Modulation of Innate Immunity in the Treatment of Inflammation-Driven and Infection-Driven Disease

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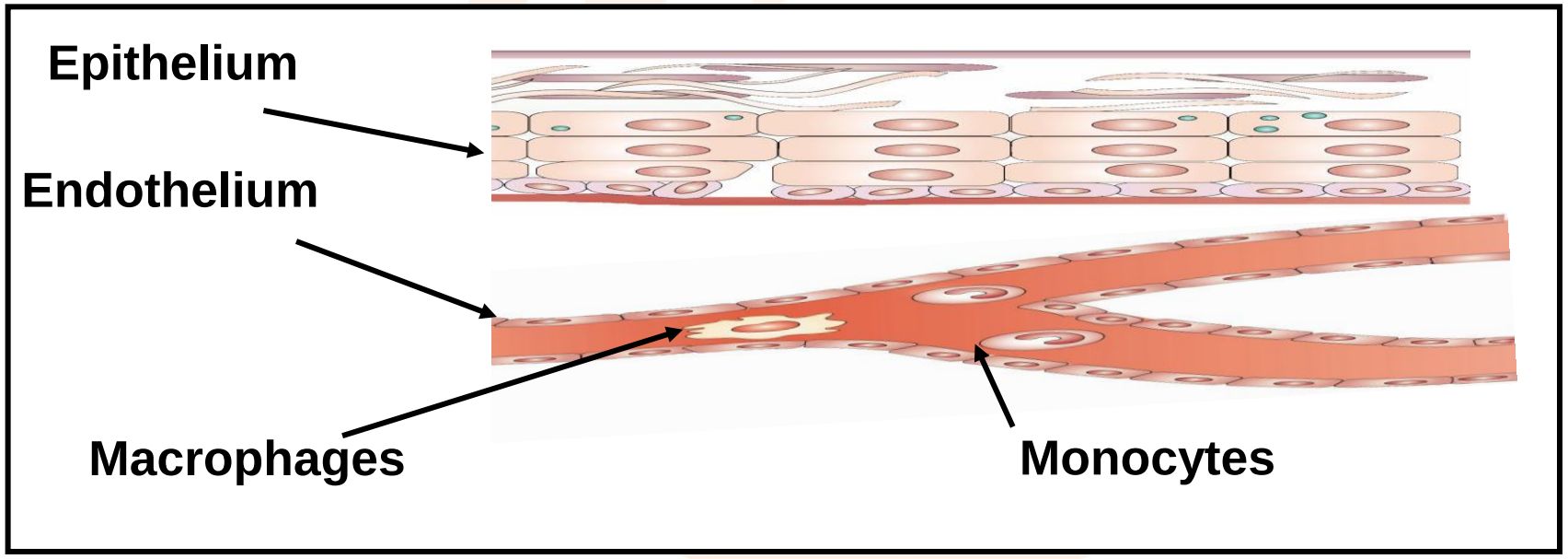
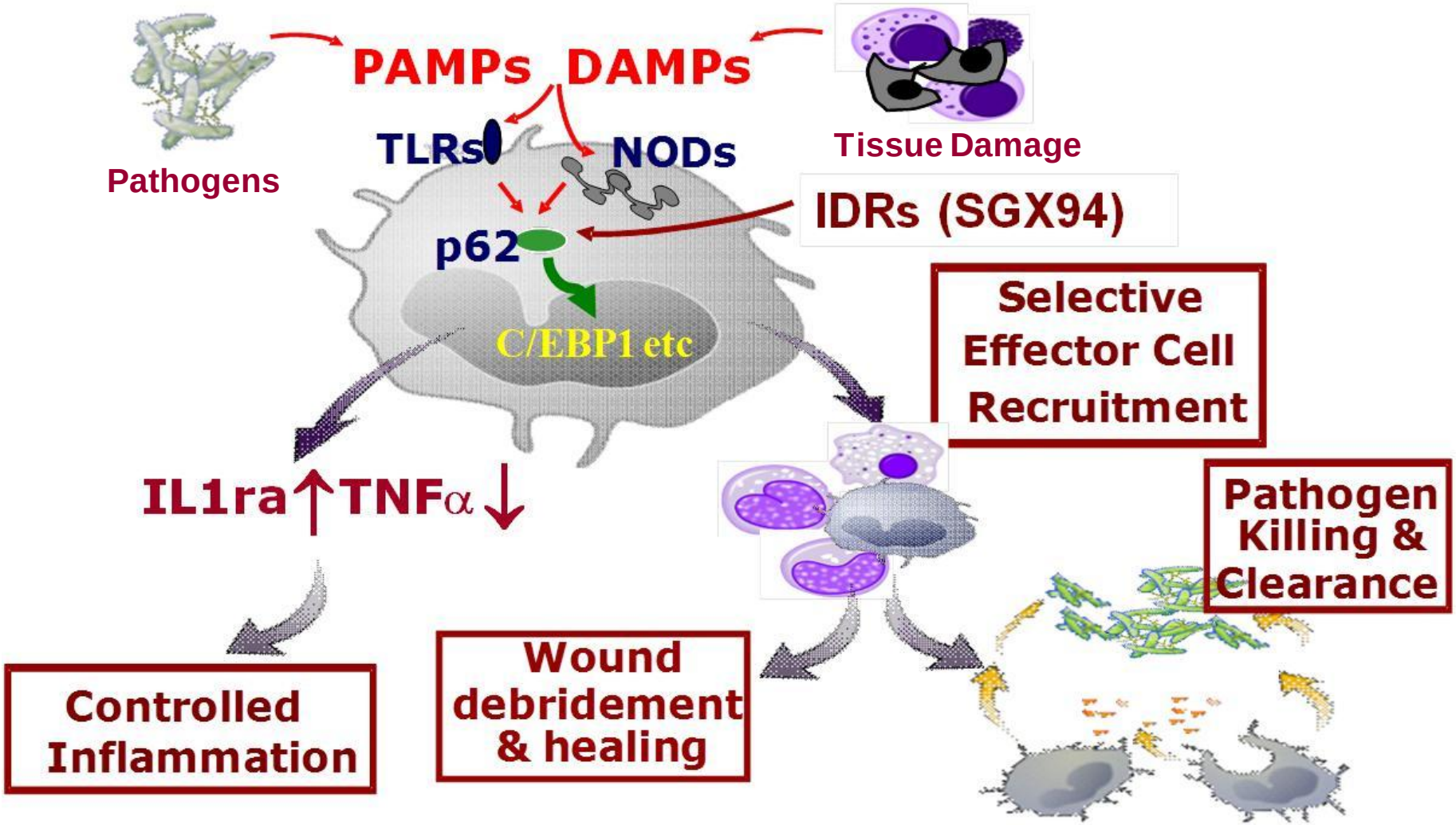
Leveraging Innate Immunity

- Rapid, non-specific response
- Involves circulating **and** tissue resident cells
- Inflammation separable from tissue healing / bacterial clearance mechanisms



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

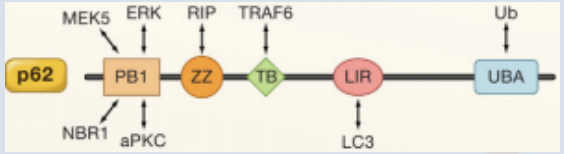
Innate Defense Regulators



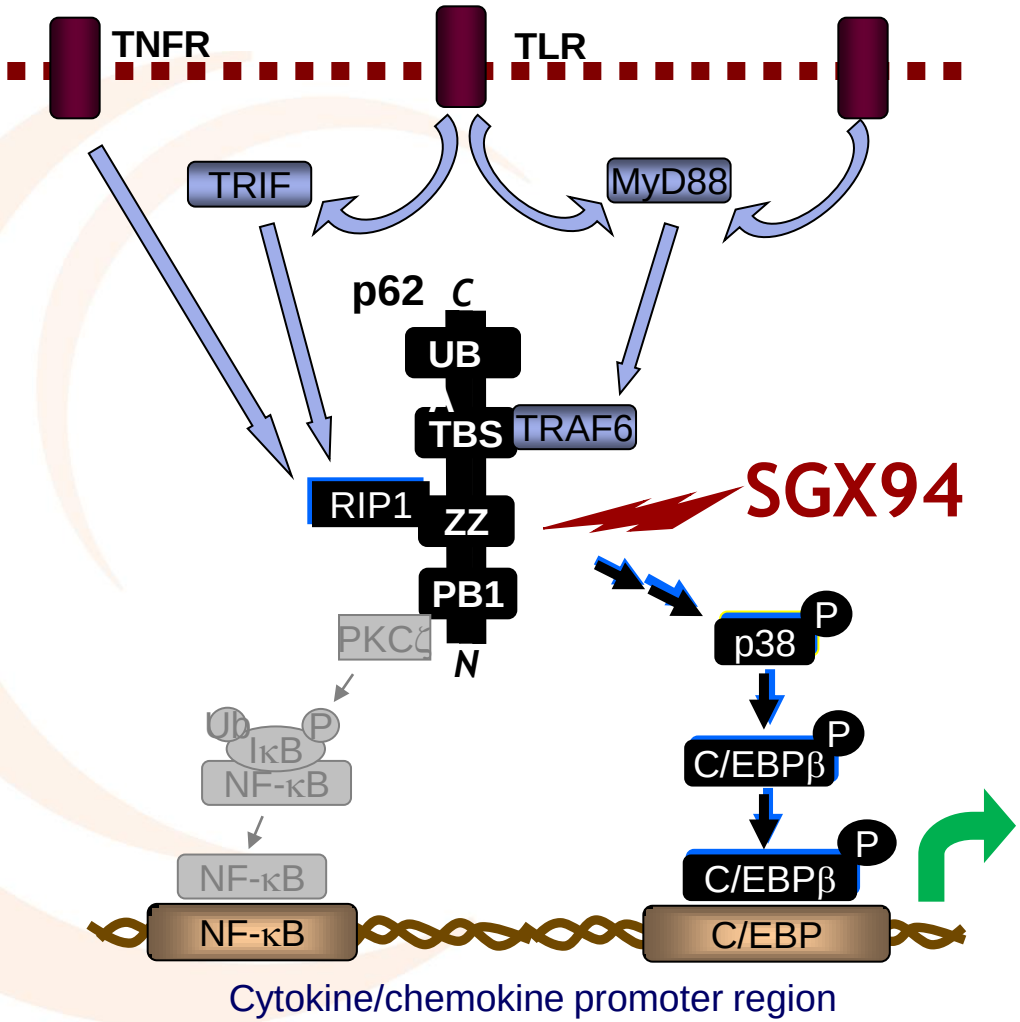
Yu et al. JBC 2009; 284(52): 36007-11.

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**



Cytokine/chemokine promoter region

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

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

Broad Spectrum Activity

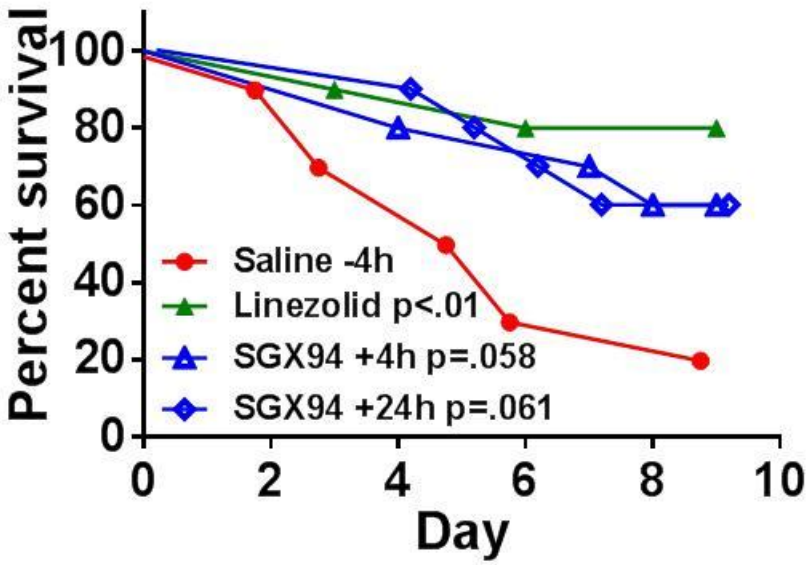
- Improves survival **and** enhances bacterial clearance
- Efficacious against various pathogens:
  - Gram-negative (*P. aeruginosa, B. pseudomallei*) ***OR*** Gram-positive (*S. aureus,* MRSA)
  - Extracellular (MRSA, *S. aureus*) ***OR*** Intracellular (*B. pseudomallei*)
  - Antibiotic sensitive (*S.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

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

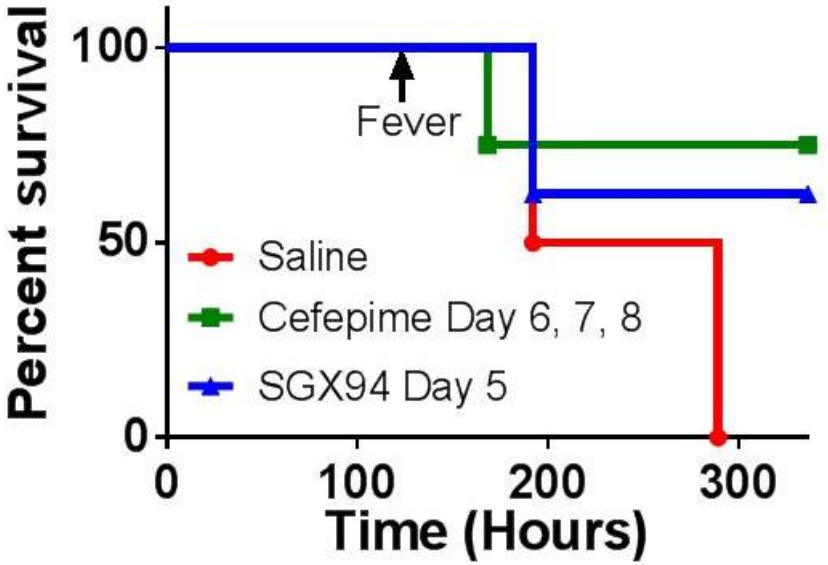
Anti-Infective

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

Gram-positive, Antibiotic-resistant Bacteremia (MRSA)



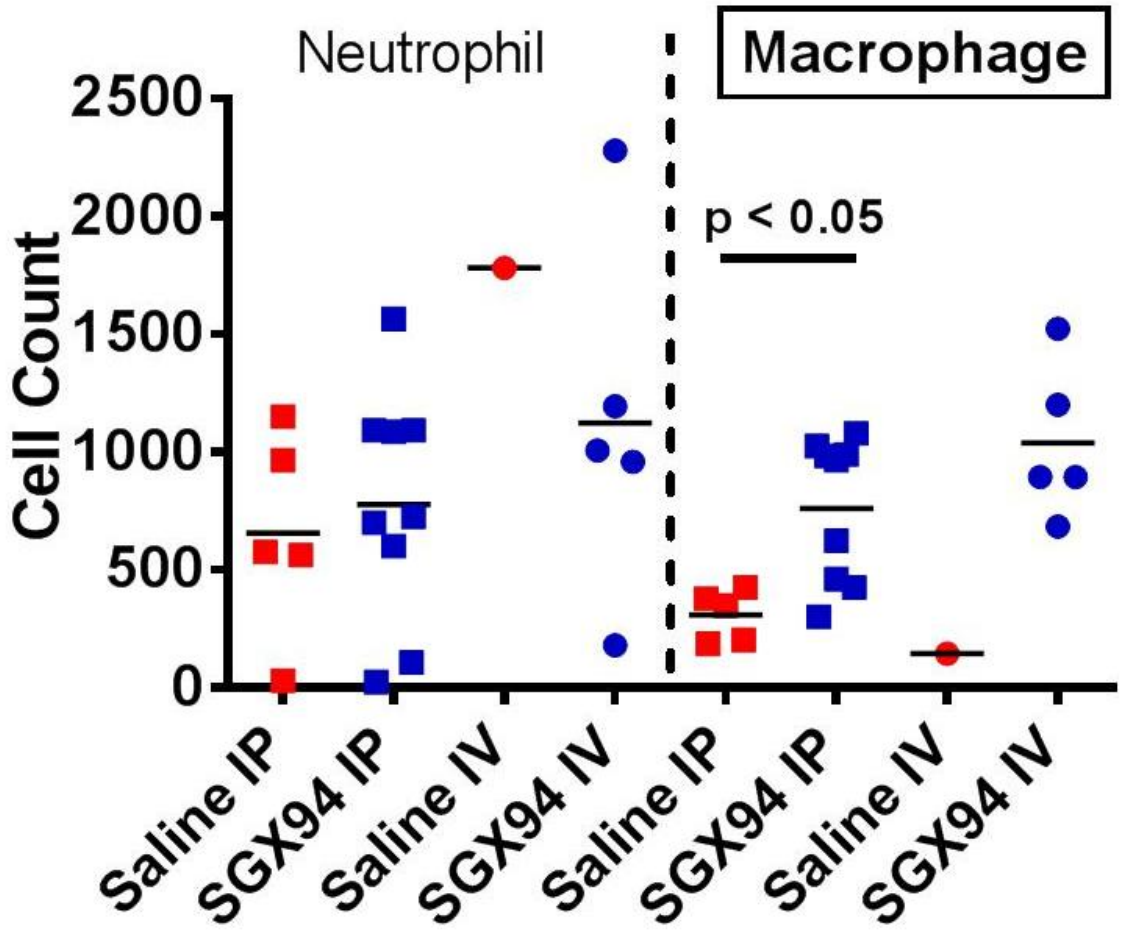
Gram-negative, Leukopenic Septicemia (*P. aeruginosa*)



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

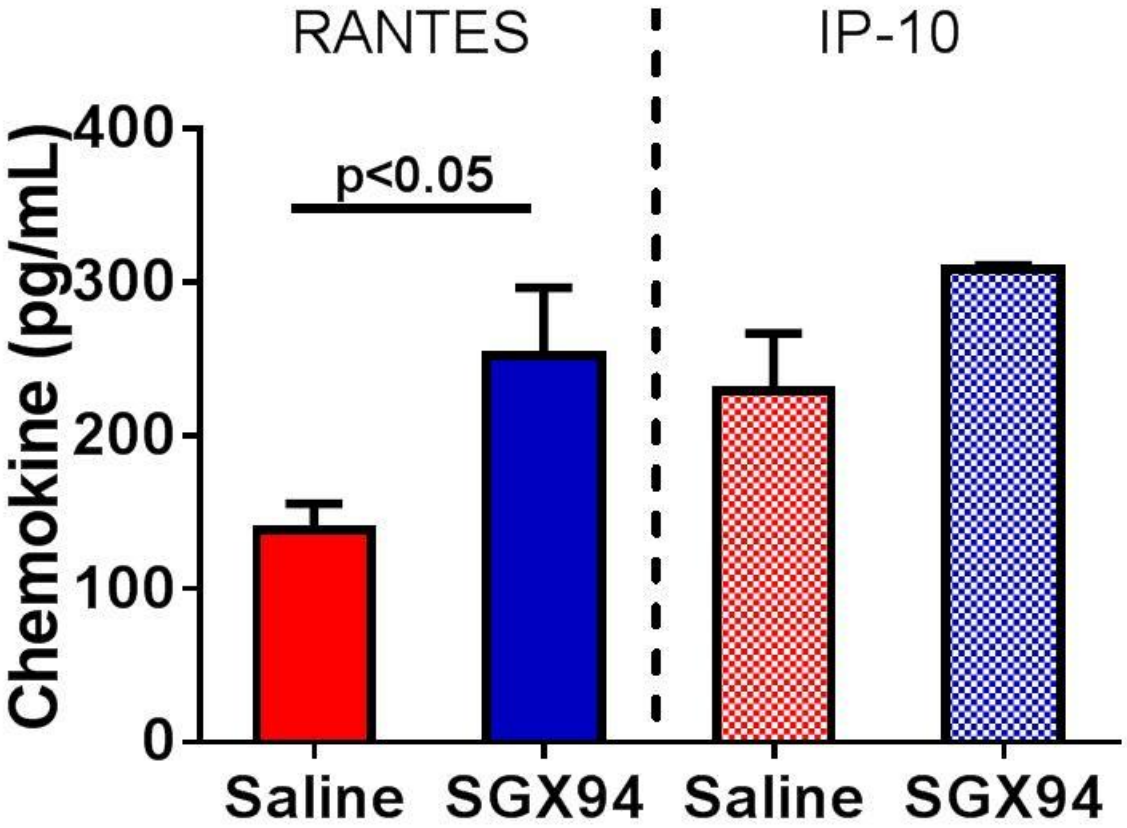
Increased Macrophage Recruitment

Peritoneal macrophages increased in MRSA IP infection



Early Chemokine Responses

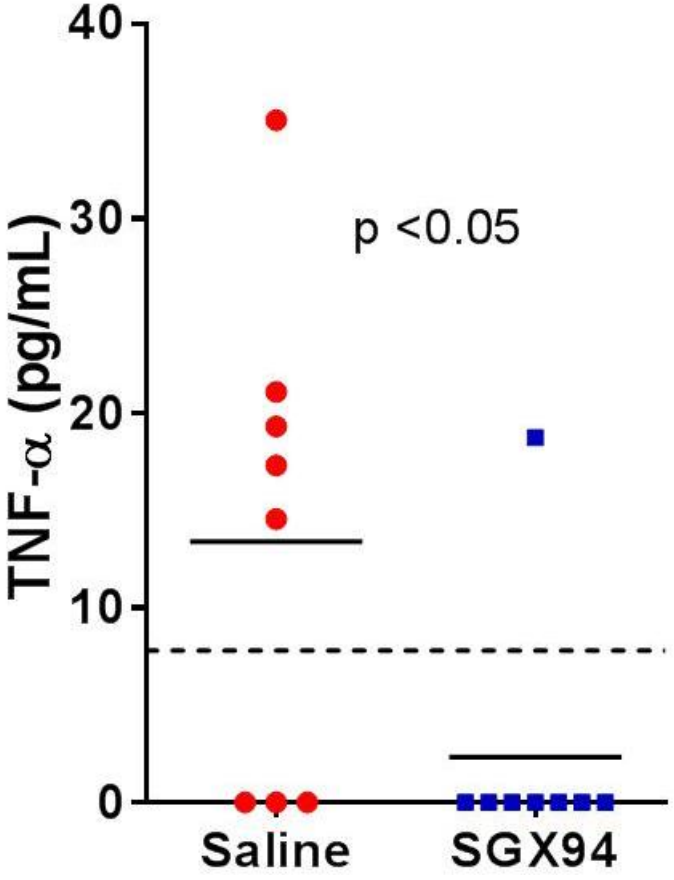
Peritoneal RANTES and IP10 increased in MRSA IP infection



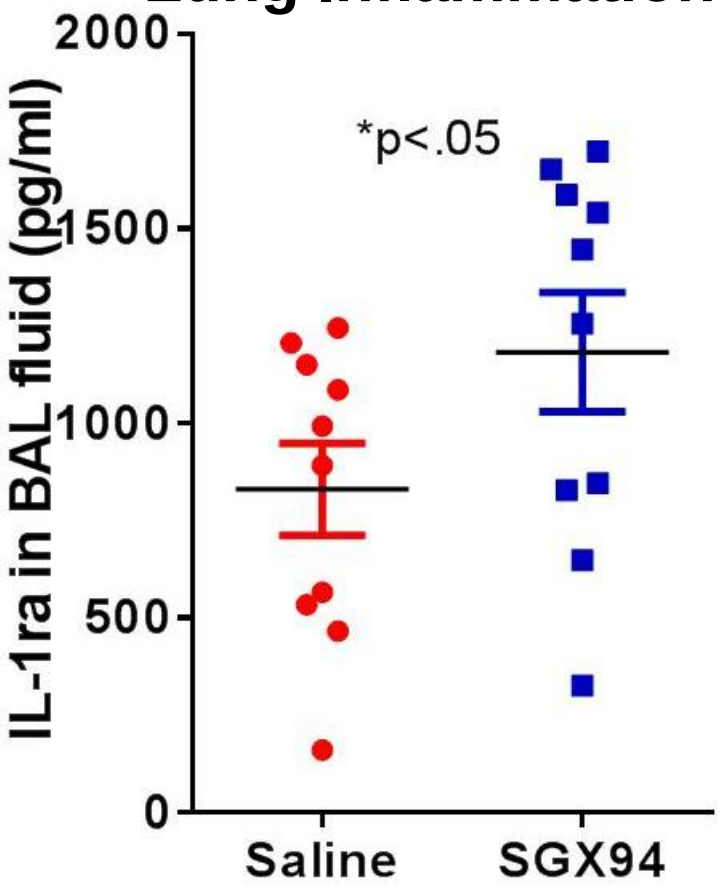
Anti-Inflammatory Action

TNFα decreased and IL-1ra increased

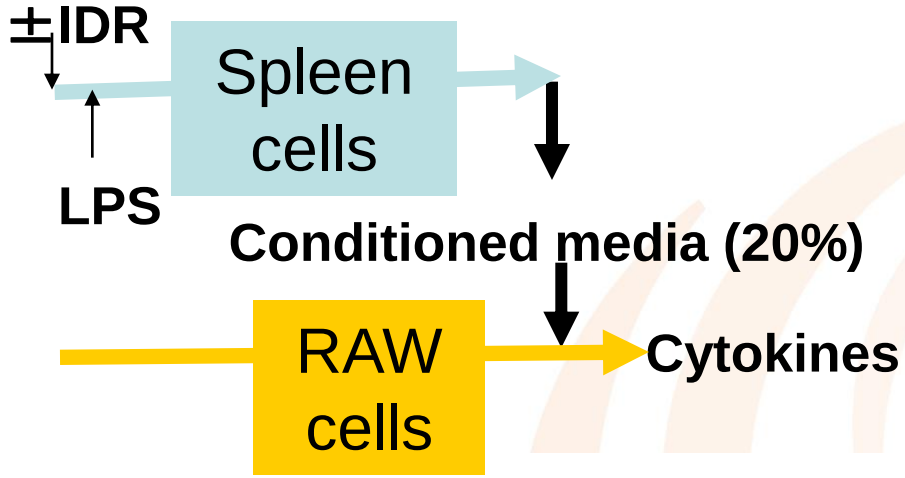
Peritoneal Infection

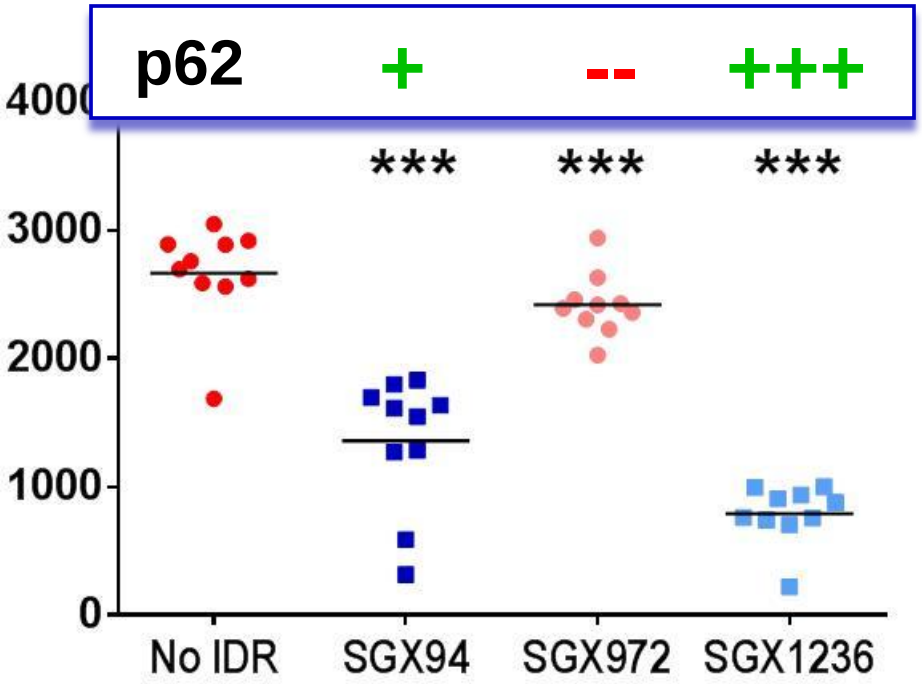


Lung Inflammation



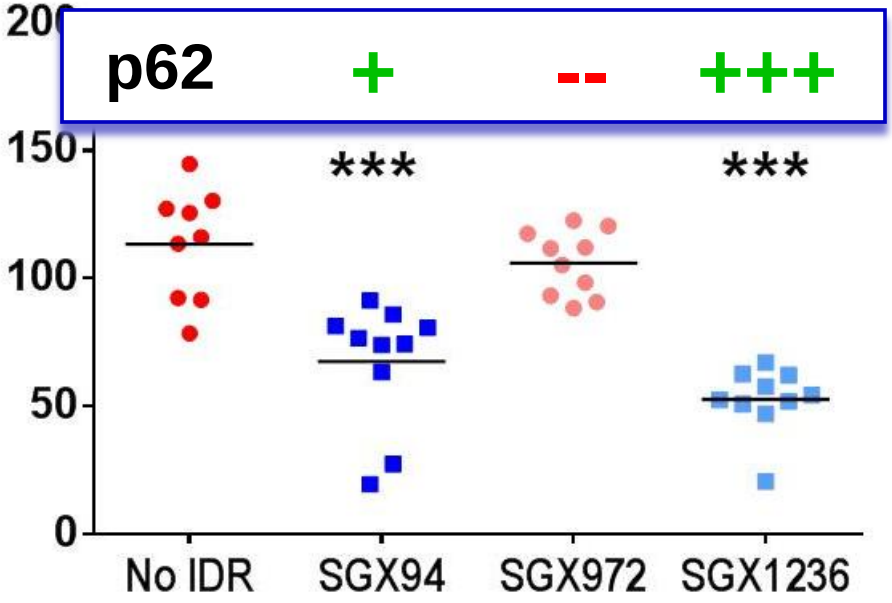
Tissue-Mediated Effects





TNFα

(pg/ml)



IL-6

(pg/ml)

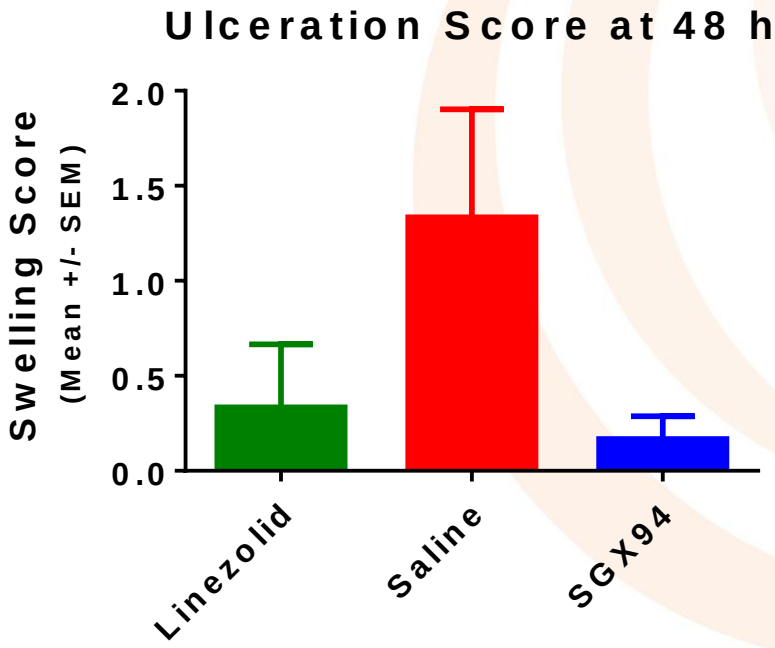
Responsiveness correlates with p62 binding affinity

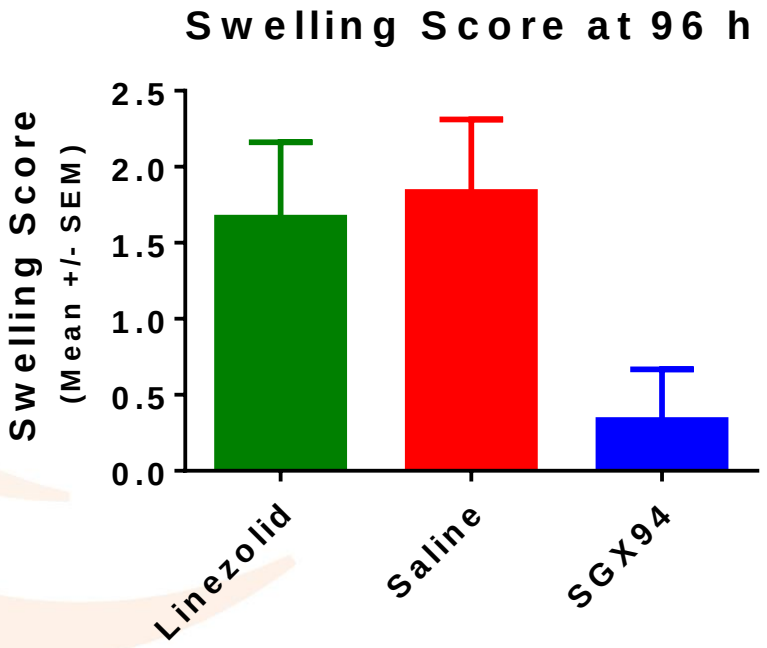
North et al. J. Biotech 2016; 226:24-34.

Tissue Healing Activity

- Epithelial damaged followed by MRSA infection

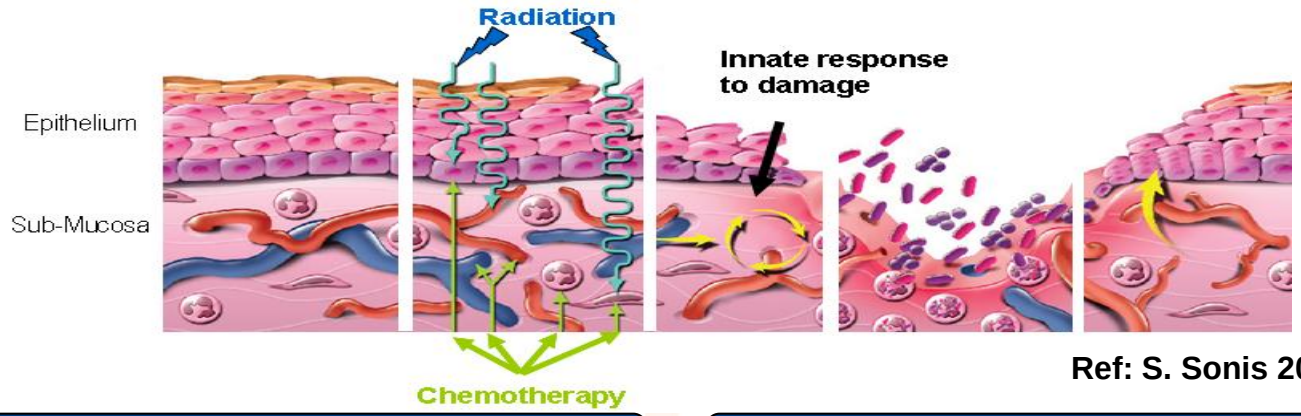
Decreased Ulceration & Swelling with Single Administration





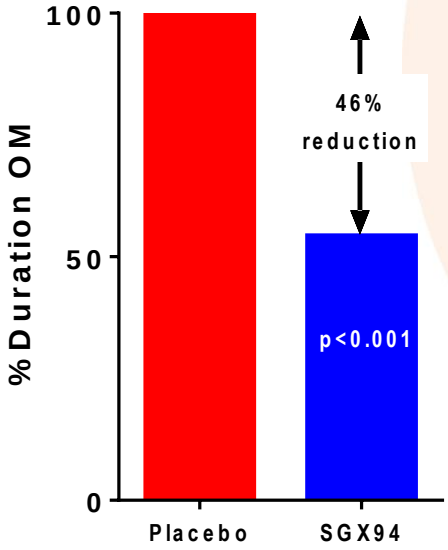
North et al. J. Biotech 2016; 226:24-34.

Chronic Injury Models: Oral Mucositis

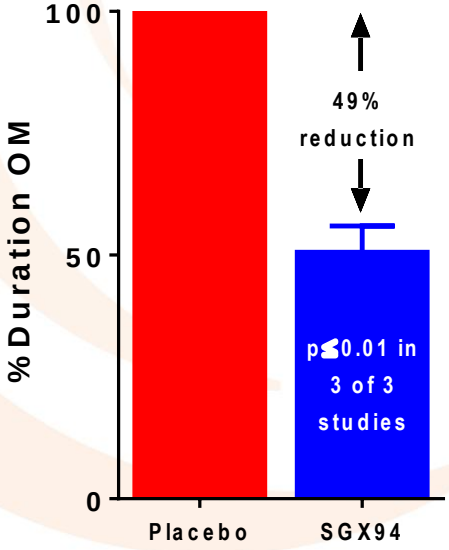


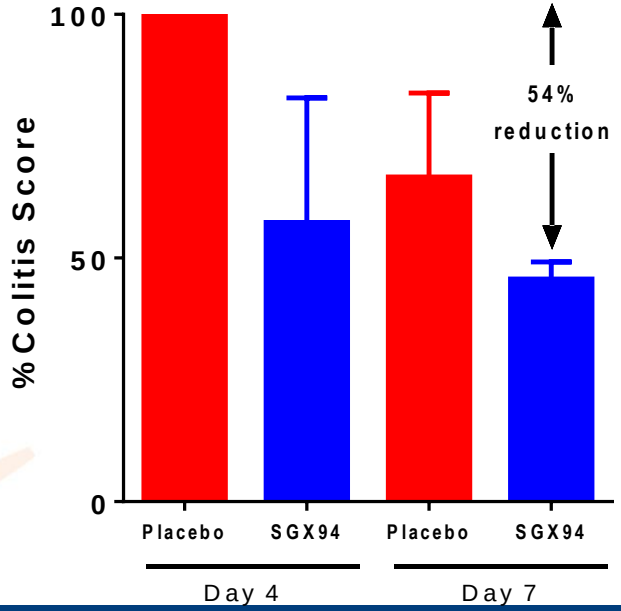
Ref: S. Sonis 2004

Radiation-Induced Mucositis



Chemotherapy- Induced Mucositis

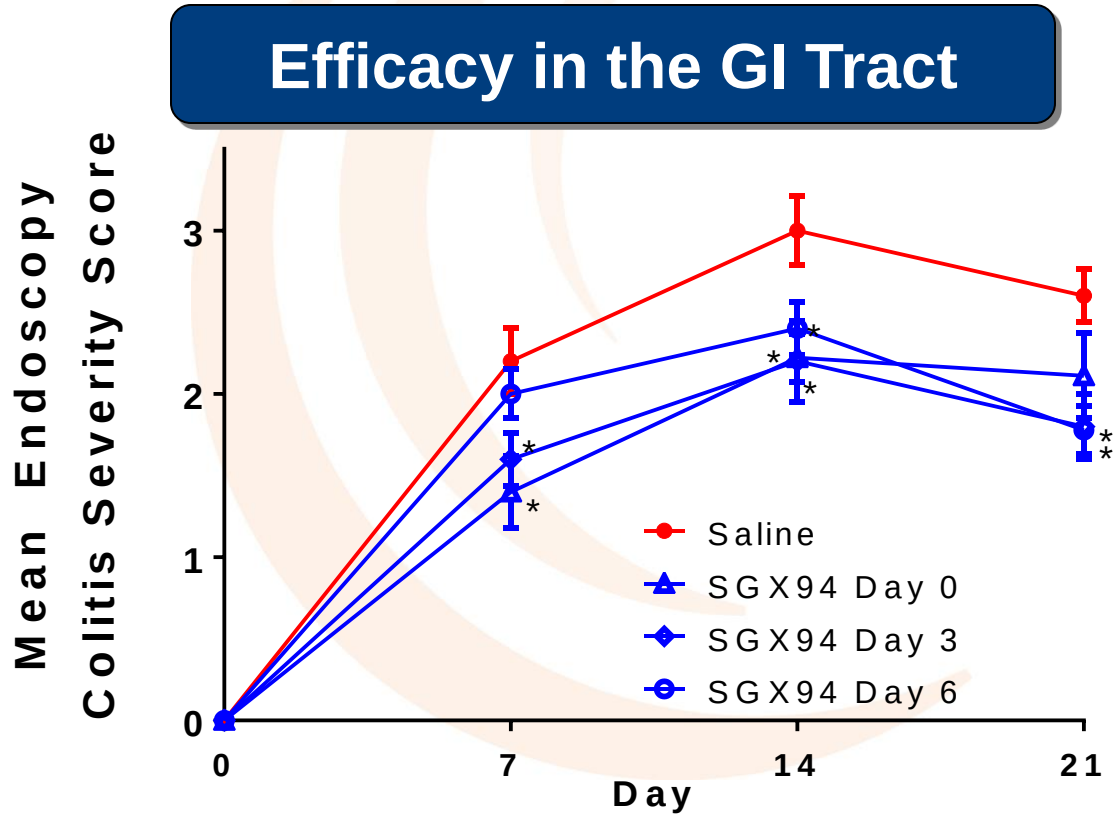




Kudrimoti et al. J. Biotech 2016; 239:115-125.

Gastrointestinal Injury: IBD Model

- Oral DSS given on Days 0 to 5 damages the GI lining.
- SGX94 is effective administered before, during or after the insult.

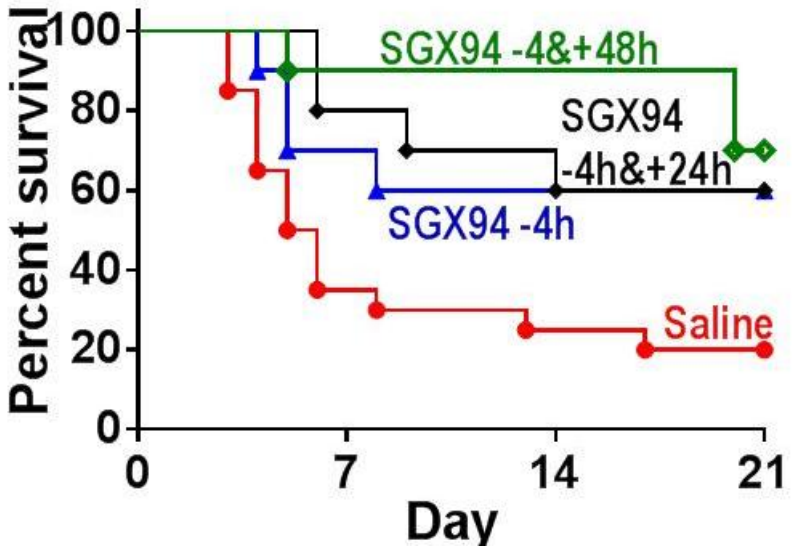


Kudrimoti et al. J. Biotech 2016; 239:115-125.

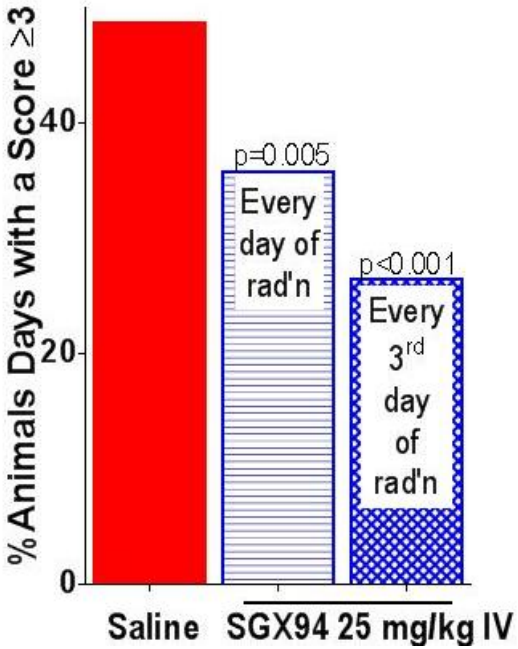
Enduring Pharmacodynamic Effect

- 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



North et al. J. Biotech 2016; 226:24-34.
Kudrimoti et al. J. Biotech 2016; 239:115-125.

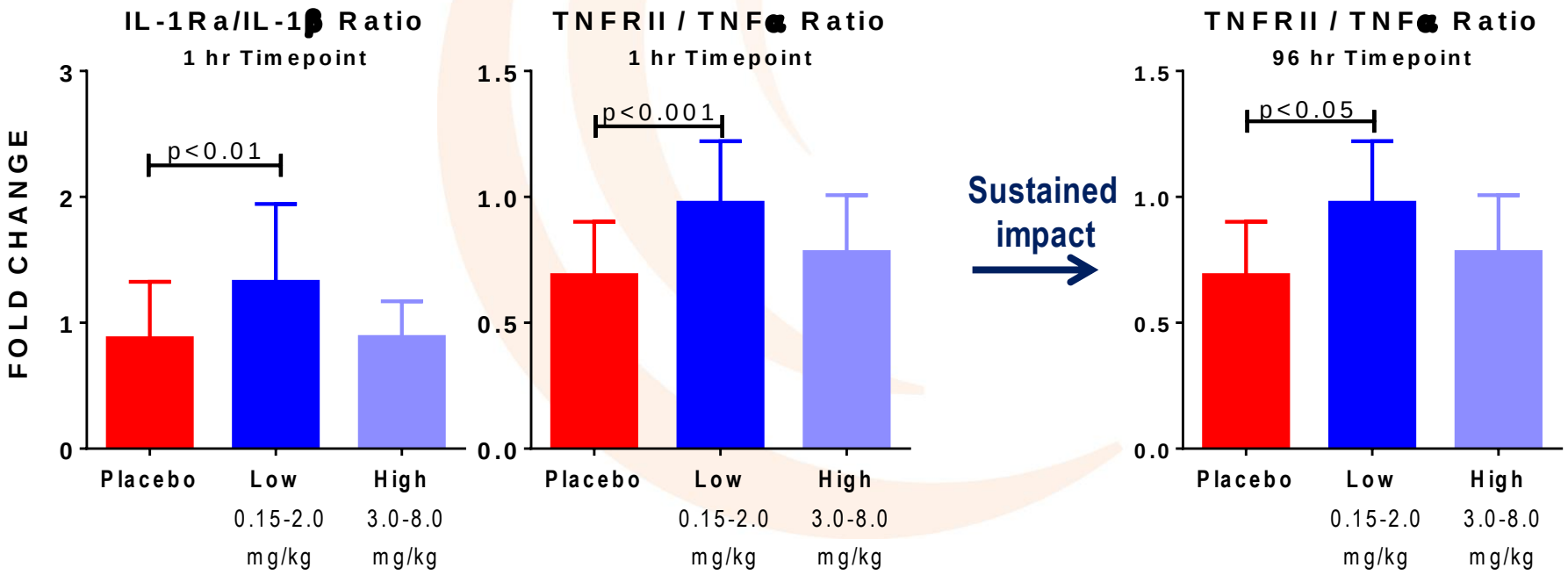
Translation to the Clinic

- 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

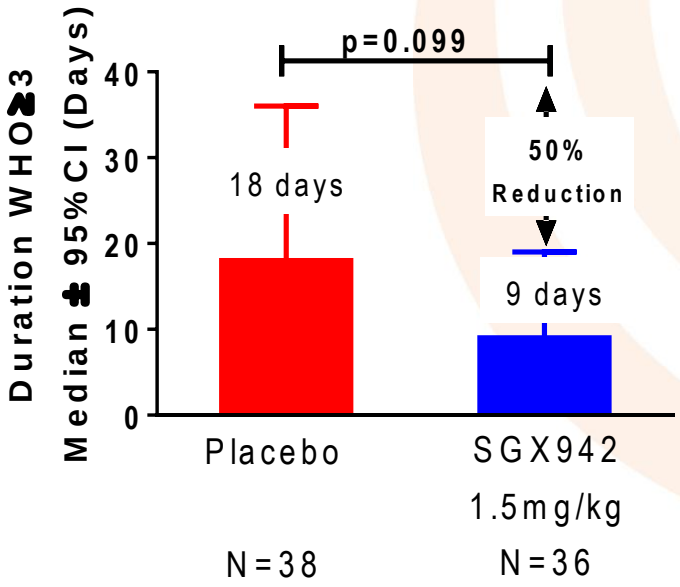


North et al. J. Biotech 2016; 226:24-34.

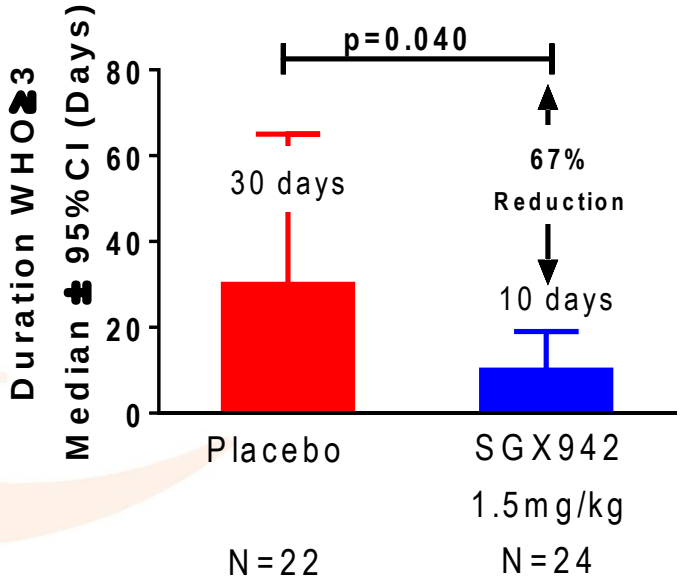
Tissue Healing/Anti-Inflammatory

- 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 3rd week (80-100 mg/m^2) cisplatin

Duration Severe OM



Duration Severe OM High Risk Subpopulation



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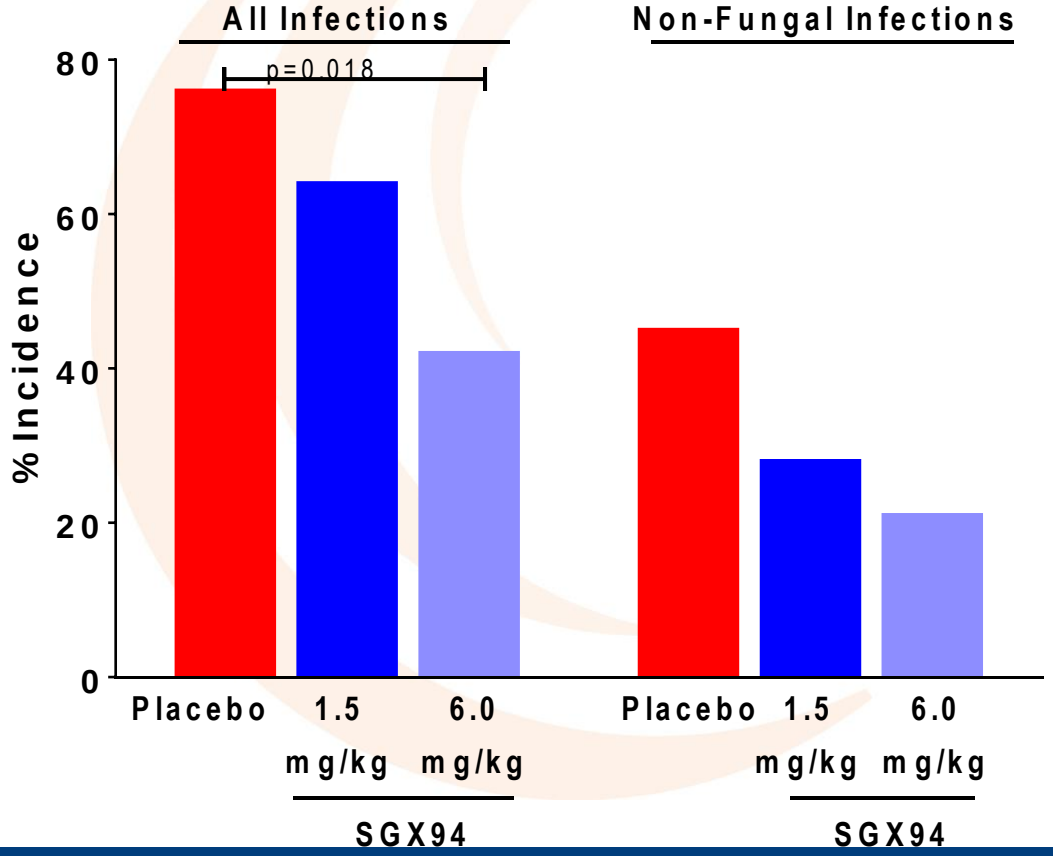
Anti-Infective

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

All and Non-Fungal (Bacterial) Infections Reduced



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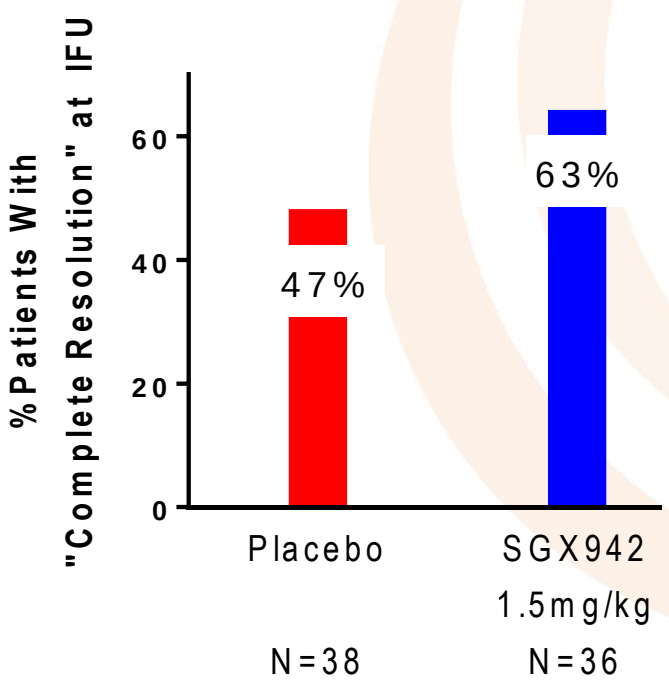
Ancillary Benefits

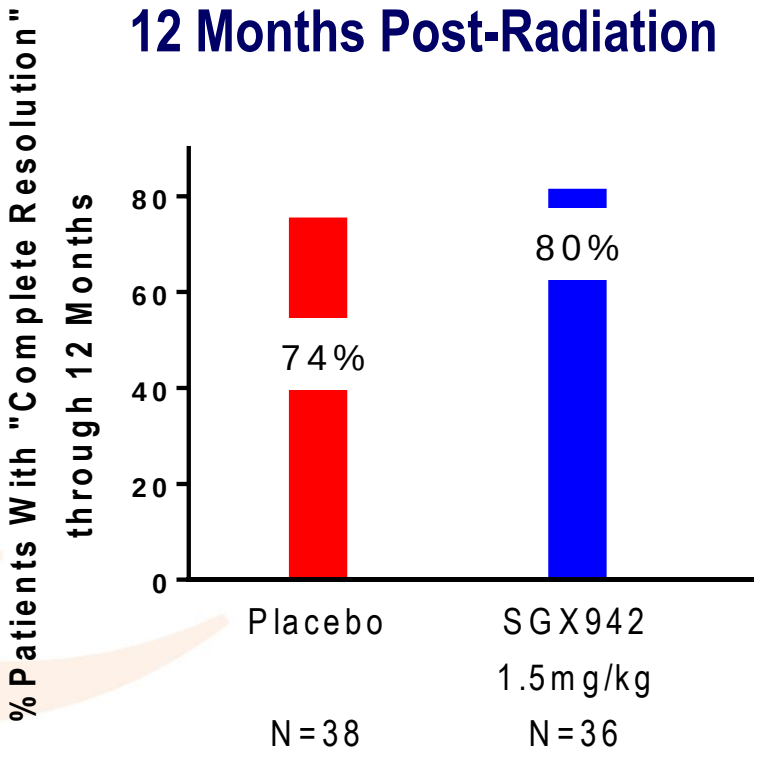
- Potential for accelerated tumor resolution

Tumor Resolution at 1 and 12 Months

%"Complete" Tumor Resolution at 1 month Post-Radiation



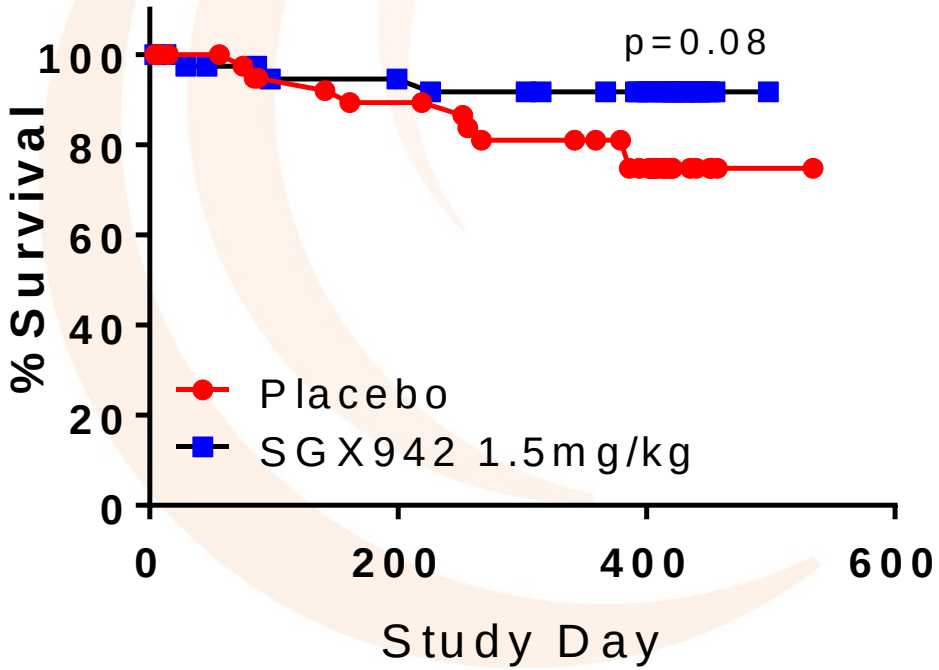
%"Complete" Tumor Resolution to 12 Months Post-Radiation



Improved Survival over 12 Months

- Patients monitored through 12 months post-radiation

Increased Survival with SGX94 Treatment



Kudrimoti et al. 2017 Biotechnology Reports. In Press . https://doi.org/10.1016/j.btre.2017.05.002

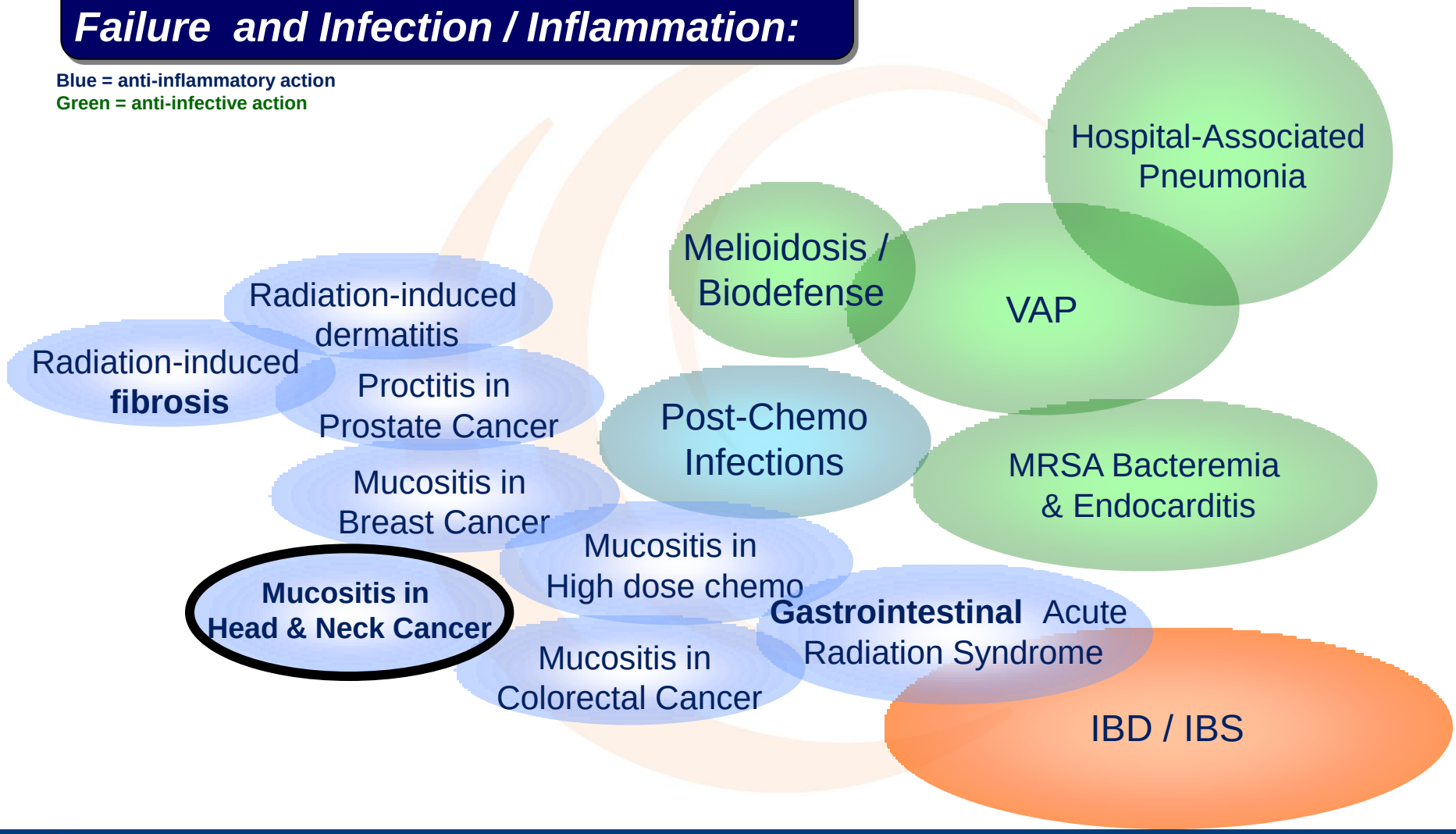
IDR Program Status

- Pharmacokinetics and nonclinical toxicology completed
- cGMP-quality drug product available
- Phase 1 healthy volunteer study completed.
- Phase 2 clinical study in oral mucositis completed
- Phase 3 clinical study in oral mucositis initiating
- Portfolio of IDR analogs:
  - Co-crystal structure solved for SGX94 in its target binding site
  - SAR against target protein binding; peptidomimetic analogs developed
- Initiated explorations of other potential clinical indications (GI disease, infectious disease, etc.)

Potential Indications

Patients at risk of Mucosal Barrier Failure and Infection / Inflammation:

Blue = anti-inflammatory action
Green = anti-infective action



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