# Host-Directed Innate Defense Regulators with Preclinical and Clinical Proof of Concept

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## ABSTRACT

**Innate Defense Regulators (IDRs) are a novel class of short, synthetic peptides that enhance the control of microbial infections while attenuating tissue damage by suppressing inflammation and enhancing tissue healing. IDRs target host innate immunity rather than the bacterium itself, evading antibiotic resistance mechanisms. The first-in-class IDR, dusquetide (SGX942), has been demonstrated to be safe in a Phase 1 single- and multiple-ascending dose study with concomitant reduction in inflammatory biomarkers. Dusquetide has also been shown to be efficacious in a variety of Gram-positive and Gram-negative infections at various sites of infections and in immunocompetent and immunocompromised CD-1, BALB/c and CD57/BL6 mice. A recent Phase 2 trial in a non-infectious disease indication (oral mucositis) in 111 head and neck cancer patients, where infection was monitored as a potential adverse event, demonstrated a reduced infection rate with dusquetide treatment.**

**Preclinical studies with dusquetide have demonstrated it is complementary to antibiotic mechanisms of action. Moreover, IDRs, both alone and/or in combination with antibiotics have been demonstrated to increase bacterial clearance and enhance survival in preclinical infection models of methicillin-resistant *S. aureus* (MRSA), *K. pneumoniae*, *P. aeruginosa* and *E. coli*. Dusquetide has been shown to be synergistic with antibiotic use in a *B. pseudomallei* infection model. The advantages of IDRs include 1) the ability to use IDRs prophylactically without fear of engendering resistance, 2) the ability to use IDRs empirically, before the causative infectious agent is fully identified and 3) the ability to use IDRs irrespective of the antibiotic resistance status of the pathogen. The broad spectrum efficacy of IDRs against both Gram-negative and Gram-positive bacteria, whether antibiotic resistant or not, and whether intracellular or extracellular, along with their ability to work in tandem with current standard of care antibiotics, clearly demonstrates the advantages of further developing innate immune modulators for the treatment of clinically important bacterial infections.**

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## CLINICAL PLANS

**Dusquetide, the lead clinical IDR candidate, is a 5-amino acid peptide with rapid pharmacokinetics and enduring pharmacodynamic affects (North et al 2016). Dusquetide is administered as a 4-minute intravenous infusion as an iso-osmolar solution in water.**

**Dusquetide (active ingredient in SGX942) is being initially developed for the treatment of oral mucositis in head and neck cancer patients receiving chemoradiation therapy (CRT). Oral mucositis is linked to the dysregulation of the innate immune response to the tissue damage caused by the CRT.**

**A Phase 1 study with SGX942 administered as a single- or multiple-ascending dose (daily for 7 days) was completed in 84 subjects and demonstrated an enhanced anti-inflammatory response at lower dose levels (0.15 – 2.0 mg/kg) with higher dose levels responding similarly to placebo subjects. SGX942 was very well-tolerated at doses as high as 8.0 mg/kg (single dose) or 6.5 mg/kg (daily dose for 7 days). No severe or serious adverse event occurred and no dose limiting toxicity observed (North et al 2016).**

**A Phase 2 study with SGX942 administered twice weekly during CRT to head and neck cancer patients was completed in 111 patients and demonstrated a significant decrease in the rate of oral mucositis at the lower dose level (1.5 mg/kg), consistent with the Phase 1 results (Kudrimoti et al 2016). Patients receiving SGX942 also had a reduced infection rate, enhanced clearance of their tumors and an enhanced survival rate (Kudrimoti et al 2017).**

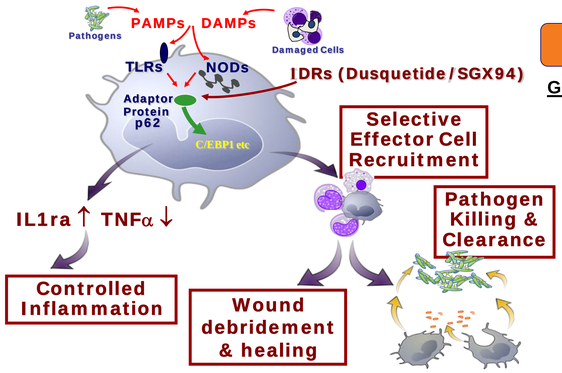
**A Phase 3 study evaluating SGX942 in the treatment of oral mucositis in head and neck cancer patients is currently recruiting in the U.S. with expansion to Europe planned this year. Infection rates are again being monitored as a specified potential adverse event (ClinicalTrials.gov NCT03237325).**

## BACKGROUND

### IDR Mechanism of Action

**IDRs, including dusquetide, modulate the innate immune system by targeting convergence points in the intracellular signaling pathways, downstream of most innate immune receptors. IDRs respond whenever the innate immune response is triggered, as a result of tissue damage (DAMPs) or pathogen detection (PAMPs), and alter the response patterns to enhance anti-microbial and tissue healing pathways while modulating inflammation, without completely ablating the inflammatory response.**

**Dusquetide specifically binds to the ZZ domain of p62 (Yu et al 2009) and selectively stabilizes TNFα-induced p62-RIP1 complex formation while having no effect on TNFα-induced p62-PKCξ complex formation. Dusquetide modulates downstream pathways by activating MAPK p38 and C/EBPβ, resulting in modulation of cytokine/chemokine production, altered protein expression in endothelial cells and monocytes and increased macrophage recruitment to the site of infection/damage (Yu et al 2009; North et al 2016).**

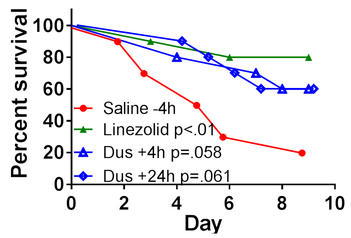



## RESULTS

### Broad Spectrum Activity

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

**Dusquetide (5 mg/kg IV) or saline (IV) was administered at the indicated times to female Balb/c mice prior to or after infection via the tail vein with MRSA (USA300, 7.1 log10 cfu). Sub-optimal antibiotic treatment (linezolid, 6.25 mg/kg) was administered orally immediately after infection. Survival was monitored for 9 days.**

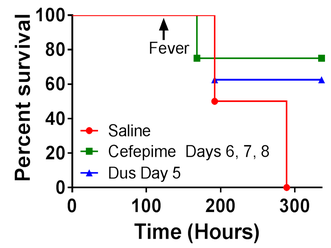



## RESULTS

### Broad Spectrum Activity

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

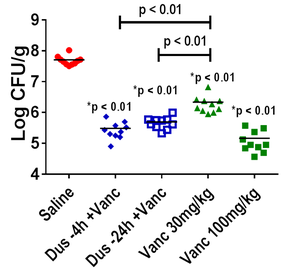
**Dusquetide (10 mg/kg IV) or saline (IV) was administered at the indicated times to rats. Rats were initially treated with antibiotics to disturb their intestinal microbiota, and then rendered leukopenic (cyclophosphamide) prior to orogastric treatment with *P. aeruginosa*. Treatment was initiated *after* appearance of fever on Day 5.**




### Antibiotic Complementarity/Synergy

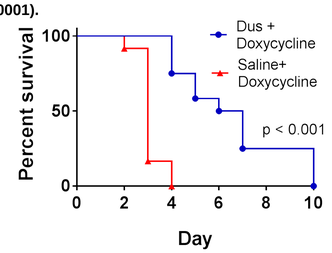
**Gram-positive, Antibiotic-resistant Bacteremia (MRSA)**

**Male CD-1 mice were rendered neutropenic by 2 IP injections of cyclophosphamide (Cp) on Days -4 and -1 before infection (150 mg/kg and 100 mg/kg Cp, respectively). Dusquetide (50 mg/kg) was administered IV at 24 or 4 h before infection. MRSA (Catalog No. 33591, ATCC, 1.24 ×10$^5$ cfu) was inoculated in the right thigh. Vancomycin (30 or 100 mg/kg) was given SC at 2 and 14 h after the bacterial inoculation. At 26 h after inoculation, the muscles of the right thigh were harvested.**




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

**Female BALB/c mice (N=12/group) were infected intranasally. Dusquetide (50 mg/kg) or saline was administered IV 4 h prior to infection and every second day to Day 8. Doxycycline (20 mg/kg) was administered orally upon infection and daily through Day 10. The combination of dusquetide + doxycycline was found to be more effective than the additive combination (p<0.0001).**



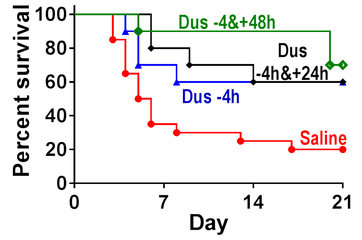

## RESULTS

### Extended Pharmacodynamic Action

**As expected for a natural peptide, dusquetide has a rapid pharmacokinetic half-life in plasma (mean residence time < 10 minutes). Despite this, the effect on the responses of the innate immune system are enduring.**

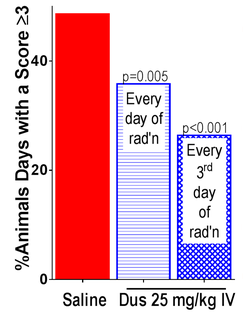
**Gram-positive, Antibiotic-resistant Bacteremia (MRSA)**

**Dusquetide (5 mg/kg IV) or saline (IV) was administered at the indicated times to female Balb/c mice (N=10/group) prior to or after infection via the tail vein with MRSA (USA300, 2×10$^7$ cfu).**




**Chronic Tissue Injury (Oral Mucositis)**

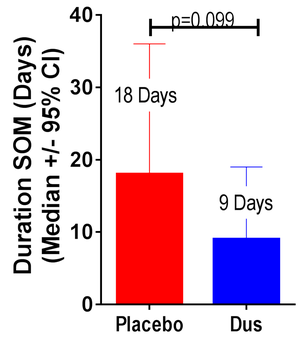
**Fractionated radiation was administered to the everted cheek pouch of Golden Syrian hamsters on Days 0, 1, 2, 3, 6, 7, 8 and 9. Dusquetide was administered on the days indicated and 2 h after radiation if applicable. OM was monitored by blinded scoring by 2 independent observers every second day throughout a 35 day window with OM reaching peak severity around Day 19.**




### Clinical Proof of Concept

**Anti-Inflammatory / Tissue Healing Activity**

**Dusquetide demonstrated anti-inflammatory action in both Phase 1 (healthy volunteer) and Phase 2 (oral mucositis in head and neck cancer patients receiving chemoradiation therapy). Consistent with preclinical studies, the strongest anti-inflammatory response was apparent at the lower dose of 1.5 mg/kg.**

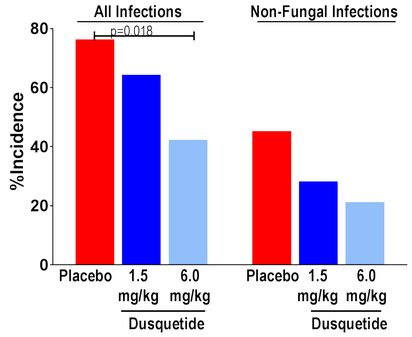



## RESULTS

### Clinical Proof of Concept

**Anti-Infective Activity**

**Patients receiving CRT for head and neck cancer are also susceptible to infections. In this Phase 2 study, the patients receiving dusquetide had a decreased incidence of infection, irrespective of the oral mucositis response, the infectious pathogen, and any concomitant therapy (antibiotics or anti-fungal agents). Dusquetide (SGX942) was administered twice weekly during the 7 week CRT).**




## CONCLUSIONS

- **Dusquetide is a first in class new chemical entity (NCE) with a novel mechanism of action, targeting an intracellular convergence point in the innate immune system.**
- **Dusquetide modulates the response of the innate immune system to a broad spectrum of triggers including infection, tissue damage and secondary inflammation.**
- **IDRs may significantly enhance antibiotic efficacy *without* increasing resistance.**
- **IDRs are effective when given prophylactically, pre-emptively or therapeutically.**
- **IDR action is independent of bacterial pathogen.**
- **A high degree of clinical translation was observed in recent Phase 1 and Phase 2 studies. A Phase 3 study in oral mucositis is currently recruiting.**

## References

1. **Yu HB et al. 2009. Sequestosome-1/p62 is the key intracellular target of innate defense regulator peptide. J Biol Chem 284: 36007-11. PMCID: 2794716.**
2. **Scott et al. 2007. An anti-infective peptide that selectively modulates the innate immune response. Nat Biotechnol 25:465-72. PMID 17384586.**
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5. **Kudrimoti M et al. 2017. Dusquetide: Reduction in oral mucositis associated with enduring ancillary benefits in tumor resolution and decreased mortality in head and neck cancer patients. Biotechnol Rep (Amst). 15:24-26. PMID 28649557.**

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