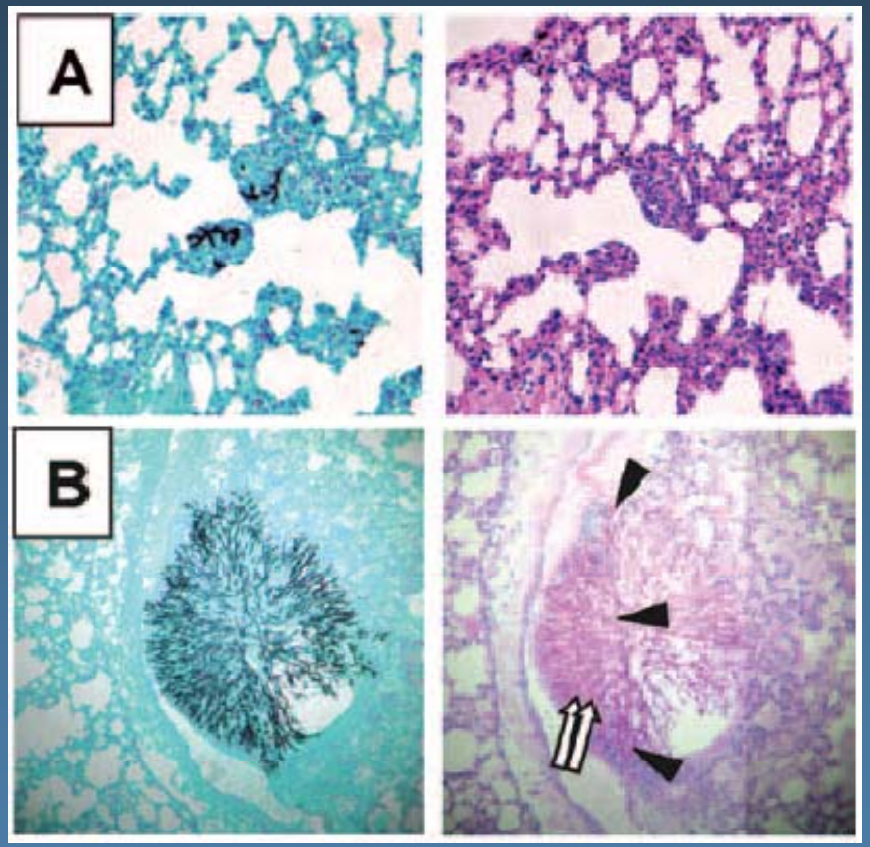
More Rapid Development of Disease in the Non-neutropenic Model

Day 4

Neutropenic
(Cortisone Acetate
+ Cyclophosphamide)

Non-neutropenic
(Cortisone Acetate)



Chiang. I&I 2008;76:3429

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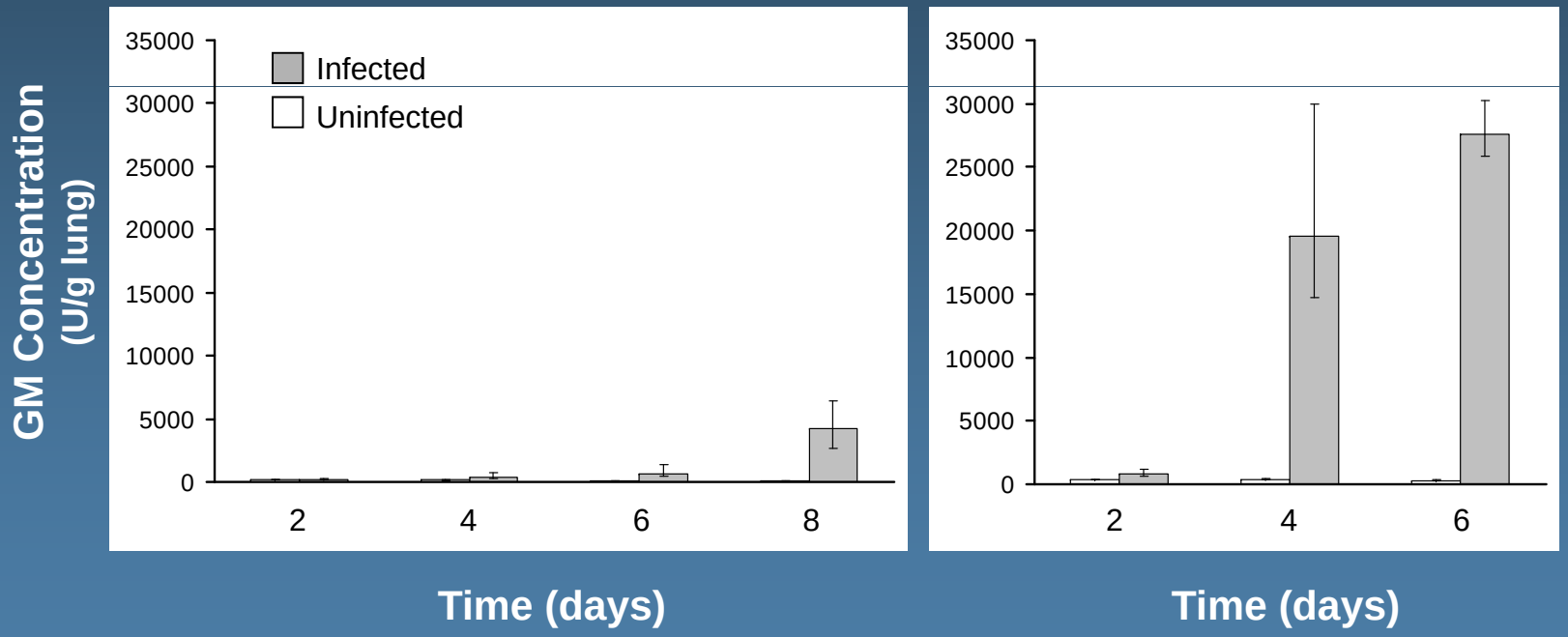
Lung GM Levels are Higher in Non-Neutropenic Mice

Neutropenic
(Cortisone Acetate
+ Cyclophosphamide)

Non-neutropenic
(Cortisone Acetate)



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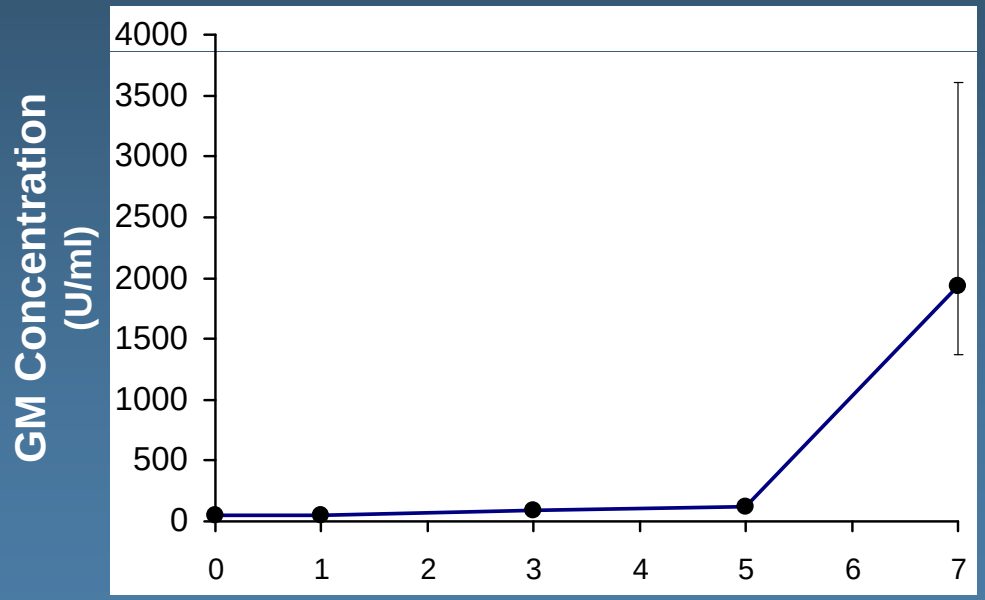
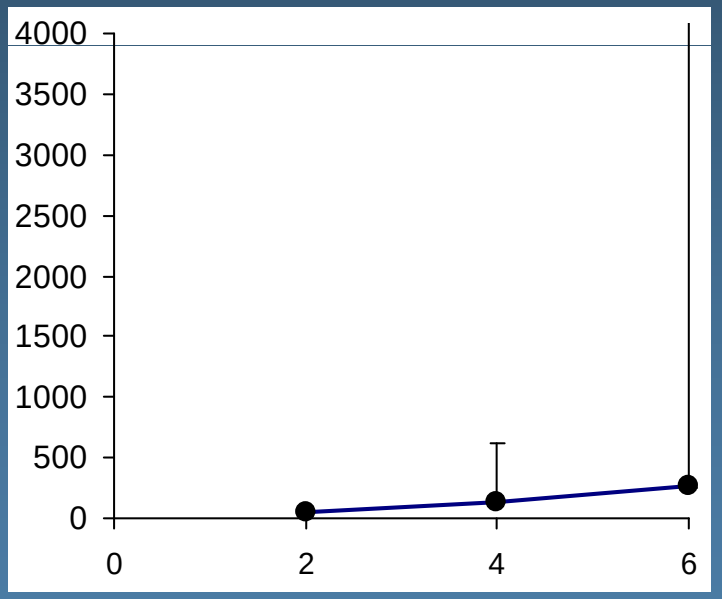
Serum GM Levels are Higher in Neutropenic Mice

Neutropenic
(Cortisone Acetate
+ Cyclophosphamide)



Non-neutropenic
(Cortisone Acetate)



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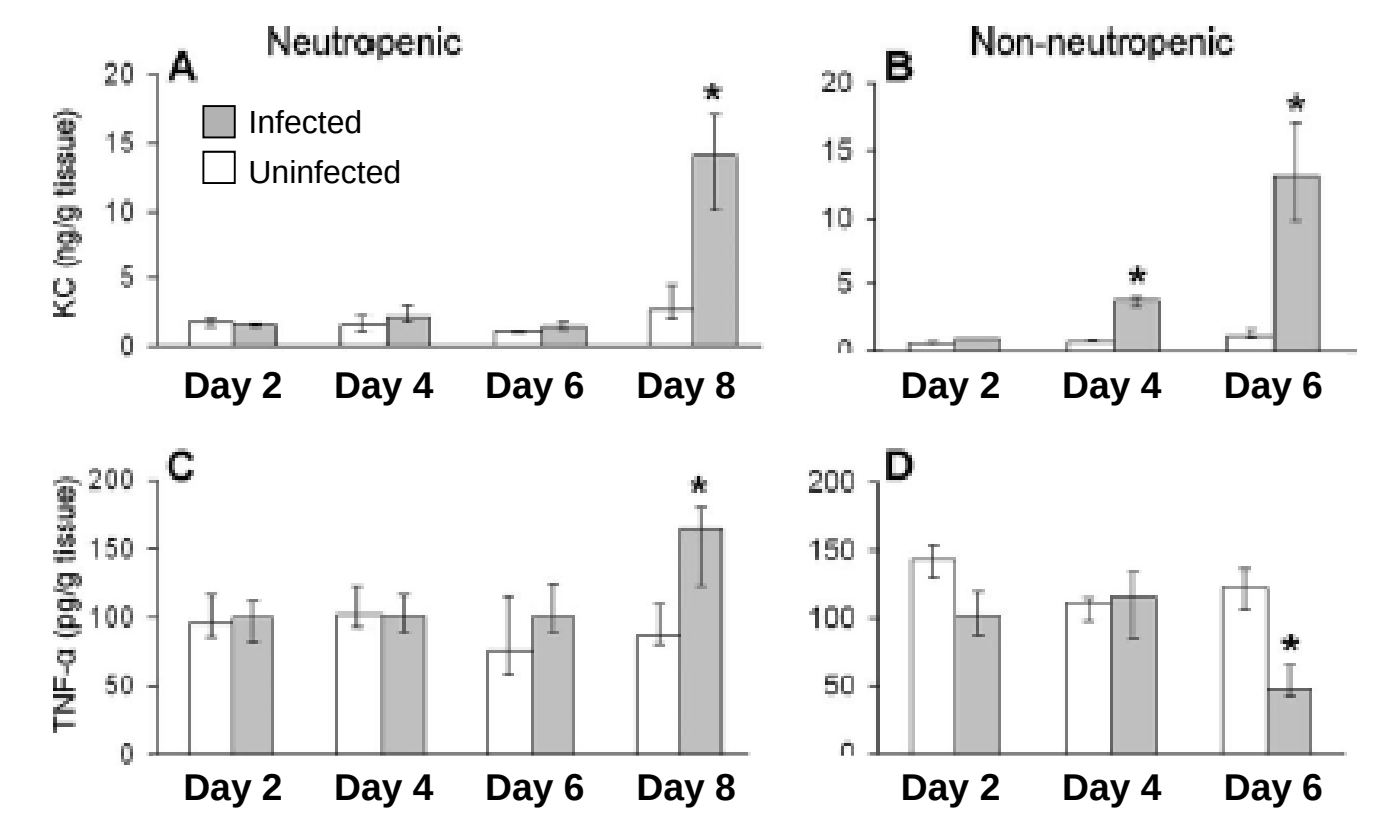
The Pulmonary Cytokine Response is Different in Neutropenic vs. Non-neutropenic Mice



Chiang. I&I 2008;76:3429

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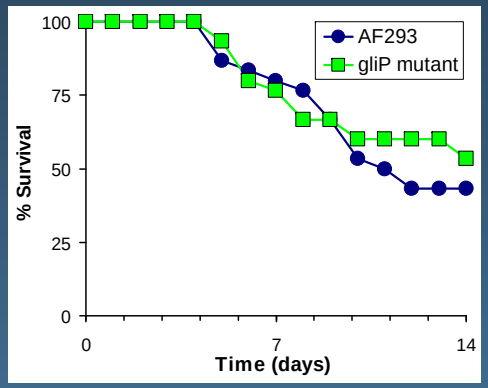
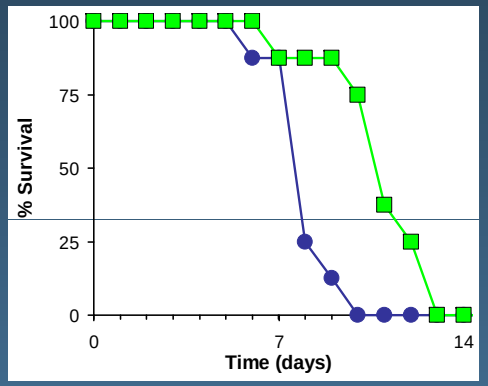
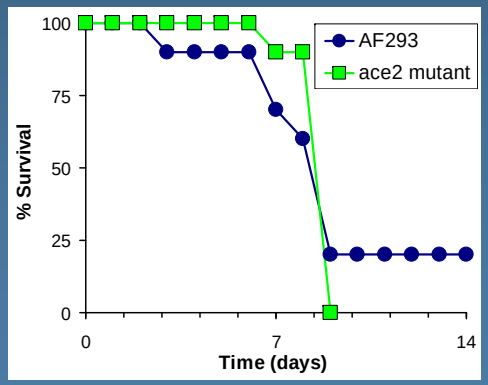
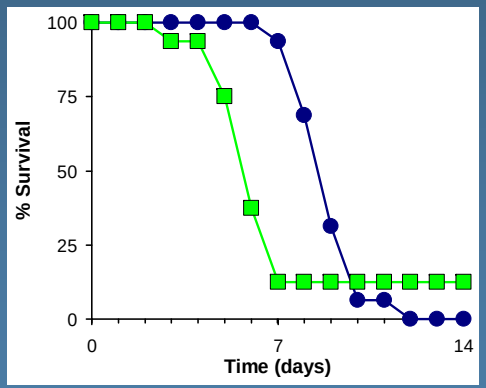
Effects of Different Types of Immuno-suppression on Virulence Mechanisms

Neutropenic | **Non-neutropenic**









Spikes. JID 2008;197:479; Ejzykowicz. Molec Microbiol 2009;72:155

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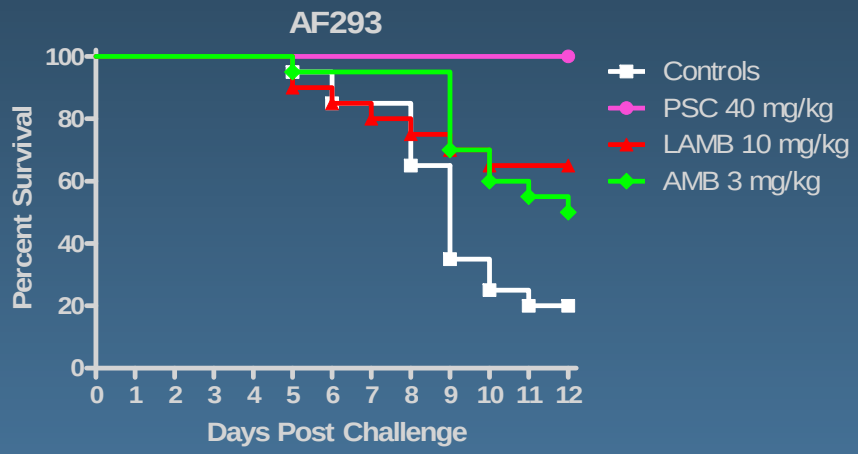
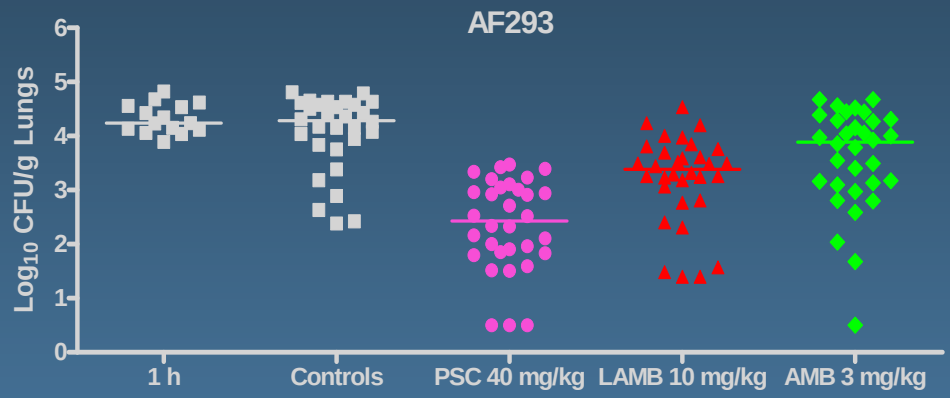
Posaconazole is Highly Efficacious in the Neutropenic Model





N≥18 mice/group. All treatments prolonged survival p≤0.0150.
N= 15 for 1h. N≥30 mice/group. All treatments reduced lung fungal burden compared to controls p≤0.0213.

Najvar LK, et al, ICCAC 2007 (abstract M-1848)

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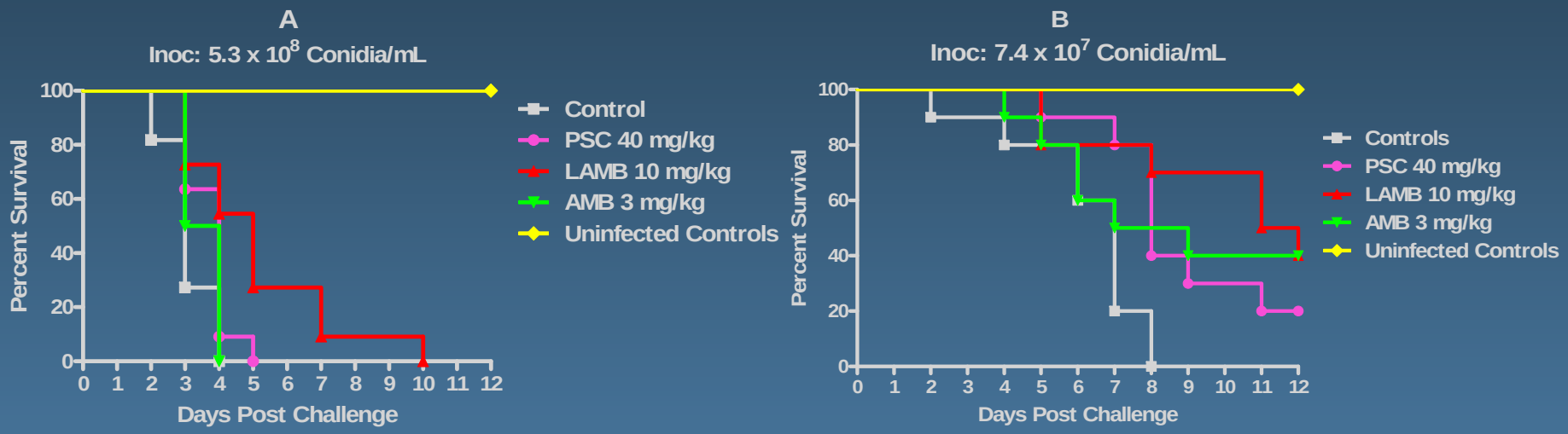
Posaconazole is Less Efficacious in the Non-neutropenic Model



N=10 mice/group. Controls all succumbed by day 4 or 8. The median survival was prolonged for LAMB (p=0.006) in A and both PSC (p=0.007) and LAMB (p=0.009) prolonged survival in B.

Najvar LK, et al, ICCAC/IDSA 2008 (abstract M-1561)

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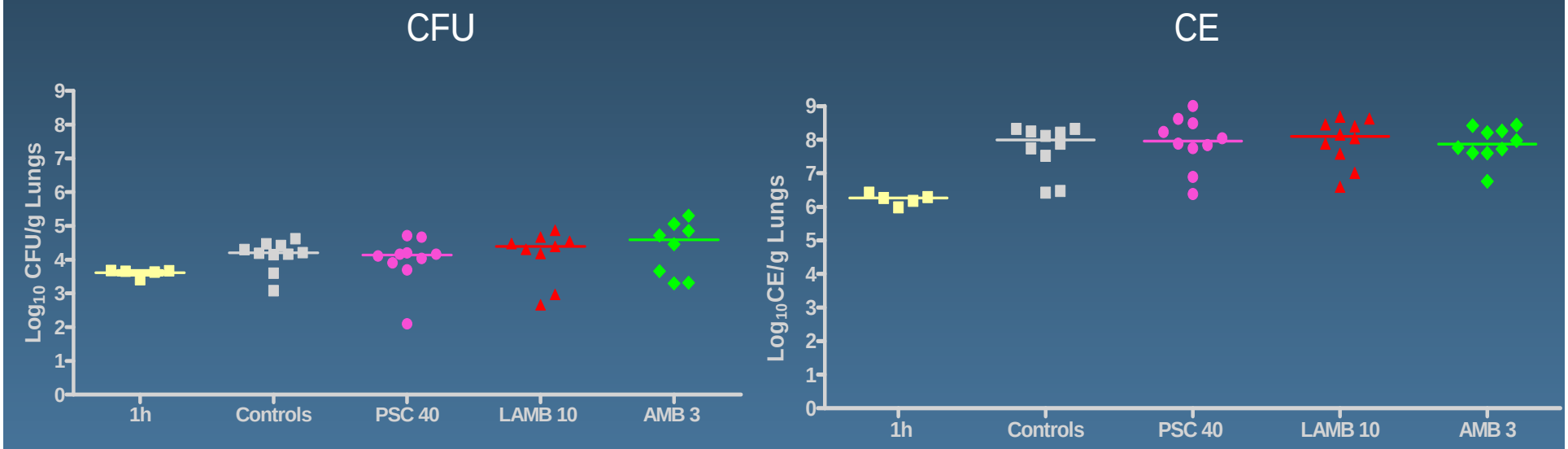
No Therapy Reduced Pulmonary Tissue Burden in the Non-neutropenic Model



Inoculum: 7.4 x 10^7 Conidia/mL. N= 5-10 mice/group. No therapy reduced the fungal burden.

Najvar LK, et al, ICCAC/IDSA 2008 (abstract M-1561)

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Summary

	Neutropenic	Non-neutropenic
Mortality	Late	Early
Pulmonary GM	Low	High
Serum GM	High	Low
Influence of AF virulence factors on mortality	Low	High
Response to posaconazole	Good	Poor

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Contributors and Collaborators

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- Marcos Olivo
- Destiny Molina

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