Reduced Infection and Mucositis in Chemotherapy-Treated Animals Following Innate Defense Modulation Using a Novel Drug Candidate

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Background

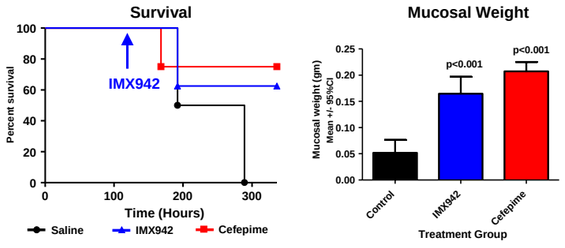
Innate Defense Regulators (IDRs) are a novel class of synthetic peptides with no antimicrobial activity that enhance the control of microbial infections while attenuating tissue damage and suppressing inflammation. The ability of IDRs to modulate the innate defense system renders them attractive drug candidates in therapeutic areas where harnessing the innate defenses would be beneficial.

The lead IDR drug candidate, IMX942, has successfully completed Phase 1 clinical studies, being very well tolerated at all dose levels tested - single doses up to 8 mg/kg and multiple doses (7 daily injections) up to 6.5 mg/kg/day. Treatment of mice with IDRs enhanced their survival in bacterial infection models. The anti-infective effect of IDRs was maintained in animals depleted of neutrophils, but abolished in animals depleted of macrophages/monocytes. Recently, the enhanced survival benefit conferred by IDR treatment has been shown in clinically relevant rat models of neutropenic sepsis after cyclophosphamide treatment; simultaneously, protection of the gastrointestinal mucosal barrier due to IDR treatment was also demonstrated. Further investigations in animal models of mucositis, where pathogenesis is linked to the response of the innate defense system, have demonstrated that IDRs have significant efficacy in both oral and gut mucositis.

Phase 2 studies evaluating the efficacy of IMX942 in the amelioration of mucositis and infection are currently being planned in cancer patients undergoing radio- or chemo- therapy.

Results

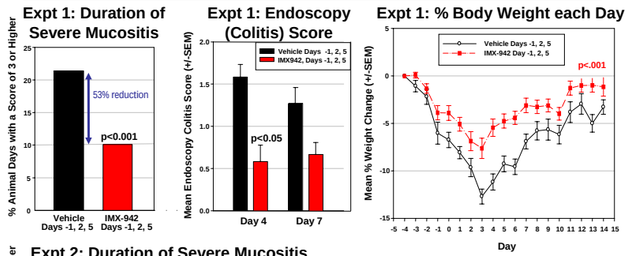
IMX942 protects against Gram-negative leukopenic infection



- IMX942, administered after the start of fever, reduces subsequent sepsis and death;
- IMX942-enhanced survival correlates with protection of the GI barrier (increased mucosal weight);
- Data support both Mucositis and Febrile Neutropenia as potential IMX942 indications.

Female Sprague-Dawley rats were administered 10mg/kg Cefamandole IM Q48h starting on day -4 and continuing to the end of the study. Cyclophosphamide 75mgkg IP was administered on days 0 and 3. 1x10^6 CFU/ml *P. aeruginosa* was given by orogastric feedings on days 0, 2 and 4. Due to the breakdown of the gastrointestinal mucosal barrier, rats developed fever by day 5, and began dying of sepsis by day 7. IMX942 (10mg/kg IV) or Saline (IV) was administered once after the appearance of fever on day 5. Cefepime was administered on days 6, 7 and 8 (25mg/kg IM). Survival was monitored in an initial study (N=8 IMX942, Saline, N=4 Cefepime). Mucosal weight was assessed in a repeat experiment with matched termination of animals on days 6, 7 and 8 (N=9 IMX942 and Saline, N=11 Cefepime).

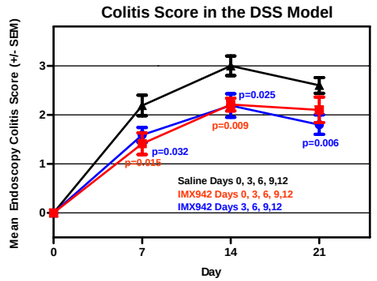
IMX942 attenuates chemotherapy-induced oral and gut mucositis



Male C3H/HeN mice (N=12/grp) were administered 60 mg/kg 5-FU IP on days -4 and -2. On day 0 a chemical burn was applied to the underside of the tongue. Oral mucositis was documented with daily photography and gut mucositis was assessed with video endoscopy on days 4 and 7. Body weights were monitored daily. IMX942 was administered IV at the times and doses shown. Saline control was administered IV on days -1, 2 and 5. Two representative experiments are shown.

- IMX942 has a beneficial effect on multiple readouts of oral and gastrointestinal mucositis;
- IMX942 treatment is dose proportional, and is effective after damage is initiated.

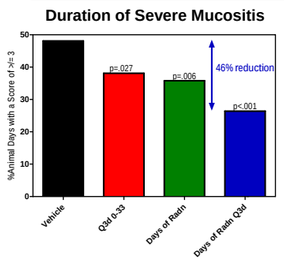
IMX942 attenuates gastrointestinal damage in a colitis model



- IMX942 attenuates colitis without the increased weight loss associated with steroid treatment;
- IMX942 treatment is effective after damage is initiated.

Colitis was induced in mice by exposure to 3% DSS-treated drinking water from Day 0 to Day 5. Animals were dosed with 25 mg/kg IMX942 or Saline IV as indicated (N=10/grp). Animals were weighed daily and assessed visually for the presence of diarrhea and/or bloody stool. On Days 7, 14, and 21 colitis severity was assessed using video endoscopy.

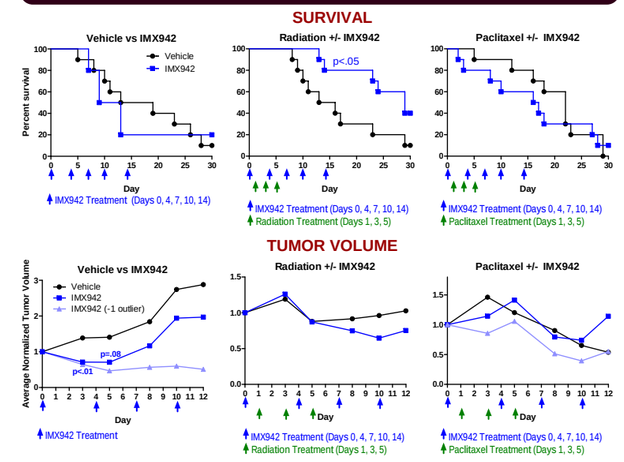
IMX942 attenuates radiation-induced oral mucositis



- A clinically relevant dosing regimen demonstrated the best efficacy in this study.
- Peak mucositis scores were also decreased from an average of 3.4 in the vehicle group to 3.0 in all other groups.

On study days 0, 1, 2, 3, 6, 7, 8 and 9, male Syrian Golden Hamsters (N=12/grp) were given acute radiation (7.5 Gy) to their everted left buccal cheek pouch. 25 mg/kg IMX942 was administered IV either every 3rd day between days 0 and 33, on every day of radiation or on every 3rd day during radiation treatment (days 0, 3, 6, and 9). Mucositis was evaluated clinically, starting on day 7 and thereafter on alternate days until day 35.

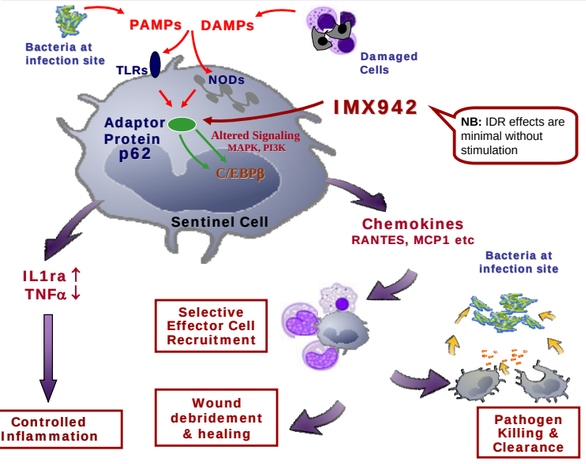
IMX942 does not enhance tumor growth or interfere with tumor treatment



- No adverse events were associated with IMX942;
- Unexpected deaths occurred in all groups in the study, irrespective of treatment;
- IMX942 alone may shrink tumor volume and did not effect the tumor response to chemotherapy or radiation treatment.

Female nu/nu mice (N=10/grp) were implanted with estrogen pellets and injected SC with MCF-7 cells (breast cancer cell line). Treatments were started when the average tumor size was 100 mm^3 (Day 0). Saline or 25mg/kg IMX942 was administered on days 0, 4, 7, 10, and 14. Radiation (2 Gy) or paclitaxel (6 mg/kg IP) were administered on days 1, 3 and 5. Survival, body weight and tumor volume were monitored over the ensuing 30 days. Due to low survival after day 12, average normalized tumor volumes are only shown to day 12.

Cellular Mechanism of IMX942



Innate defense signalling networks are triggered in sentinel cells via TLR or NOD receptor sensing of pathogen or damage-associated molecular patterns. Binding of IMX942 to its intracellular protein target, p62 (sequestosome-1)[1], alters the signalling downstream of TLRs and NODs. IDRs have been shown to transiently increase local chemokine levels (CCL5 and CXCL10), enhance macrophage recruitment to the site of infection and improve the resolution of bacterial infection alone or in conjunction with antibiotics. The anti-infective effect of IDRs was maintained in animals depleted of neutrophils, but abolished in animals depleted of macrophages/monocytes, indicating an important role for macrophages in IDR mediated host protection at the site of infection[2].

1. Yu et al. Journal of Biological Chemistry 284: 36007-36011 (2009).
2. Scott et al. Nature Biotechnology 25: 465-472 (2007)

Conclusions

- **IMX942 protects against febrile neutropenia caused by infection.**
- **IMX942 protects against oral mucositis after chemotherapy or radiation treatment.**
- **IMX942 protects against gastrointestinal damage in models of chemotherapy-induced mucositis and DSS-induced colitis.**
- **IMX942 does not enhance tumor growth or interfere with tumor treatment.**

Inimex Pharmaceuticals Incorporated

Conflict of interest: OD, JRN and MA are employees of Inimex Pharmaceuticals Inc. JP and SO received research funding from Inimex Pharmaceuticals Inc. BW performs consulting services for Inimex Pharmaceuticals Inc. SS performs consulting services for Inimex Pharmaceuticals Inc, Novartis, Biovitrium, Johnson and Johnson, Clinical Assistance Programs, Pfizer, Merck and SciClone Pharmaceuticals. SS also has an equity ownership in Biomodels LLC and is a member of SciClone's Scientific Advisory Board.