Innate Defense Regulators as a Treatment for Melioidosis

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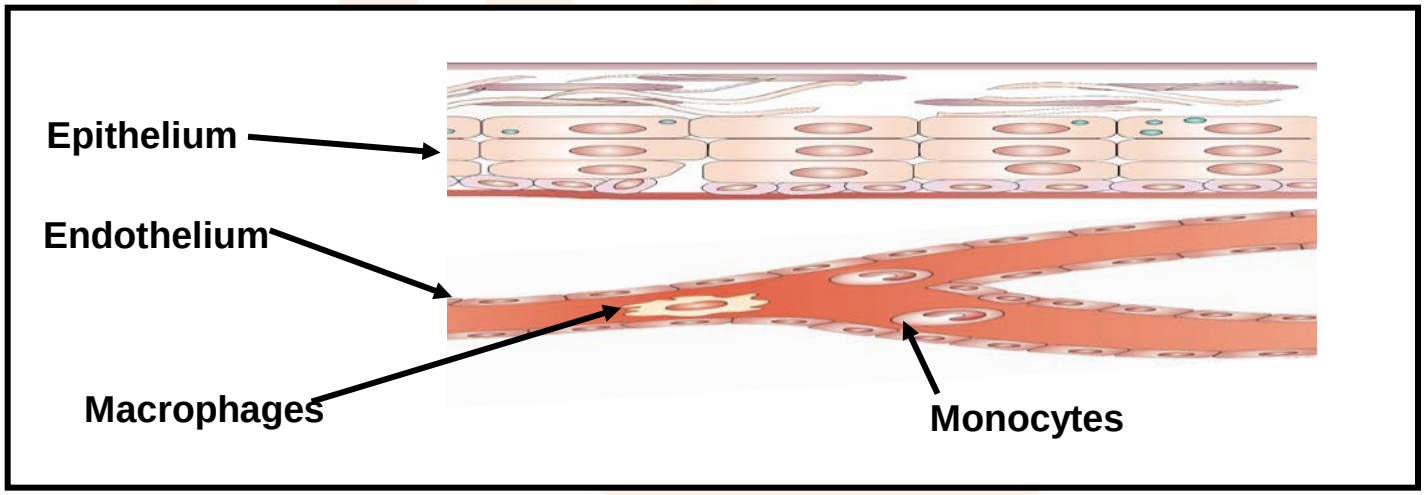
Innate Immunity

- Non-specific, rapid response
- Triggers the adaptive immune system
- Involves circulating and tissue resident cells.
- Inflammation separable from tissue healing / bacterial clearance mechanisms.



Melioidosis

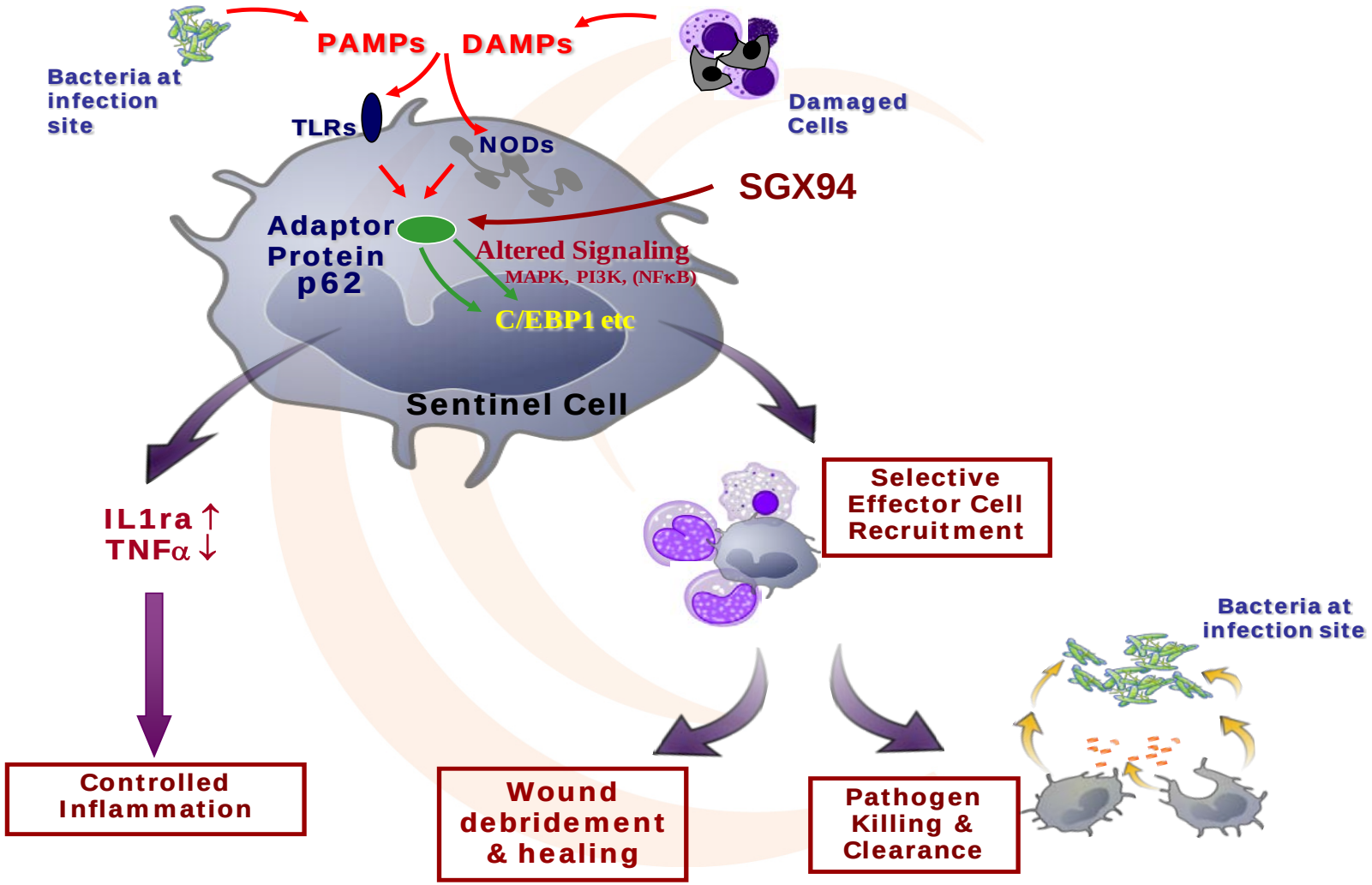
- Caused by *Burkholderia pseudomallei*
  - nonspore-forming motile saprophytic Gram-negative intracellular bacterium
  - Tropical disease present in soil and endemic in N. Australia & SE Asia
  - Transmitted to humans via inhalation, inoculation or ingestion
- Biothreat: NIAID category B pathogen and top 5 biothreat identified in the 2012 PHEMCE strategy document
  - Easily found in the environment
  - Capacity for aerosol delivery
  - High mortality
- Naturally resistant to antibiotics
- Particularly problematic in diabetics and those with suppressed immune systems

Diagnosis and Current Therapies

- Widely variable disease presentation with pneumonic disease associated with the poorest outcomes

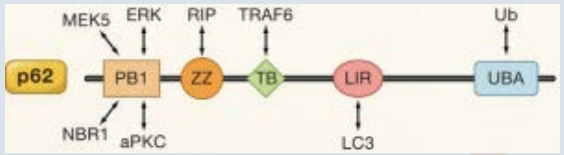
- Antibiotic treatment is insufficient:
  - Only third generation cephalosporins (e.g., ceftazidime), carbapenems, and amoxicillin-clavulanate useful
  - Long treatment windows required increasing risk of further resistance
  - Delayed treatment is ineffective
  - High relapse rate
  - Prophylactic use of antibiotics is contra-indicated
  - Use of antibiotics in absence of confirmed diagnosis can be ineffective due to incorrect selection of antibiotics

Innate Defense Regulators



SGX94 Targets Sequestosome-1 (p62)

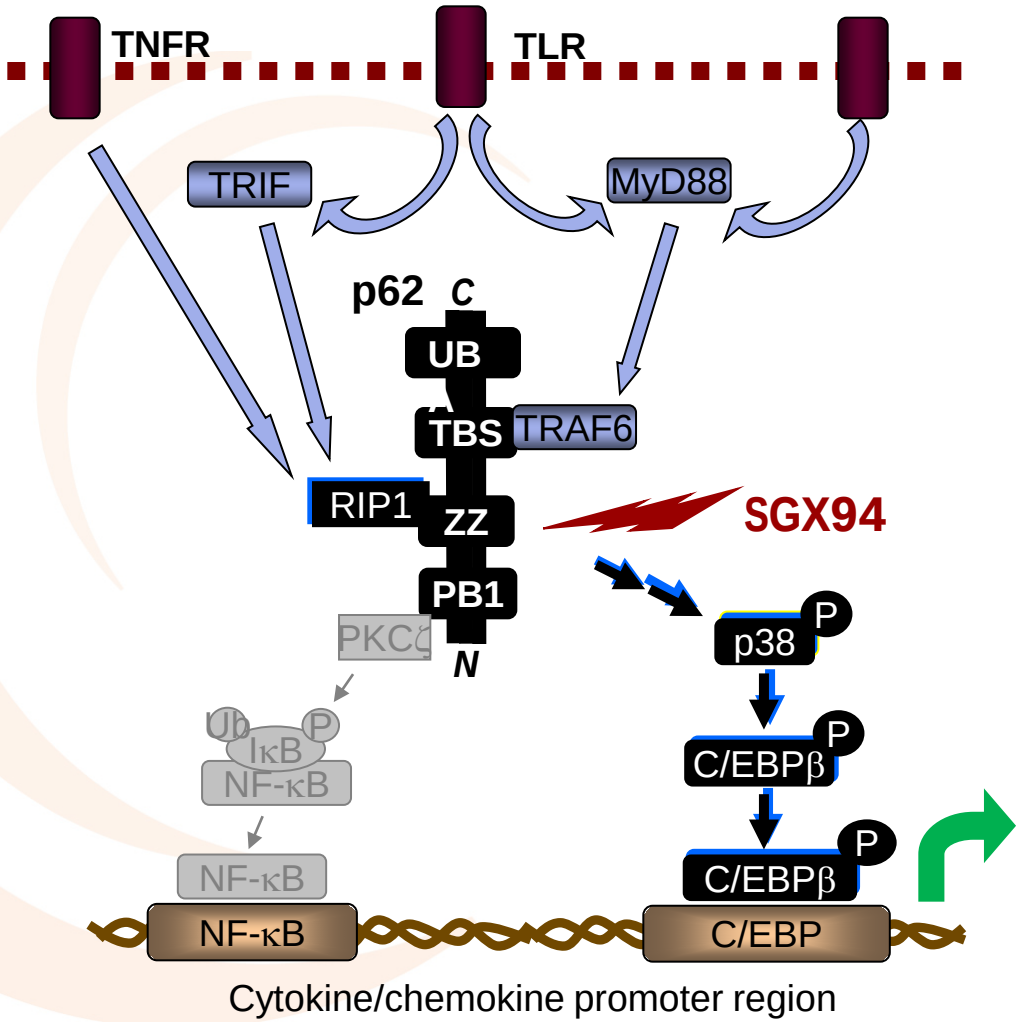
- SGX94 specifically binds to the ZZ domain of p62



- 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



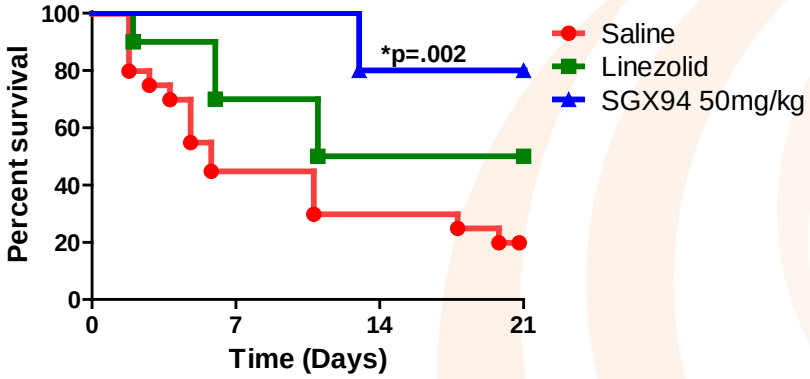
Jorge Moscat and Maria T. Diaz-Meco. Cell 137, June 12, 2009

Yu et al. J Biol Chem. 2009;284,36007-11

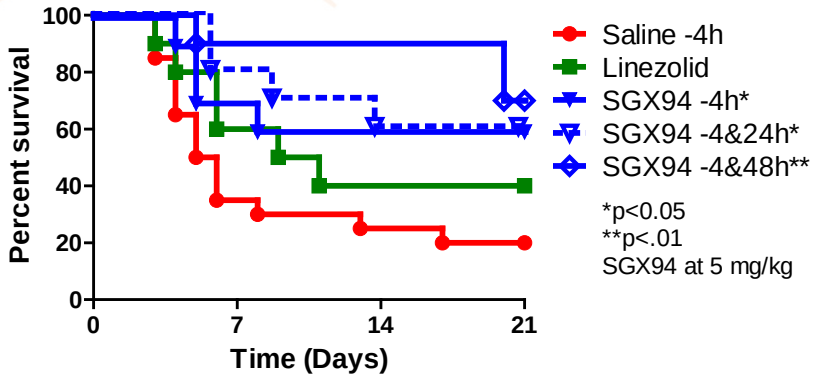
MRSA Bacteremia

Therapeutic & Prophylactic Effect, Prolonged Survival, Extended PD Effect

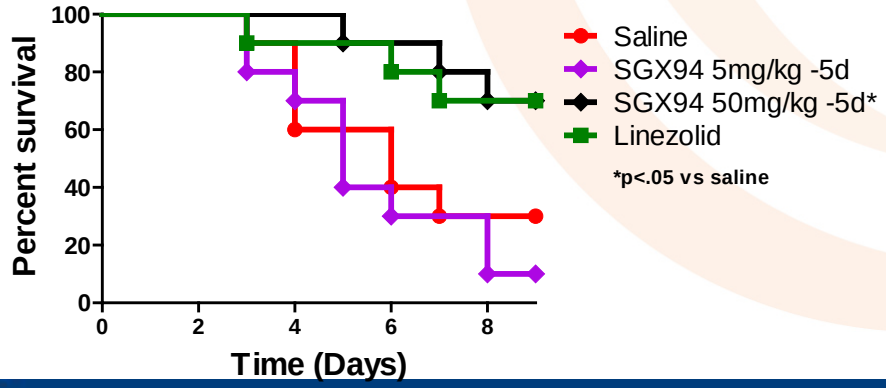
Single dose prolongs survival for up to 21 d



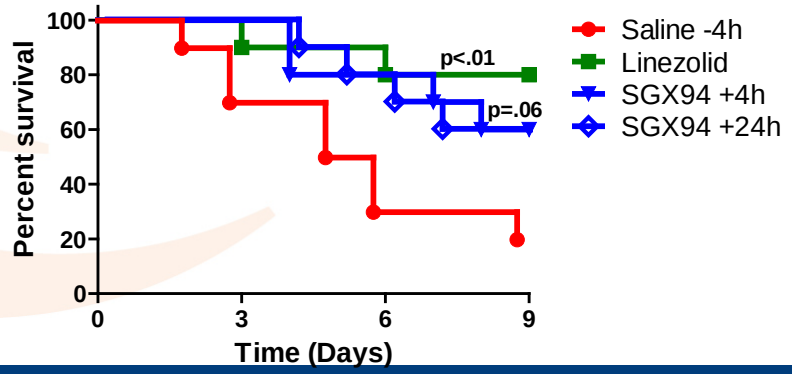
Extended pharmacodynamic effect



Prophylactic effect



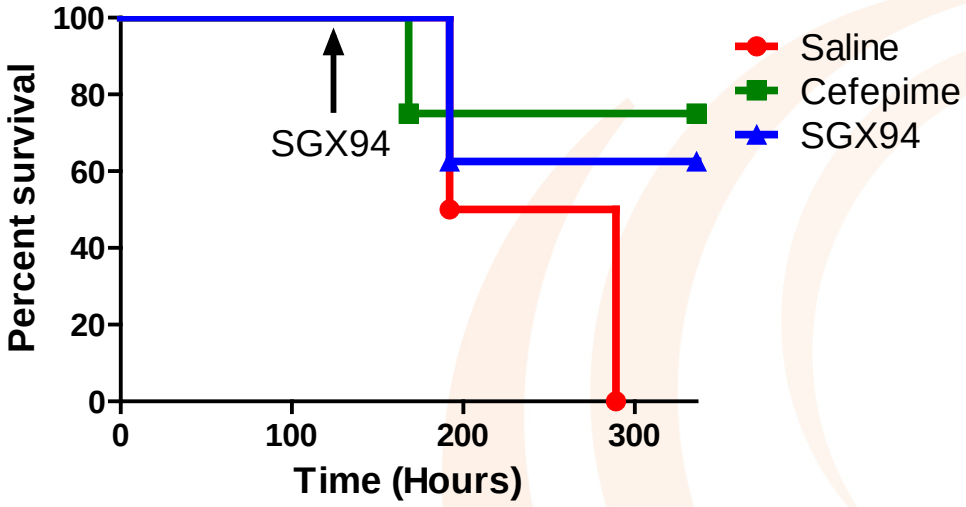
Therapeutic effect

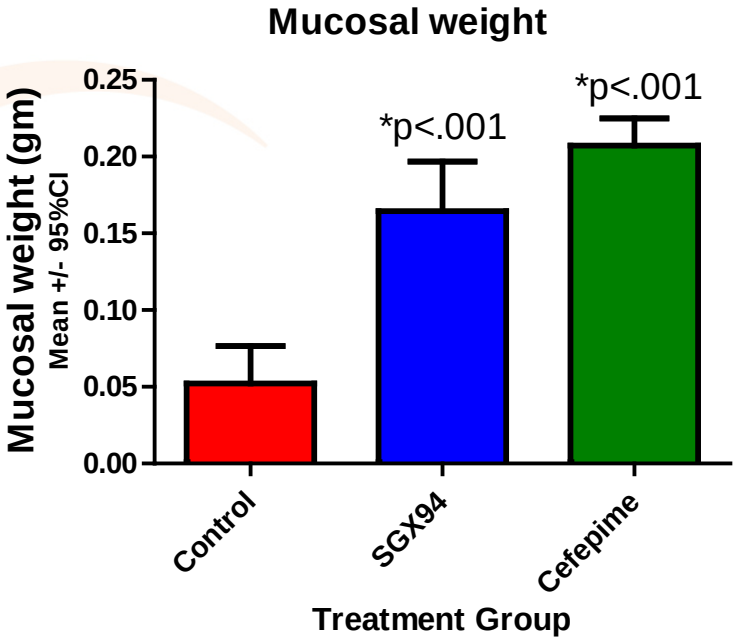


Scott et al. Nat Biotechnol 2007;25: 465-72.

Increased Survival in a Gram-Negative Infection

Efficacy despite Neutropenia





Summary:

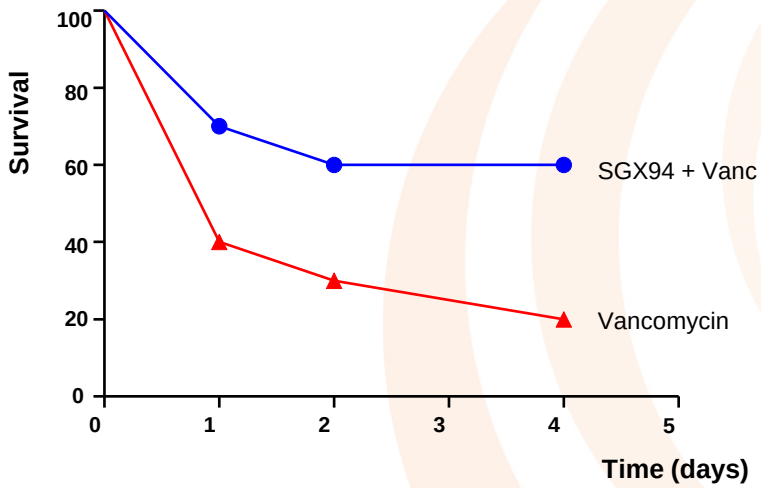
- **Therapeutic SGX94 reduces subsequent sepsis and death in this challenging model;**
- **SGX94-enhanced survival correlates with protection of the GI barrier (increased mucosal weight);**

STUDY DESIGN:

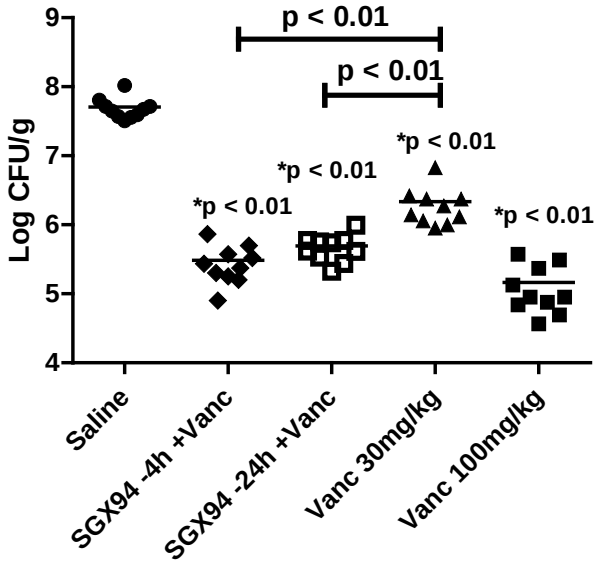
- Day -4: IM Cefamandole 10 mg/kg to female Sprague-Dawley rats (to disturb the gut microbiota)
- Day 0 & 3: IP Cyclophosphamide 75 mg/kg (to render leukopenic)
- Day 0, 2 & 4: $1x10^6$ CFU/ml *P. aeruginosa* by orogastric feeding (pathogen repopulation of the gut)
- Day 5 (Start of fever): IV SGX94 10 mg/kg (Survival N=8, mucosal weight N=9) or IV Saline (Survival N=8, mucosal weight N=9).
- Days 6, 7, 8: IM Cefepime 25mg/kg (Survival N=4, mucosal weight N=11).

Complements Antibiotics

SGX94 enhances survival when antibiotic therapy is inadequate



SGX94 enhances bacterial clearance when antibiotic therapy is inadequate



MRSA Bacteremia

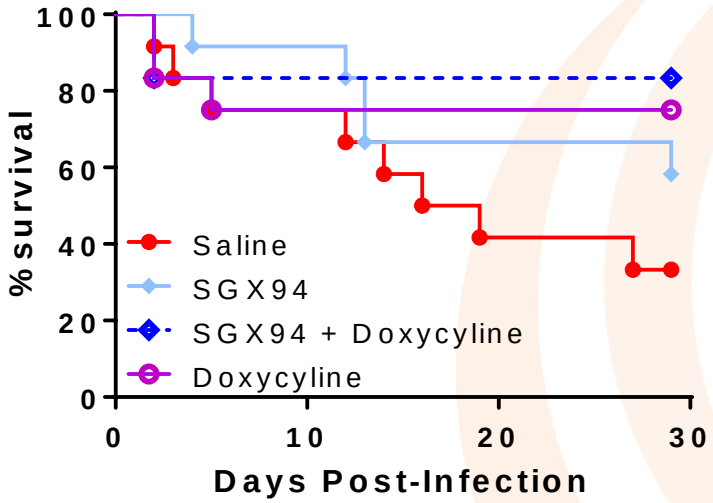
- 50 mg/kg SGX94 IV, 48 h before IP MRSA (N=10/gp)
- 3 mg/kg Vancomycin SC
- 1 & 5 h post infection

MRSA Thigh Abscess

- 50 mg/kg SGX94 IV, 24 or 4 h pre IM MRSA in neutropenic CD-1 mice (N=10/gp)
- 30 or 100 mg/kg Vancomycin SC 2 & 14 h post infection
- SGX94 was tested in addition to 30 mg/kg Vancomycin

Efficacy in Melioidosis

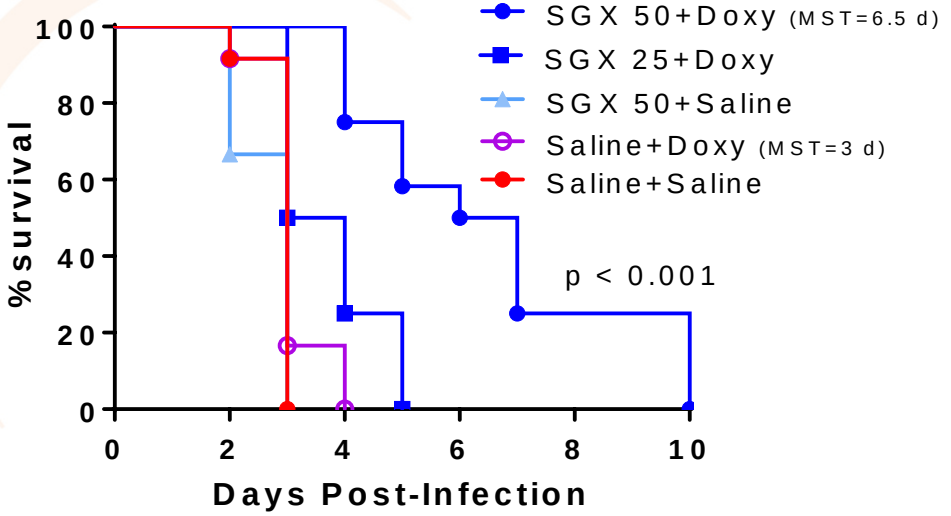
Peritoneal Infection



STUDY DESIGN:

- Female Balb/c mice (N=12/group) were injected IP with *Bps* (96243, 1x10^4 cfu).
- Saline or SGX94 (50 mg/kg IP) was administered 2 hr prior to infection and on days 2, 4, 6 and 8 post-infection.
- Doxycycline (1 mg/mouse) was administered orally on days 1-7

Lung Infection



STUDY DESIGN:

- Female Balb/c mice (N=12/group) were infected IN with *Bps* (1026b, 4xLD50). SGX94 or saline was administered 4 hours prior to infection and on days 2, 4, 6, and 8 post-infection.
- Doxycycline (20 mg/kg) was administered orally upon infection and daily through day 10.
- MST = median survival time

IDR Program Status

- Phase 2 clinical study in oral mucositis ongoing
- cGMP - quality SGX94 available in IV formulation:
  - Fully synthetic, 5 amino acid peptide. Very stable and highly water soluble
- Pharmacokinetics and nonclinical toxicology completed
- Phase 1 healthy volunteer studies completed:
  - Placebo-controlled, single and multiple ascending dose study
- Portfolio of IDR analogs;
  - Co-crystal structure solved for SGX94 in its target binding site
  - SAR against target protein binding; peptidomimetic analogs developed

Next Steps

- Optimize dosing regimens in combination with antibiotic for the intranasal pneumonic model
  - Therapeutic dosing
- Demonstrate efficacy in aerosol model of infection
  - Include large animal model proof of concept
- Optimize route of delivery for biodefense applications
  - Self-administered injection (IM/SC) or oral tablet
  - May involve advancing an alternate IDR analog
- Identify responding cell population/ biomarker to enable further dose optimization and facilitate the use of the Animal Rule where necessary

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