# Innate Defense Regulators: Agnostic Therapy for Antibiotic Resistant Disease

***"Supercharging existing and new antibiotic therapies"***

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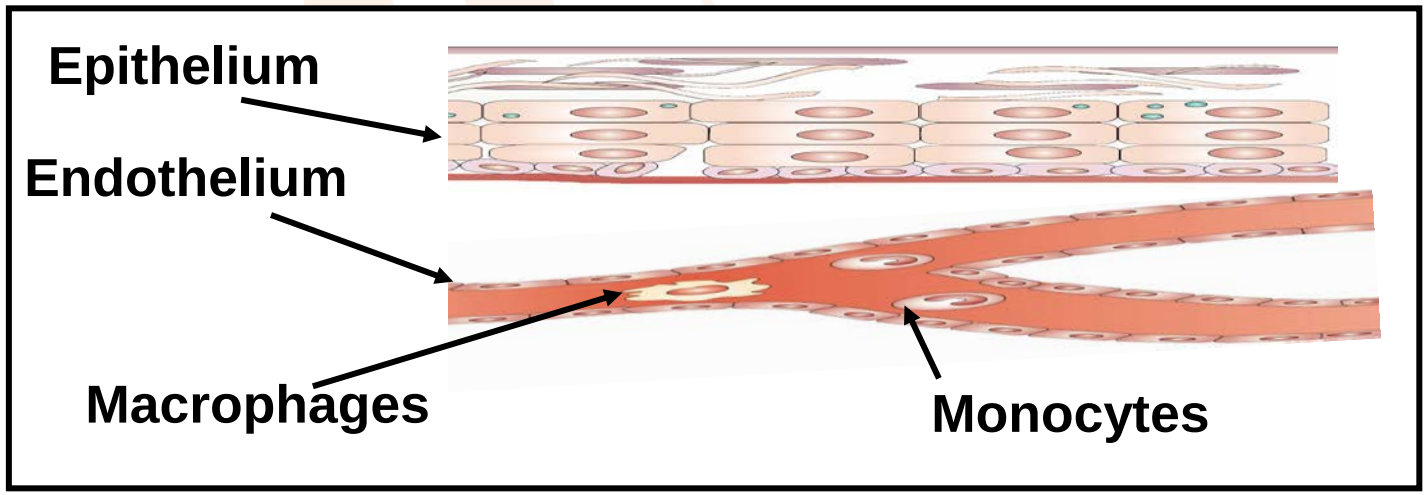
# Leveraging Innate Immunity

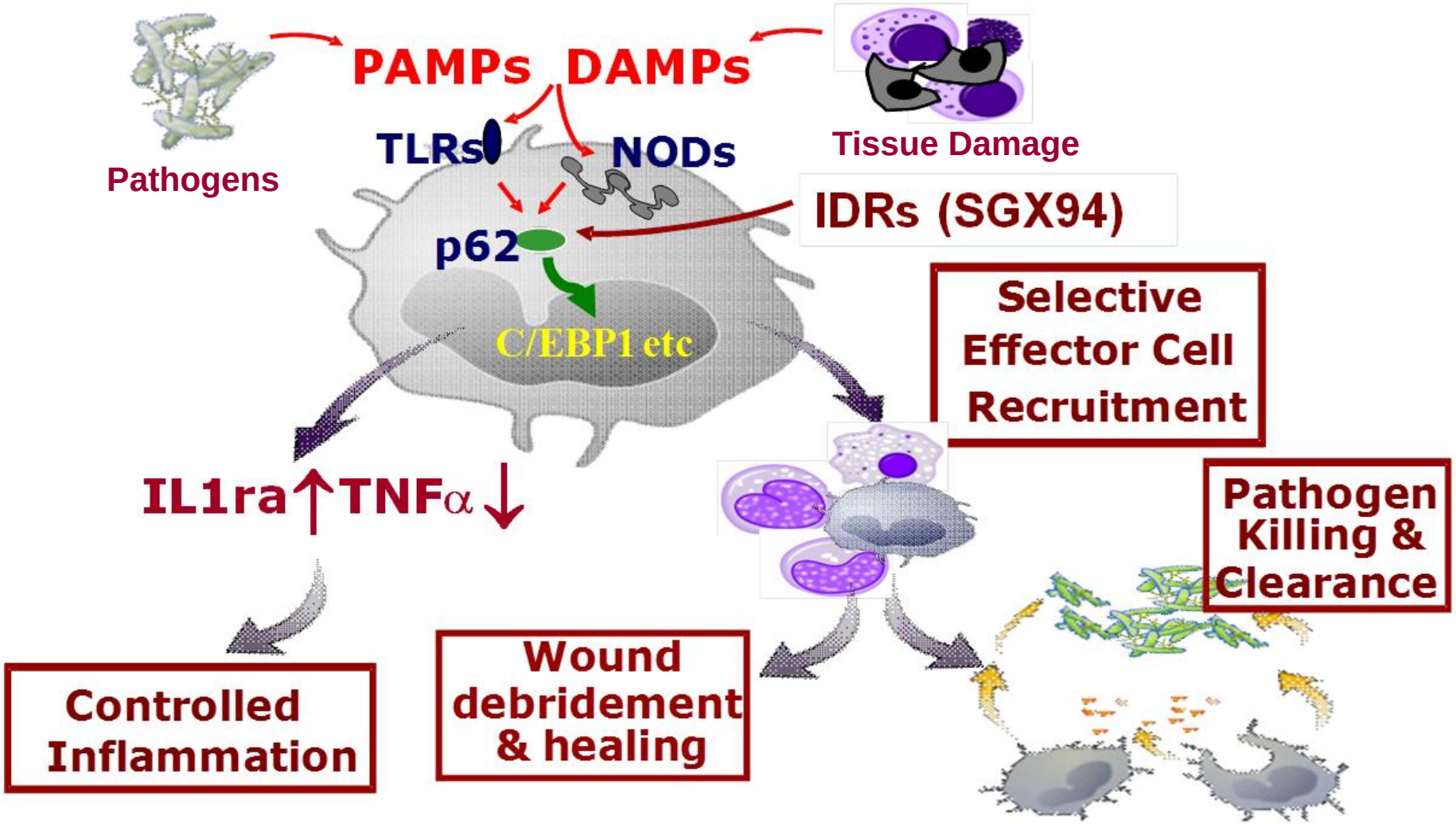
- Rapid, non-specific response
- Involves circulating **and** tissue resident cells.
- Inflammation separable from tissue healing / bacterial clearance mechanisms
- ***Antibiotics act in tandem with the innate immune system***






Yu et al. JBC 2009; 284(52): 36007-11.

# Innate Defense Regulators

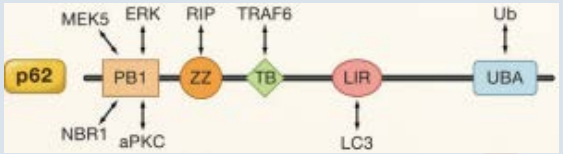




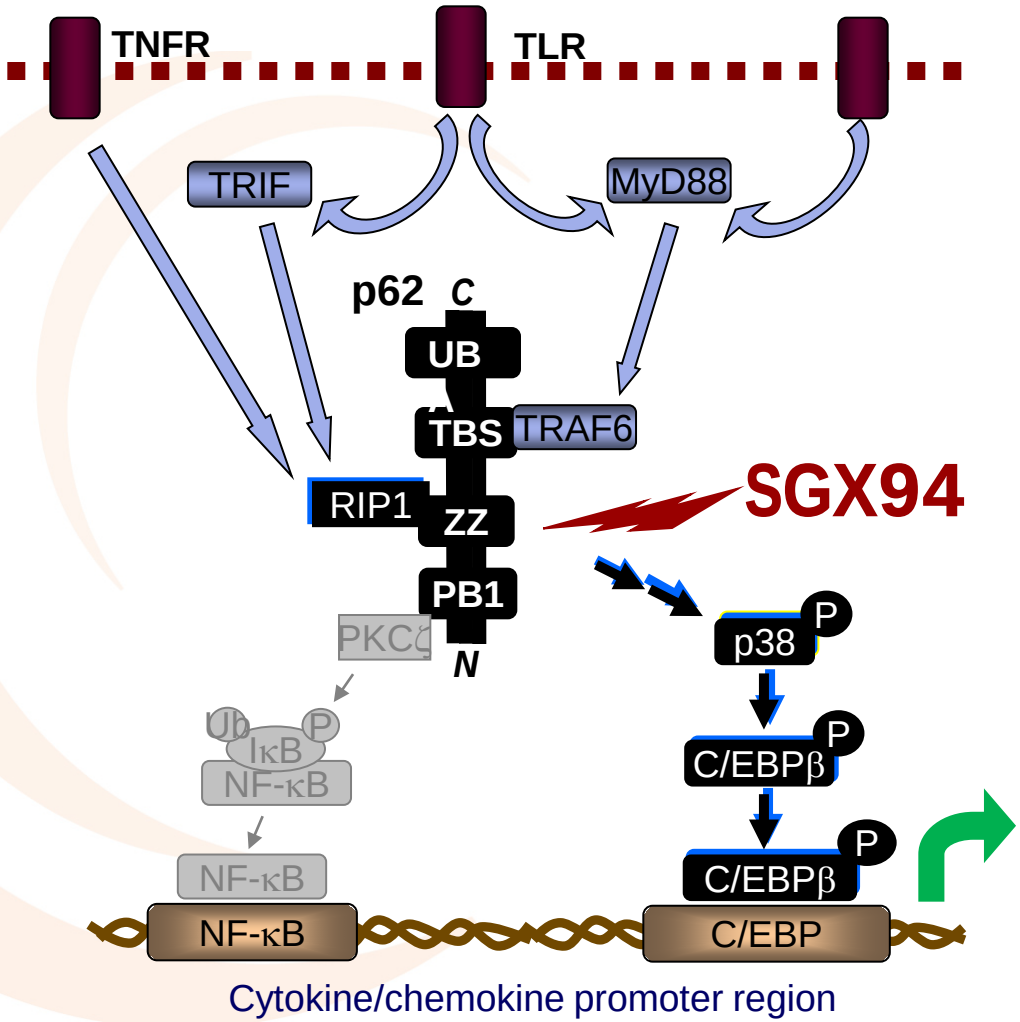

Yu et al. JBC 2009; 284(52): 36007-11.

# SGX94 Targets Sequestosome-1 (p62)

- SGX94 (dusquetide) specifically binds to the ZZ domain of p62




- Selectively stabilizes TNFα-induced p62-RIP1 complex formation
  - **No effect on TNFα-induced p62-PKCξ complex formation**
- Specifically modulates downstream pathways by activating MAPK p38 and C/EBPβ
  - **Does not modulate NF-κB activity**
- **Results in:**
  - **Modulation of cytokine/chemokine production**
  - **Altered protein expression in endothelial cells, monocytes**
  - **Increased macrophage recruitment to the site of infection/damage**




Jorge Moscat and Maria T. Diaz-Meco. Cell 137, June 12, 2009



Yu et al. JBC 2009; 284(52): 36007-11.

# Broad Spectrum Activity

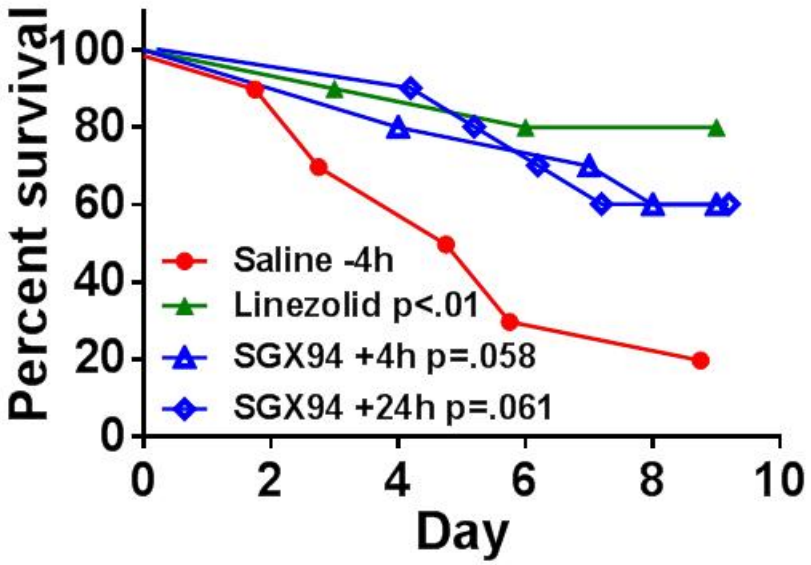
- Improves survival **and** enhances bacterial clearance
- Efficacious against various pathogens:
  - Gram-negative (*P. aeruginosa, B. pseudomallei*) ***OR*** Gram-positive (*S. aureus,* MRSA)
  - Extracellular (MRSA, *S. aureus*) ***OR*** Intracellular (*B. pseudomallei*)
  - Antibiotic sensitive (*S. aureus*) ***OR*** Antibiotic resistant (MRSA, *B. pseudomallei*)
- Effective at various anatomic locations
- Active in immune compromised animals
- Aids in resolution of tissue damage
- Modulates inflammation
- ***Enhances antibiotic action when antibiotics alone are suboptimal***


Scott et al. Nat Biotechnol 2007;25: 465-72.
North et al. J. Biotech 2016; 226:24-34.

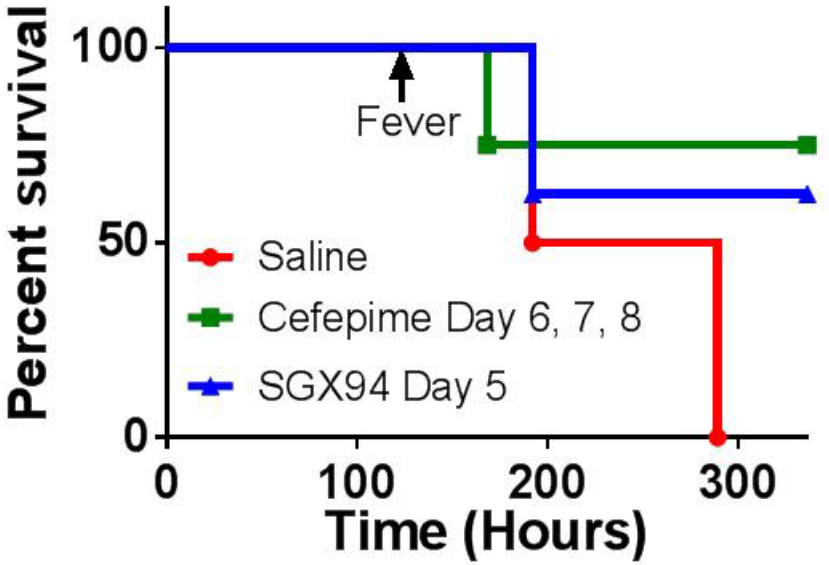
# Anti-Infective

- Improves **survival** with ***therapeutic*** administration, including in immune-compromised animals

**Gram-positive, Antibiotic-resistant Bacteremia (MRSA)**




**Gram-negative, Leukopenic Septicemia (*P. aeruginosa*)**

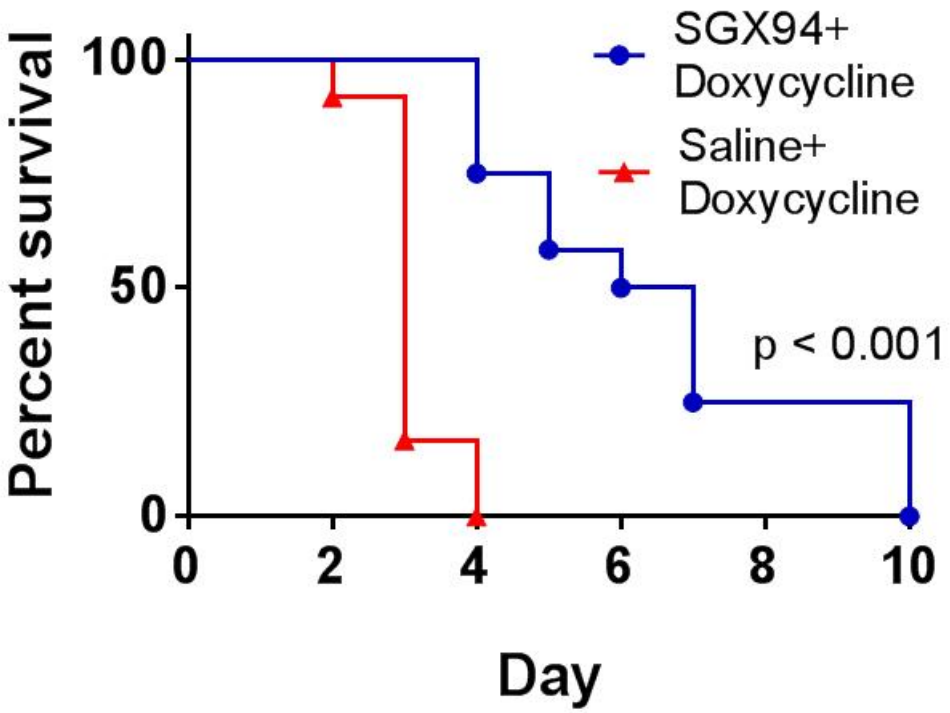





North et al. J. Biotech 2016; 226:24-34.

# Complements Antibiotic Action

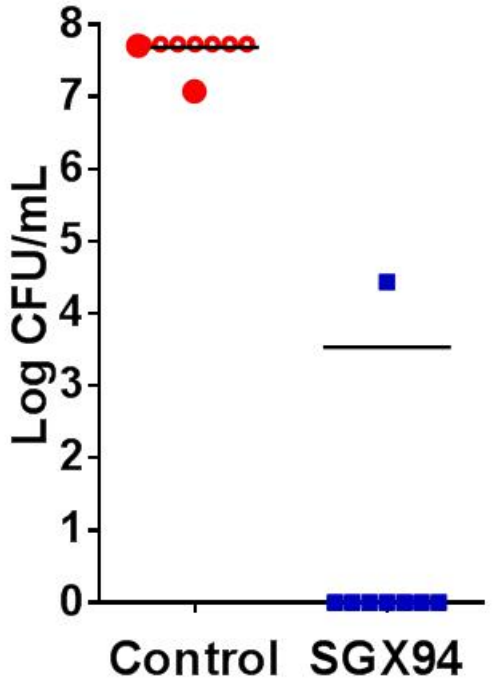
**Combination treatment with lung infection:**
**Gram-negative, Antibiotic-resistant *B. pseudomallei***



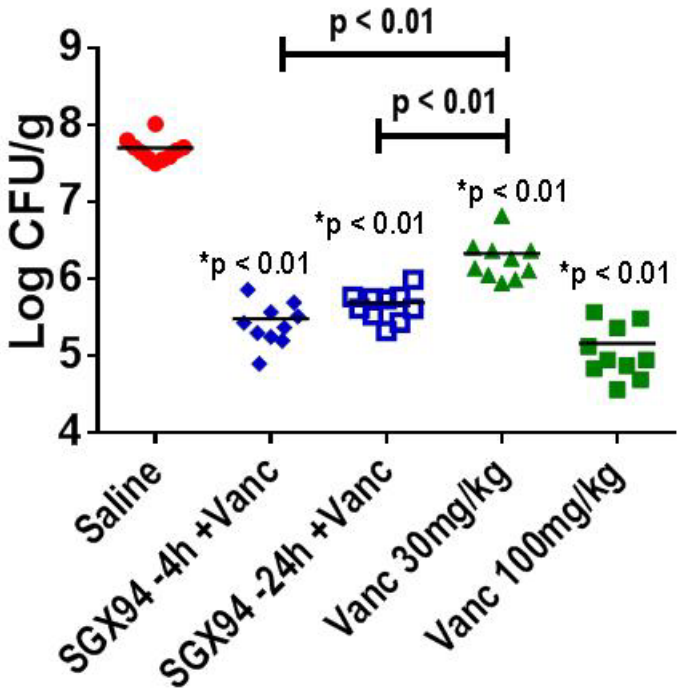
# Bacterial Clearance

**Enhances bacterial clearance – alone or in conjunction with antibiotics**

## *S. aureus* Peritoneal Infection: Stand Alone Therapy




## MRSA Thigh Infection: Combination Treatment

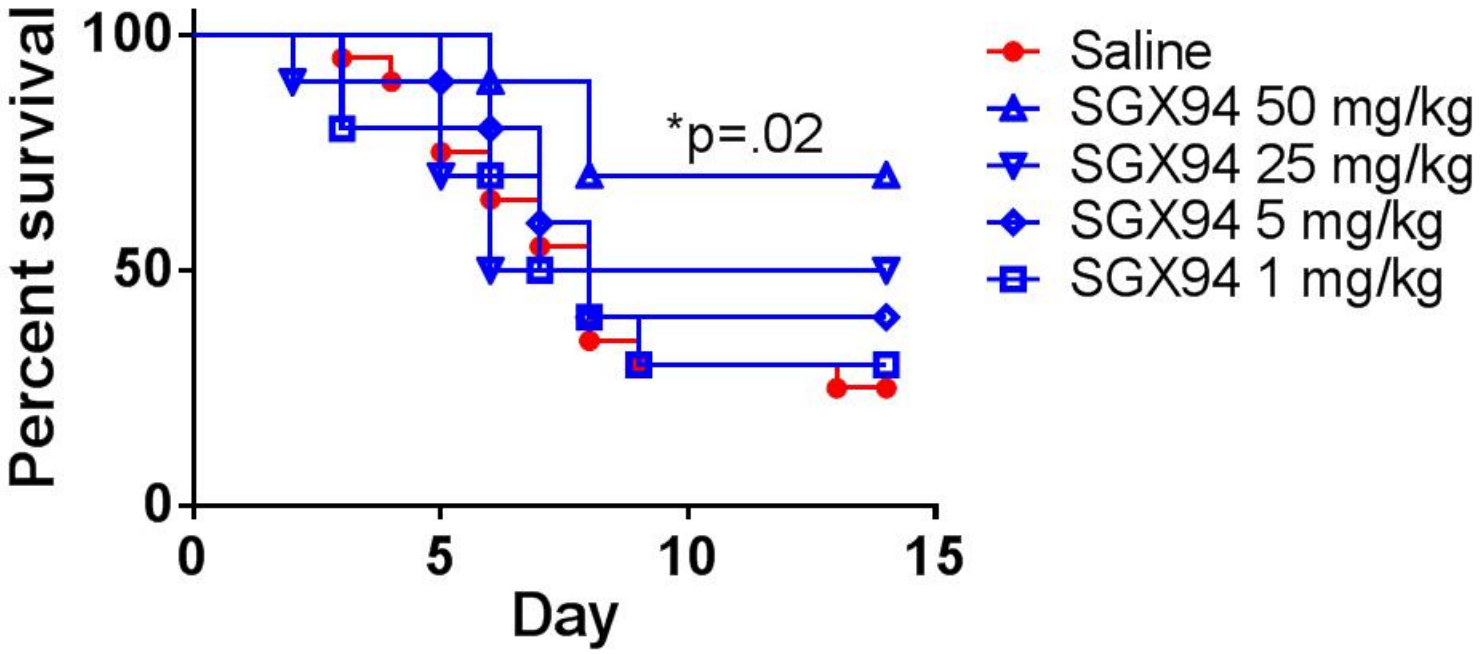





North et al. J. Biotech 2016; 226:24-34.

# Anti-Infective Dose Response

## MRSA Bacteremia in Nude Mice with Treatment 4 hours prior to Infection

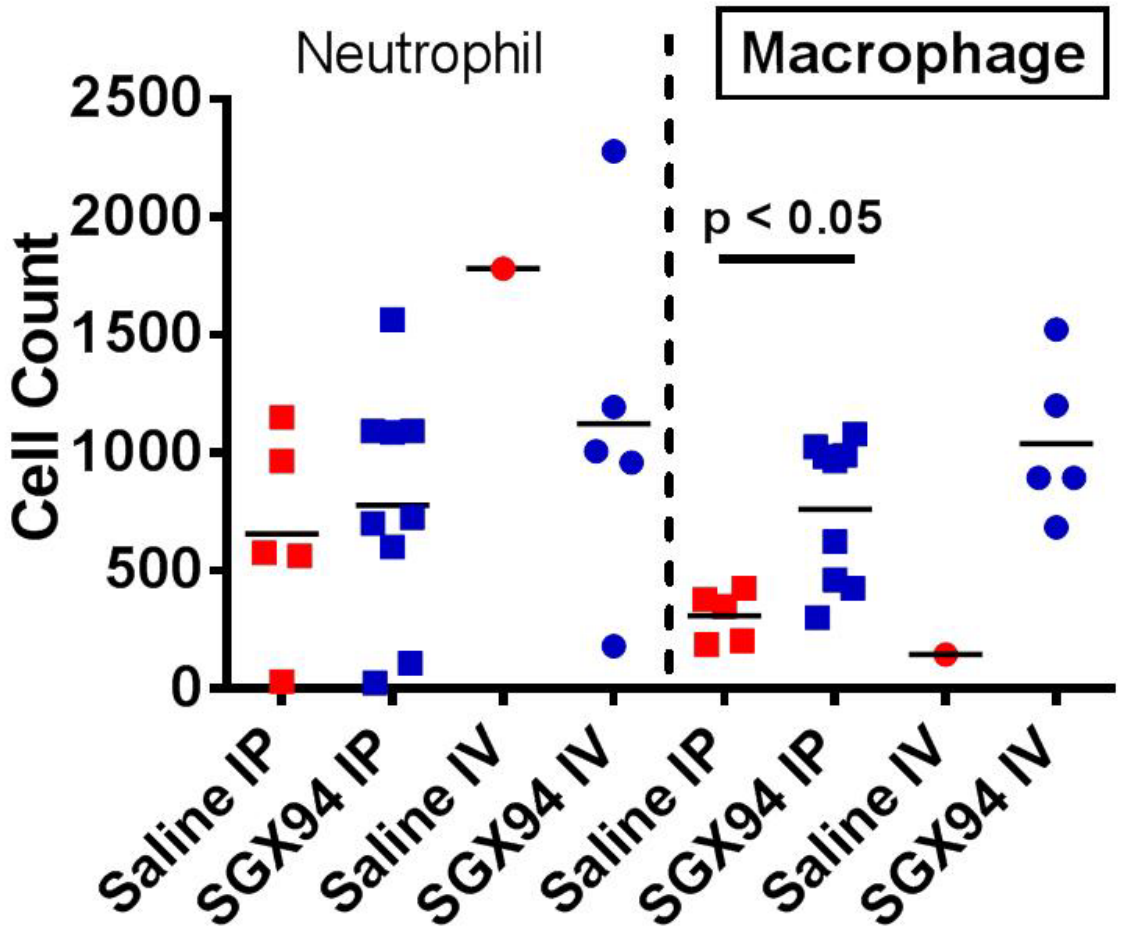





North et al. J. Biotech 2016; 226:24-34.

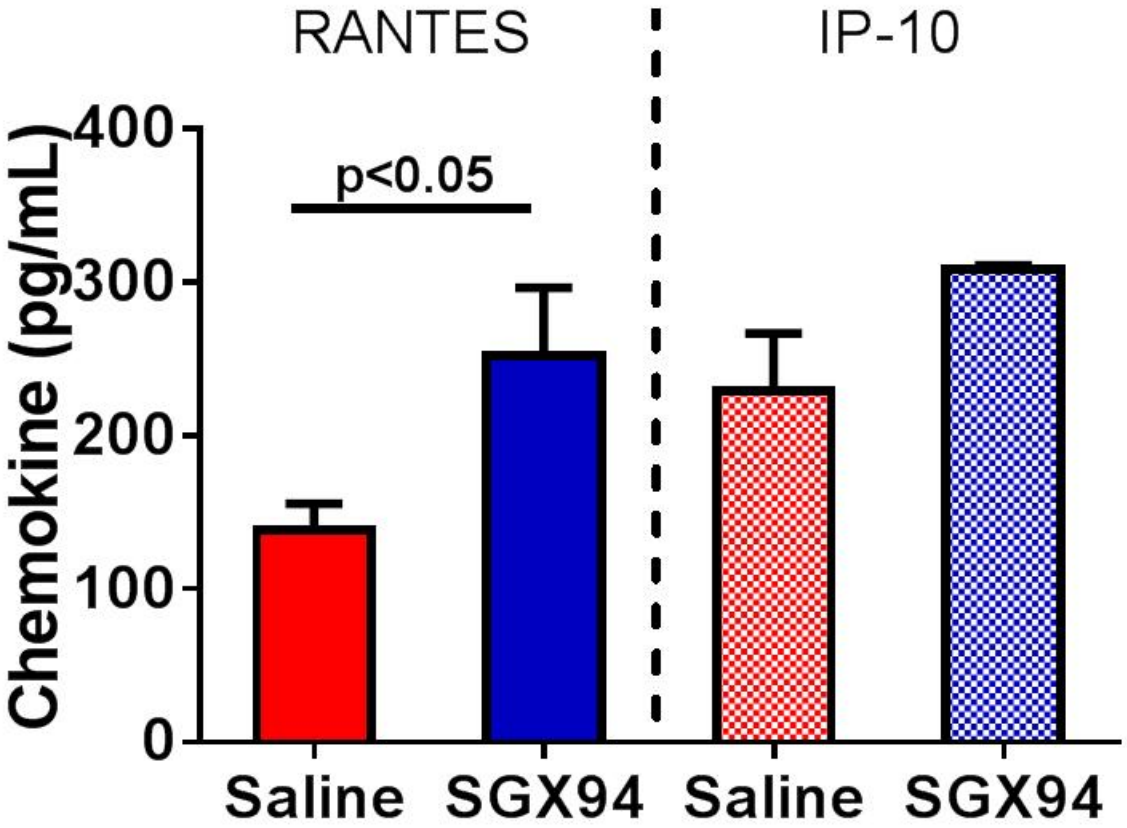
# Increased Macrophage Recruitment

**Peritoneal macrophages increased in MRSA IP infection**



# Early Chemokine Responses

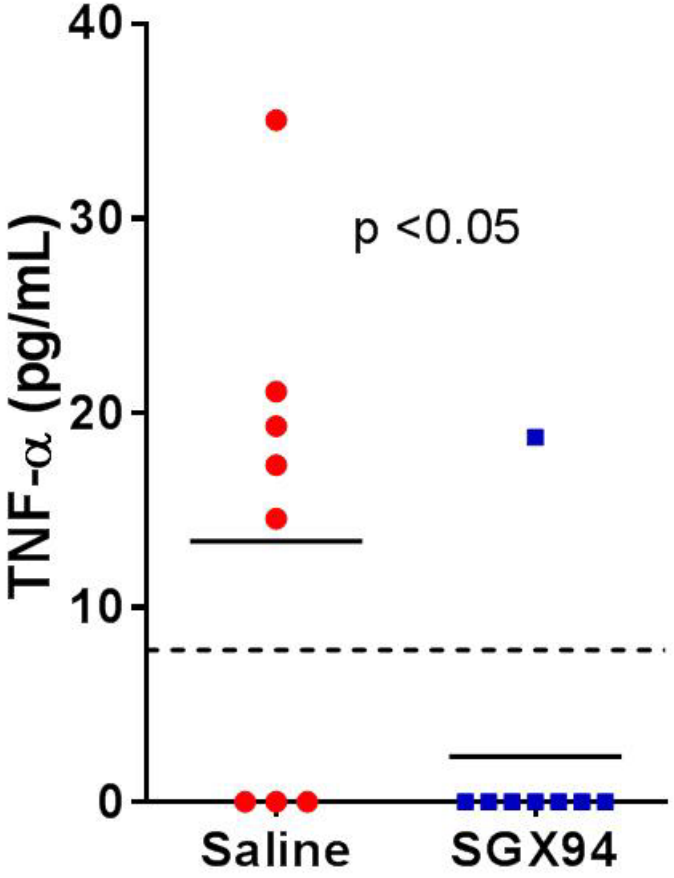
**Peritoneal RANTES and IP10 increased in MRSA IP infection**



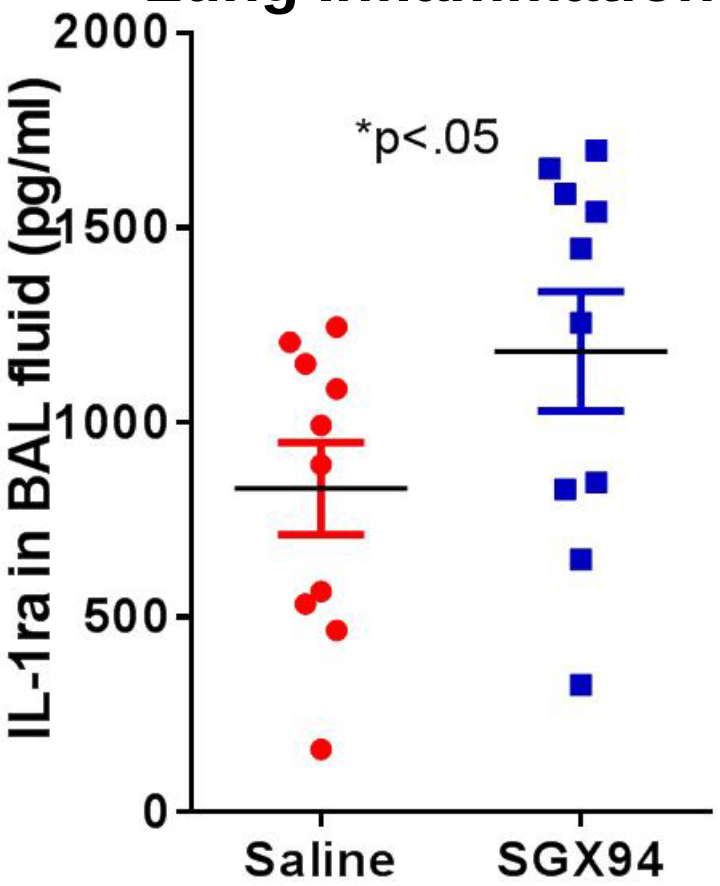
# Anti-Inflammatory Action

**TNFα decreased and IL-1ra increased**

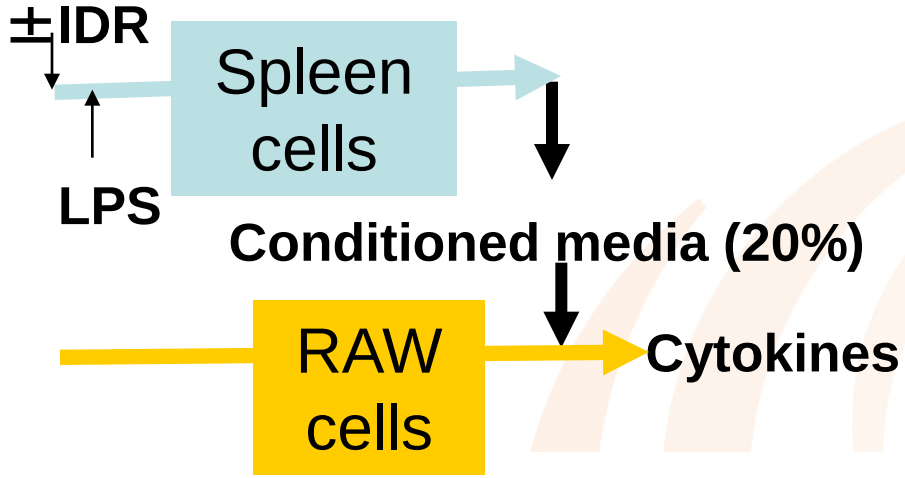
## Peritoneal Infection

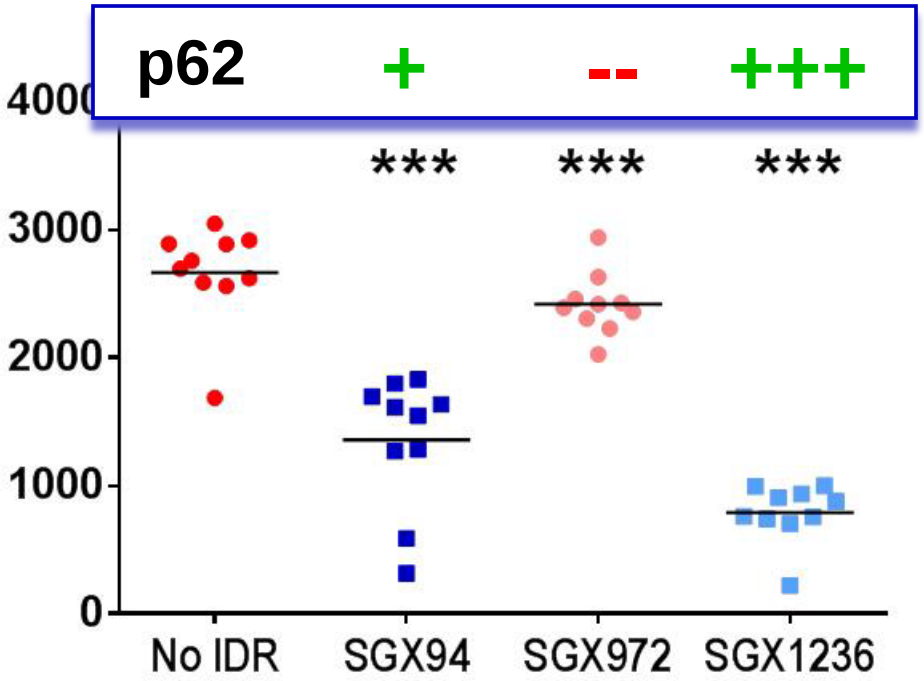



## Lung Inflammation



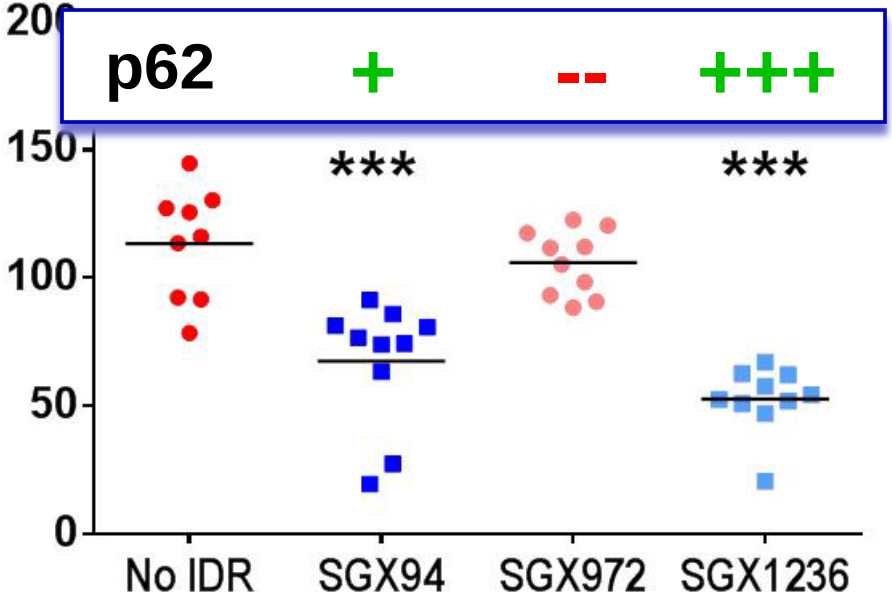
# Tissue-Mediated Effects




**TNFα**

**(pg/ml)**




**IL-6**

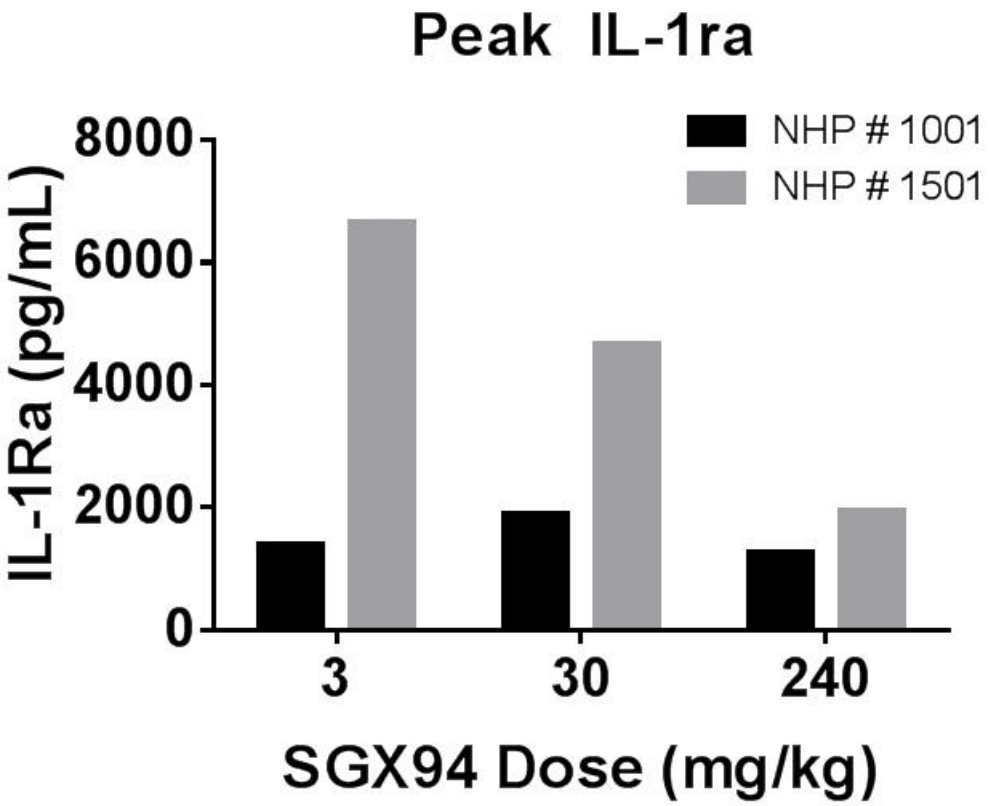
**(pg/ml)**

**Responsiveness correlates with p62 binding affinity**



North et al. J. Biotech 2016; 226:24-34.

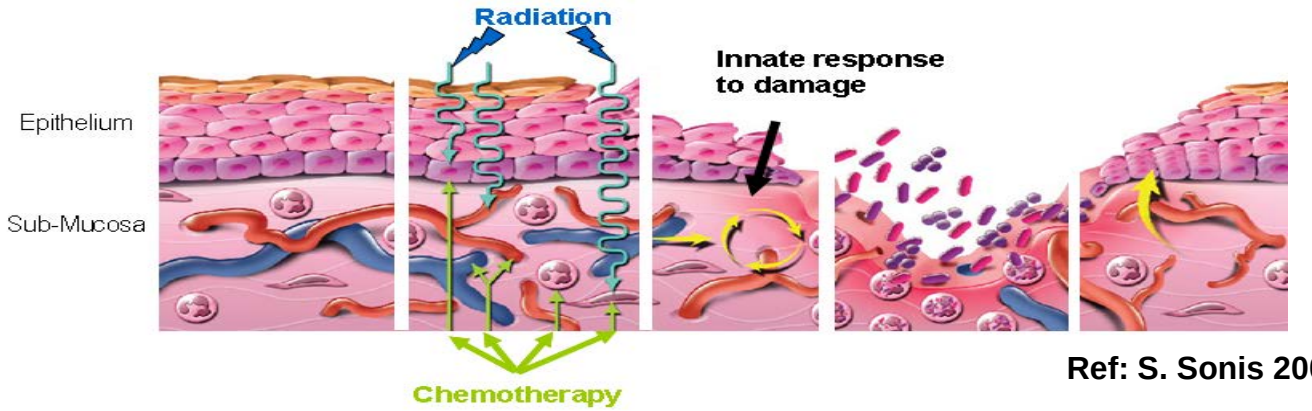
# Anti-Inflammatory Dose Response





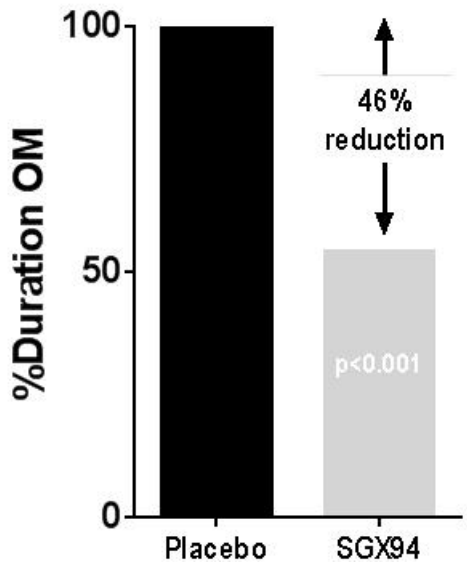

North et al. J. Biotech 2016; 226:24-34.

# Chronic Injury Models: Oral Mucositis

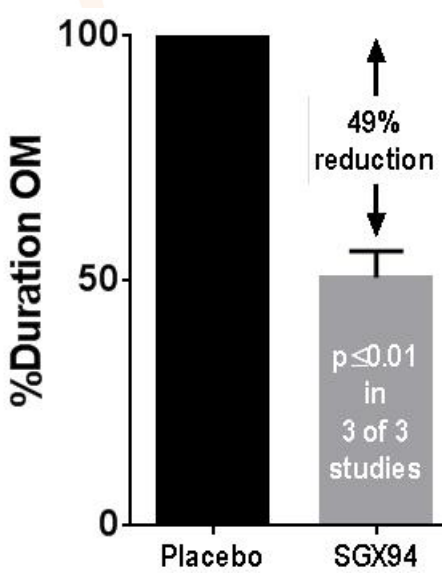


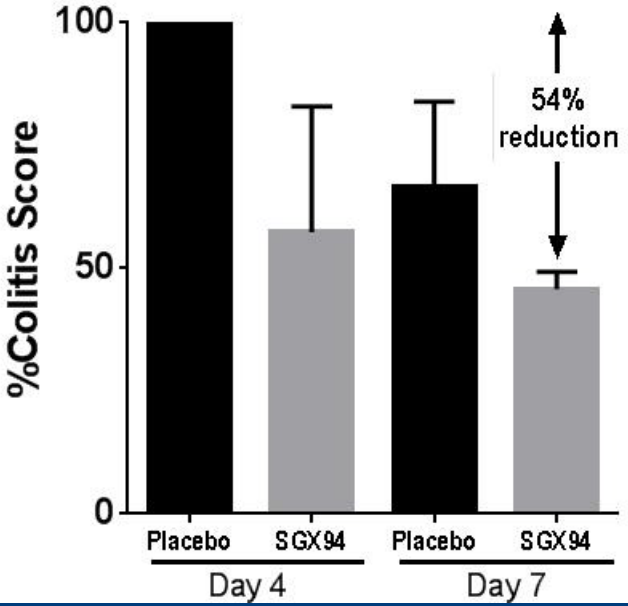

Ref: S. Sonis 2004

## Radiation-Induced Mucositis




## Chemotherapy- Induced Mucositis



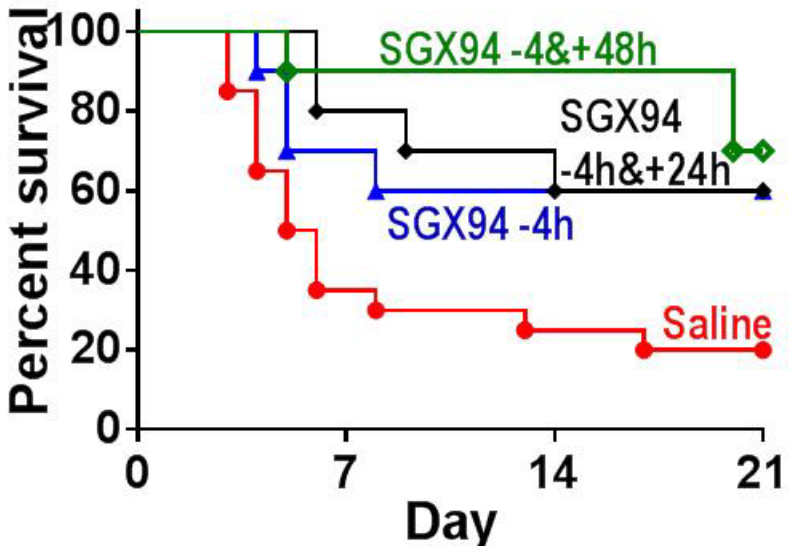



Kudrimoti et al. J. Biotech 2016; 239:115-125.

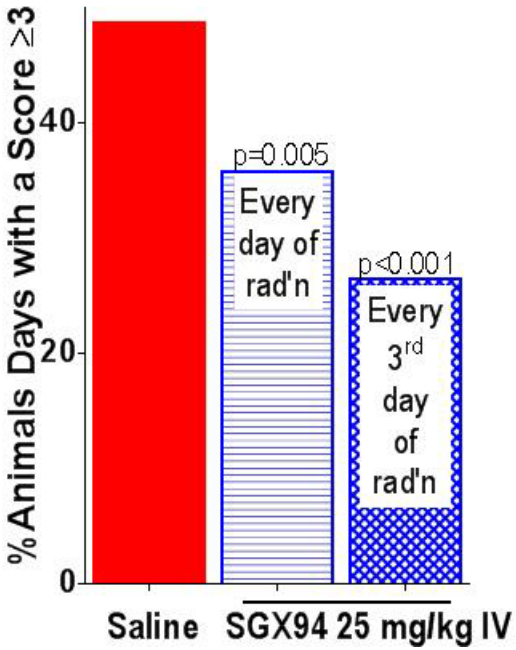
# Enduring Pharmacodynamic Effect

- Rapid PK (expected for peptide product)
- Repeat administration within 24-48 hours has no additional benefit
- Treatment up to 5 days prior to infection is effective

## Gram-positive, Antibiotic-resistant Bacteremia




## Oral Mucositis Model



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Kudrimoti et al. J. Biotech 2016; 239:115-125.

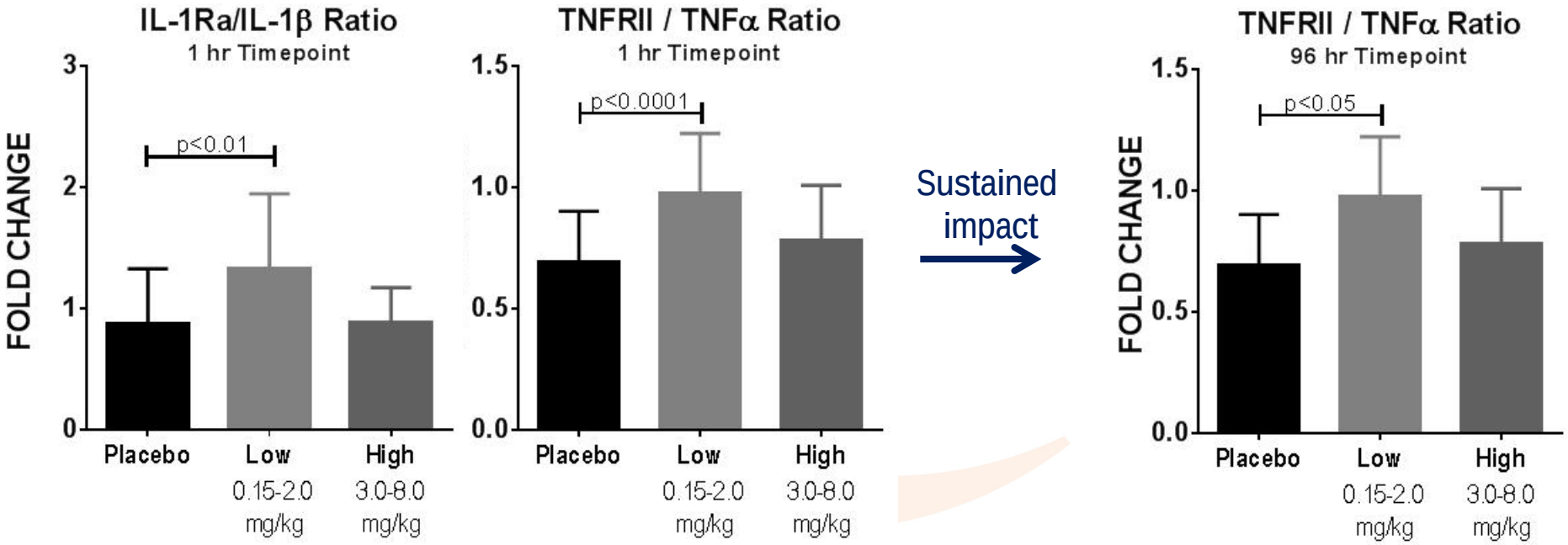
# Translation to the Clinic

- Innate immune system present in all orders of mammals
  - Highly conserved
- Target protein p62 highly conserved
  - 91% sequence identity mouse-human
  - 99% sequence identity orangutan-human
- Phase 1 study in 84 healthy human volunteers
- Phase 2 study in 111 head and neck cancer patients at risk of severe oral mucositis
- *Complete concordance between nonclinical and clinical findings*

# Anti-Inflammatory

- Whole blood samples collected at various timepoints post-dosing are stimulated with LPS (endotoxin) for 4 hours

**Anti-Inflammatory Effect Stronger at Low Dose**
**Enduring PD Response**



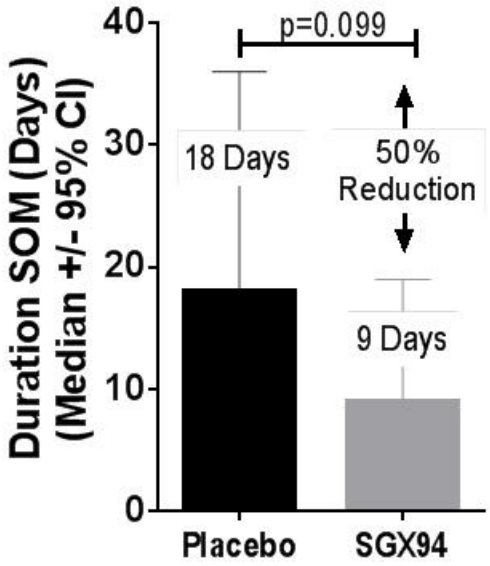



North et al. J. Biotech 2016; 226:24-34.

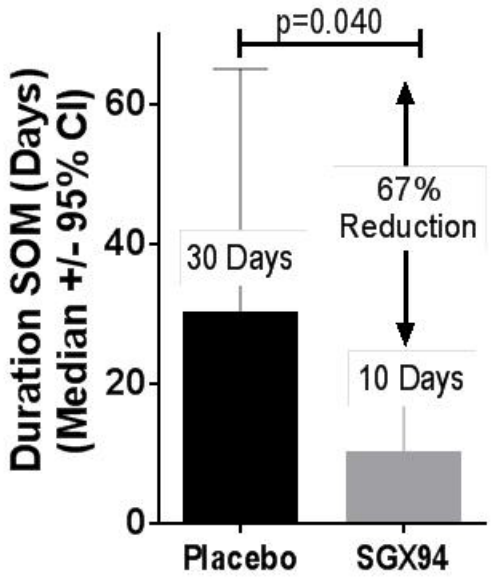
# Tissue Healing/Anti-Inflammatory

- Enrolled 111 head and neck cancer (HNC) patients planned to receive at least 55 Gy radiation and either weekly (30-40 mg/m$^2$) or every 3$^{rd}$ week (80-100 mg/m$^2$) cisplatin

**Duration Severe OM**




**Duration Severe OM High Risk Subpopulation**



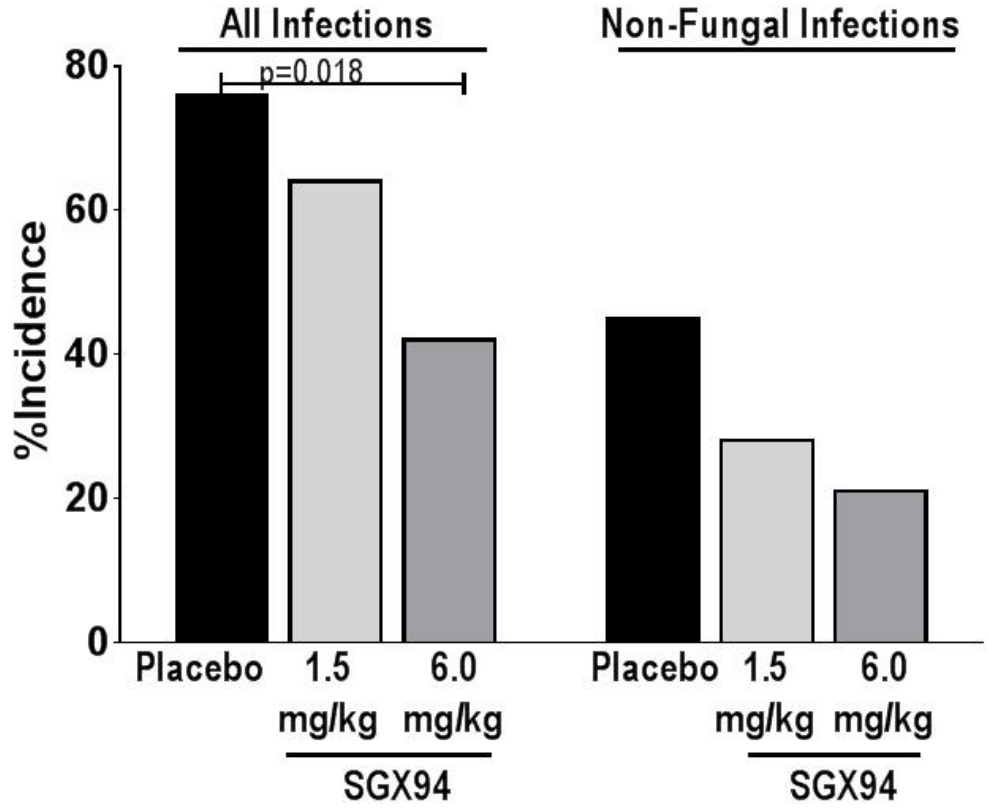



Kudrimoti et al. J. Biotech 2016; 239:115-125.

# Anti-Infective

- Recorded infection as a monitored adverse event (Phase 2 study)
- All concurrent antibiotic treatments allowed

## All and Non-Fungal (Bacterial) Infections Reduced






Kudrimoti et al. J. Biotech 2016 239:115-125.

# Infectious Disease

- Broad-spectrum activity
  - Does not require positive identification of pathogen
  - Effective irrespective of antibiotic resistance
  - Will work in at-risk populations (immune-compromised)
- Combination activity:
  - Can be combined with standard of care antibiotic therapy – tested for interference with most major antibiotic classes
  - No PK interference with other drugs likely (rapid degradation by blood/tissue peptidases; kidney/liver functions not required)

# IDR Program Status

- Phase 2 clinical study in oral mucositis completed
- Phase 3 clinical study in oral mucositis initiating 2017
- cGMP - quality drug product available
- Pharmacokinetics and nonclinical toxicology completed
- Phase 1 healthy volunteer studies completed
- Portfolio of IDR analogs:
  - Co-crystal structure solved for SGX94 in its target binding site
  - SAR against target protein binding; peptidomimetic analogs developed

# Conclusions

- IDRs, such as SGX94, represent a new class of compound with unique mechanism of action targeting p62
- IDRs may significantly enhance antibiotic efficacy *without* increasing resistance
  - Does not interfere with antibiotic action on either a PD or PK basis
- IDR action is independent of bacterial pathogen characteristics:
  - Broad-spectrum activity
  - Targets both tissue mediated and circulating innate immune responses
  - Extended PD action
- High degree of clinical translation observed in recent Phase 2 clinical study

# Acknowledgements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- National Institute of Dental and Craniofacial Research Small Business Innovation Research grant (SBIR; R43)