Innate Defense Regulators (IDRs) – Agnostic Therapy to Treat Bacterial Infections and Fight Resistance

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ABSTRACT

Background: Innate Defense Regulators (IDRs) are a novel class of synthetic peptides that enhance the control of microbial infections while attenuating tissue damage and modulating inflammation. IDRs target host innate immunity rather than the bacterium itself, evading antibiotic resistance mechanisms. IDRs act at key nodal points in the intracellular signaling network of innate immune cells, and have demonstrated efficacy in preclinical models of bacterial infection with both gram-positive and gram-negative bacteria, whether administered therapeutically or prophylactically and whether administered as a stand-alone agent or in conjunction with antibiotics.

Material/methods: The lead clinical IDR, dusquetide, was evaluated in an 84 subject single- and multiple-ascending dose Phase 1 study with concomitant evaluation of inflammatory responses and in a 111 patient double-blind, placebo-controlled, Phase 2 study treating oral mucositis in head and neck cancer (HNC) patients. Oral mucositis is a consequence of innate immune dysregulation causing excessive inflammation and provides an important framework for the clinical translation of IDRs. Dusquetide was administered as a 4-minute intravenous infusion in both studies. Incidence of infection in HNC patients was monitored throughout the Phase 2 study.

Results: Dusquetide was found to be safe and well-tolerated in the Phase 1 study with no serious or severe adverse events attributed to its use. Moreover, *ex vivo* evaluation of inflammatory stimulation of blood from the healthy volunteers with endotoxin revealed a more anti-inflammatory response in subjects administered dusquetide at doses between 0.15 – 2.0 mg/kg while higher doses (3.0 – 8.0 mg/kg) revealed a response similar to the placebo subjects. Similarly the Phase 2 study in oral mucositis revealed a statistically significant reduction in the median duration of oral mucositis at the 1.5 mg/kg dose level, primarily mitigating the inflammatory response prevalent in oral mucositis. The incidence of non-fungal (bacterial) infection in these oral mucositis patients was also significantly reduced in the HNC patients at both 1.5 and 6.0 mg/kg. The Phase 2 results were completely consistent with the results from both preclinical and Phase 1 clinical studies.

Conclusions: IDRs have been shown to "re-balance" the response of innate immune cells to innate immune stimuli occurring through most pattern recognition receptors. The interplay between anti-inflammatory, anti-infective and tissue healing responses yields a complex dose response where anti-inflammatory responses are increased at low doses and bacterial anti-infective responses are increased across a wider dose response range. The advantages of IDRs include 1) the ability to use IDRs preventively without fear of engendering resistance, 2) the ability to use IDRs before the causative infectious agent is fully identified and 3) the ability to use IDRs irrespective of the antibiotic resistance status of the organisms. The broad spectrum efficacy of IDRs against both Gram-negative and Gram-positive bacteria whether antibiotic resistant or not and whether intracellular or extracellular, and 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 serious infections.

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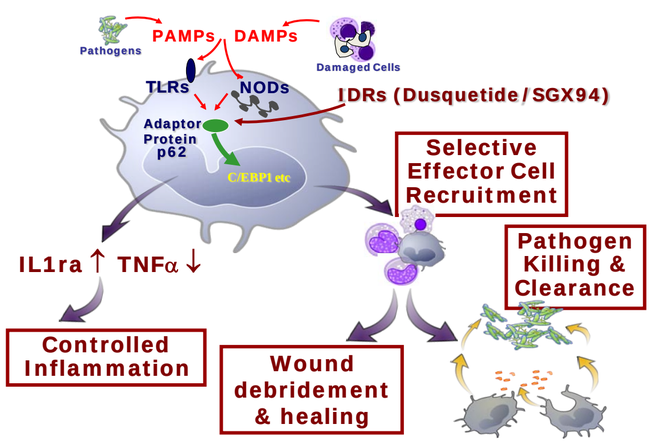
MECHANISM

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 activates MAPK p38 and C/EBPβ, resulting in modulation of cytokine production and increased macrophage recruitment to the site of infection/damage (Yu et al 2009; North et al 2016).



CLINICAL STUDIES

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

Dusquetide (active ingredient in SGX942) is being initially developed for the treatment of oral mucositis in HNC 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 (ClinicalTrials.gov NCT02013050) with SGX942 administered twice weekly during CRT to HNC 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), with safety and efficacy results 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).

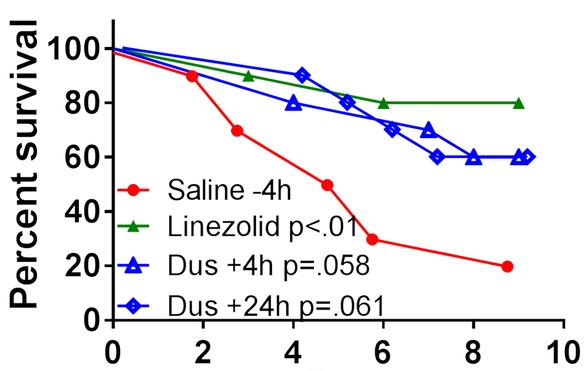
A Phase 3 study evaluating SGX942 in the treatment of oral mucositis in HNC patients is currently recruiting in the U.S. with expansion to Europe planned this year. Infection rates are again being monitored as a specified potential adverse event (ClinicalTrials.gov NCT03237325).

RESULTS

Broad Spectrum Activity

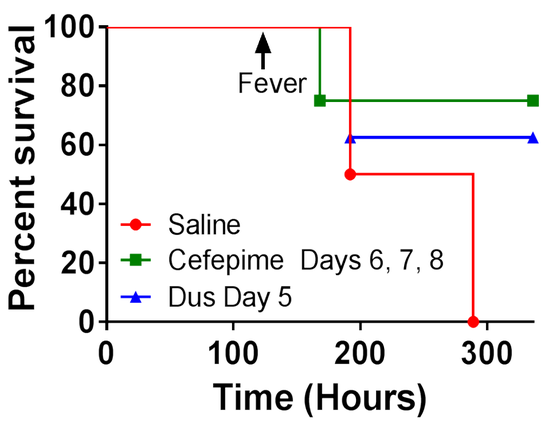
Gram-positive, Antibiotic-resistant Bacteremia (MRSA)

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.



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.

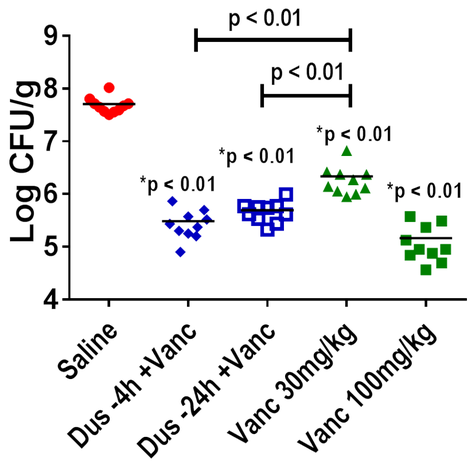


RESULTS

Antibiotic Complementarity

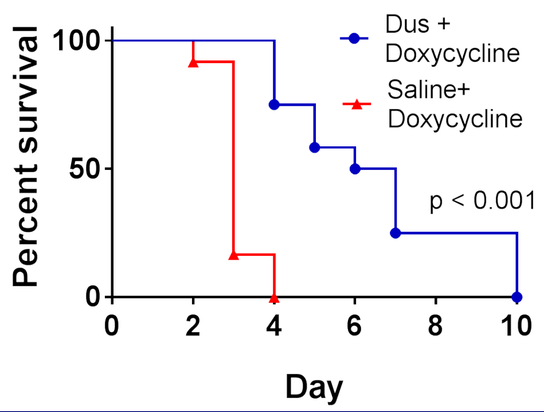
Gram-positive, Antibiotic-resistant Bacteremia (MRSA)

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 $\times 10^5$ 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 ($p<0.0001$).

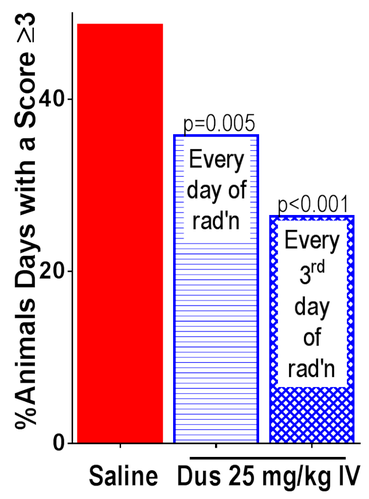


Extended Pharmacodynamics

As expected for a 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. Anti-infective studies demonstrated no added benefit to repeated dusquetide administration within a 24-48 hour window, suggesting a pharmacodynamic response of 48-72 hours (North et al 2016).

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.

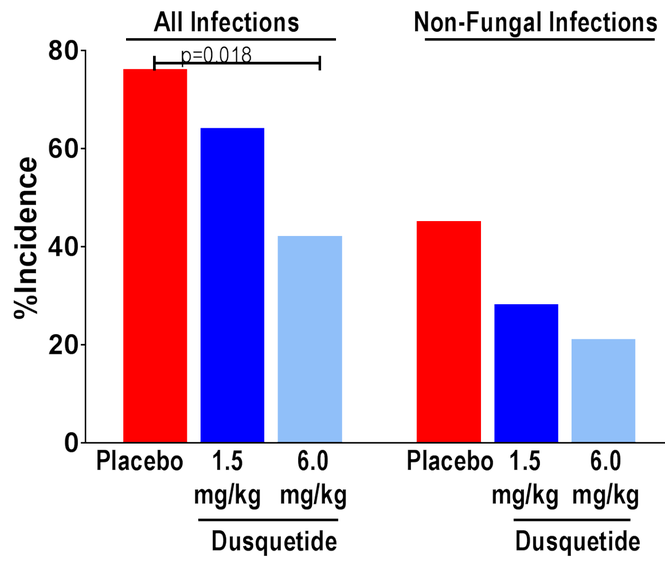


RESULTS

Clinical Proof of Concept

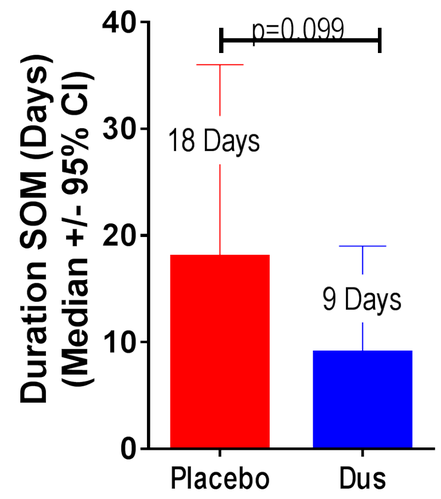
Anti-Infective Activity

Patients receiving CRT for HNC are also susceptible to infections. In the 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.



Anti-Inflammatory / Tissue Healing Activity

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



CONCLUSIONS

- 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.

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