



# Inimex

Pharmaceuticals Incorporated

## Innate Defense Regulator drugs ("IDRs")

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## Immune Defences: "Innate" and "Adaptive"

***"Threat"  
Detection***



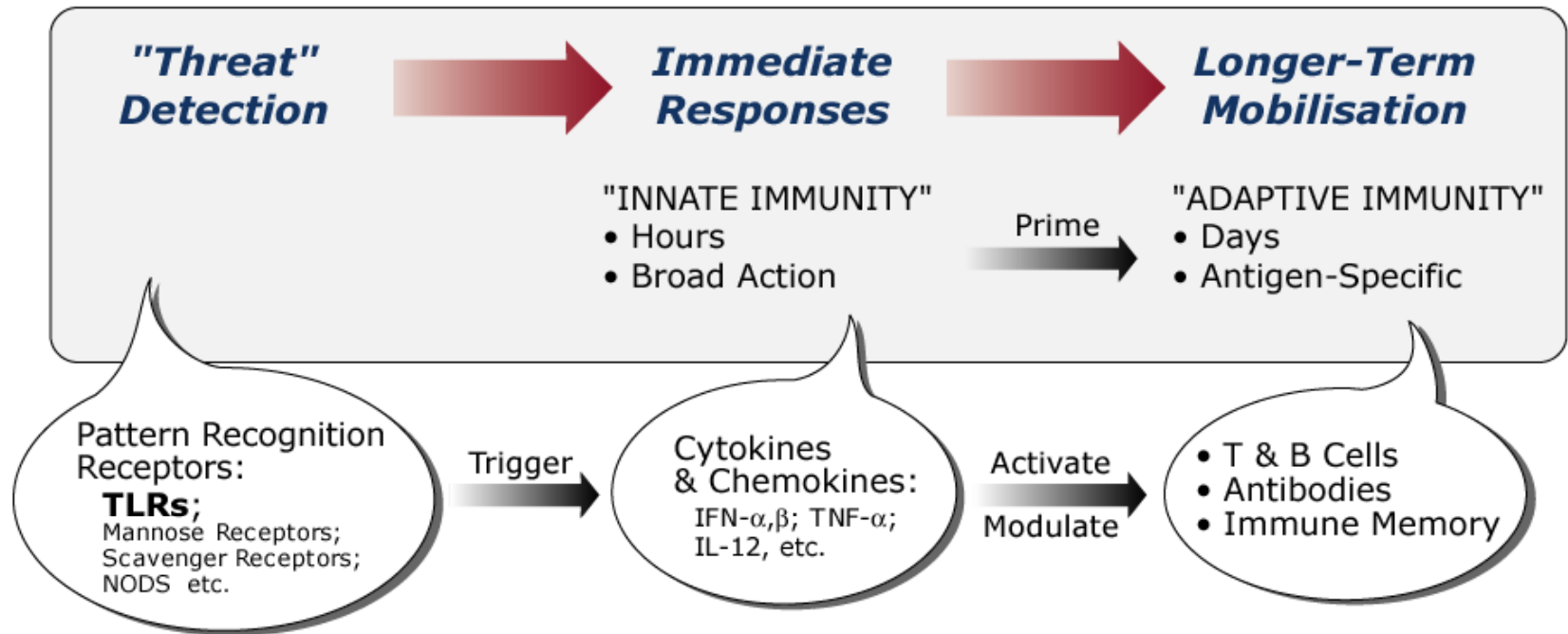


## Immune Defences: "Innate" and "Adaptive"



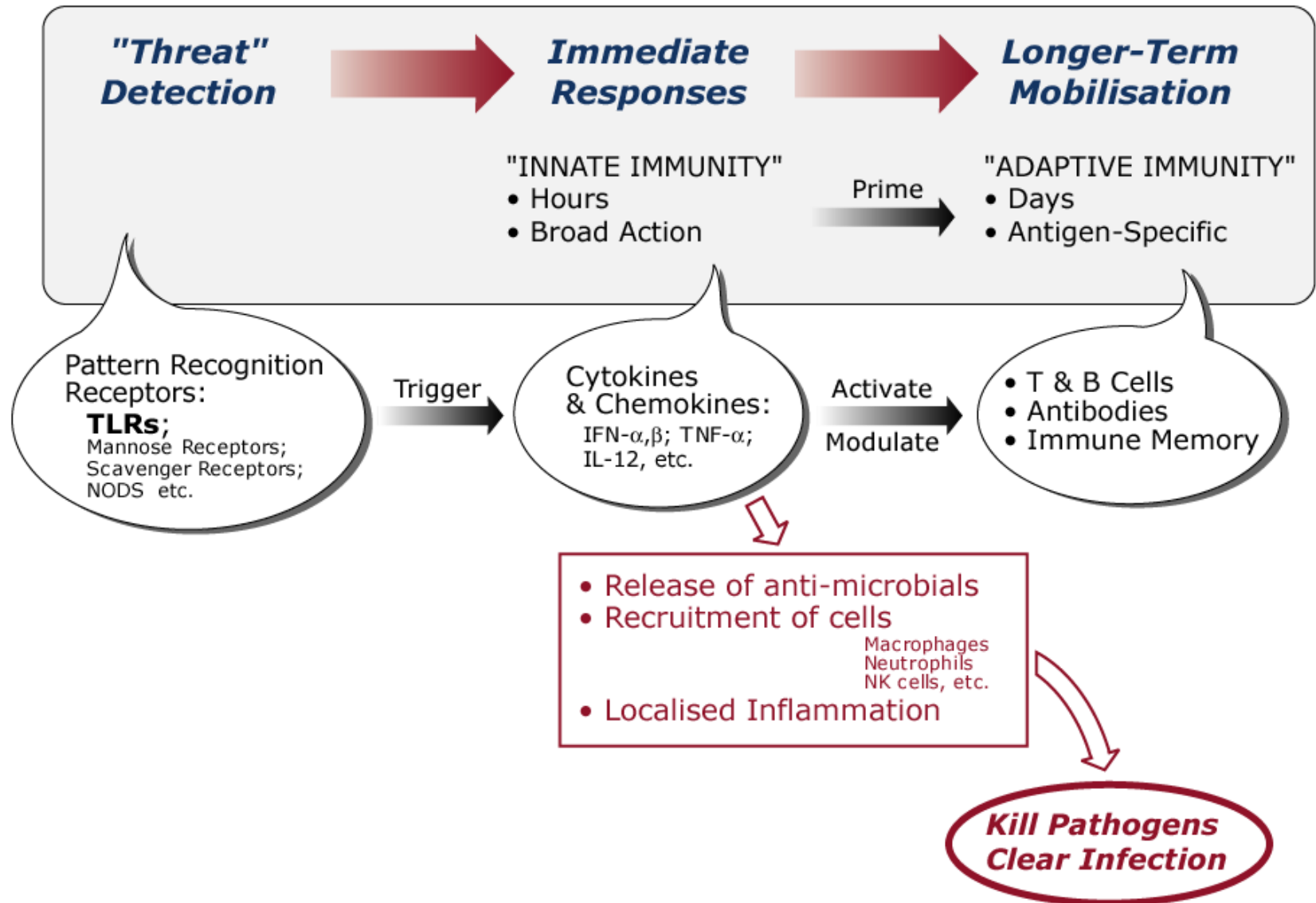


## Immune Defences: "Innate" and "Adaptive"



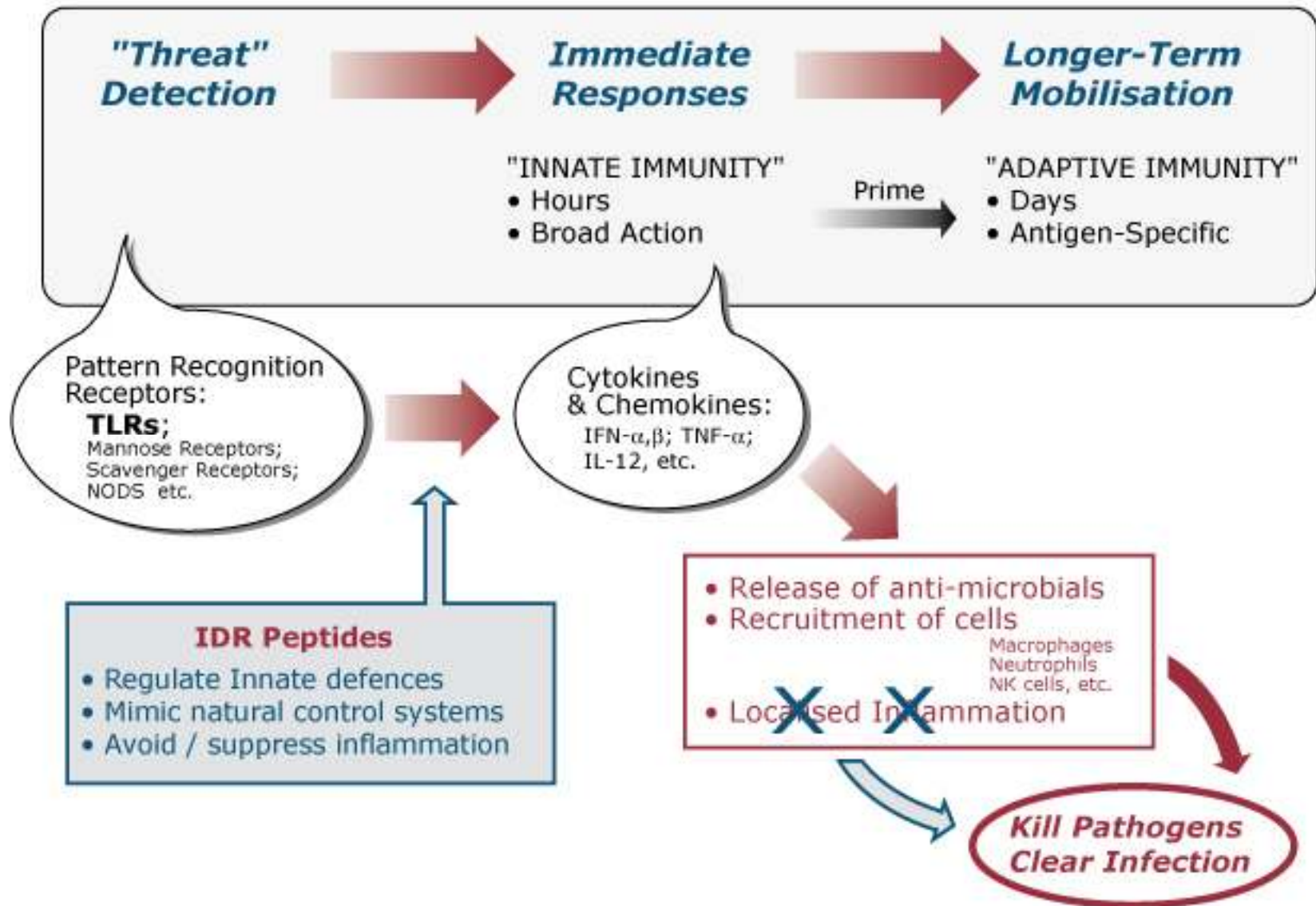


# Immune Defences: "Innate" and "Adaptive"





# IDRs Regulate Innate Immunity





## Innate Defense Regulators (IDRs)



- The Innate Defense System is the “First Line Response” to **injury** and **infection**:
  - . . . . . not antigen- or pathogen-specific;
  - . . . . . triggered by damage- or pathogen- associated molecules;
  - . . . . . occurs rapidly in all tissues;
  - . . . . . a major component of **inflammation**;
- IDR drugs regulate this response and offer pre- and post-exposure broad spectrum therapeutics to:
  - . . . . . ameliorate injury;
  - . . . . . fight drug-resistant infections and reduce inflammation;
  - . . . . . protect immunocompromised individuals;
  - . . . . . complement antibiotics.





## Key features of IDRs



- **Safe** for multiple IV administrations;
- **Rapid action** - intracellular protein target is widely distributed in body tissues and modulates multi-cellular response cascades;
- **Prolonged efficacy** after single exposure, but no drug accumulation;
- **Broad-spectrum** response to injury or pathogen challenge;
- **Independent** of adaptive immune system – effective in immunosuppressed animals.





# History of IDR Discovery & Development





## IDR Discovery



- Research at UBC on antimicrobial peptides, e.g. Human LL37 (Finlay, Hancock, et al.);
- IDR-1 synthesized 2001:
  - Modeled around cathelicidins, indolicidins, defensins, etc.;
- Protects animals from lethal bacterial infection but has no intrinsic antibacterial activity:
  - “Innate Defense Regulator”;
  - Safe for systemic administration.
- IMX942 created 2005:
  - Smaller, better pharmaceutical properties; additional safety margin.
- Molecular target – Sequestosome-1 (p62) - identified 2007.
- IMX942 amelioration of mucositis recognized 2010.

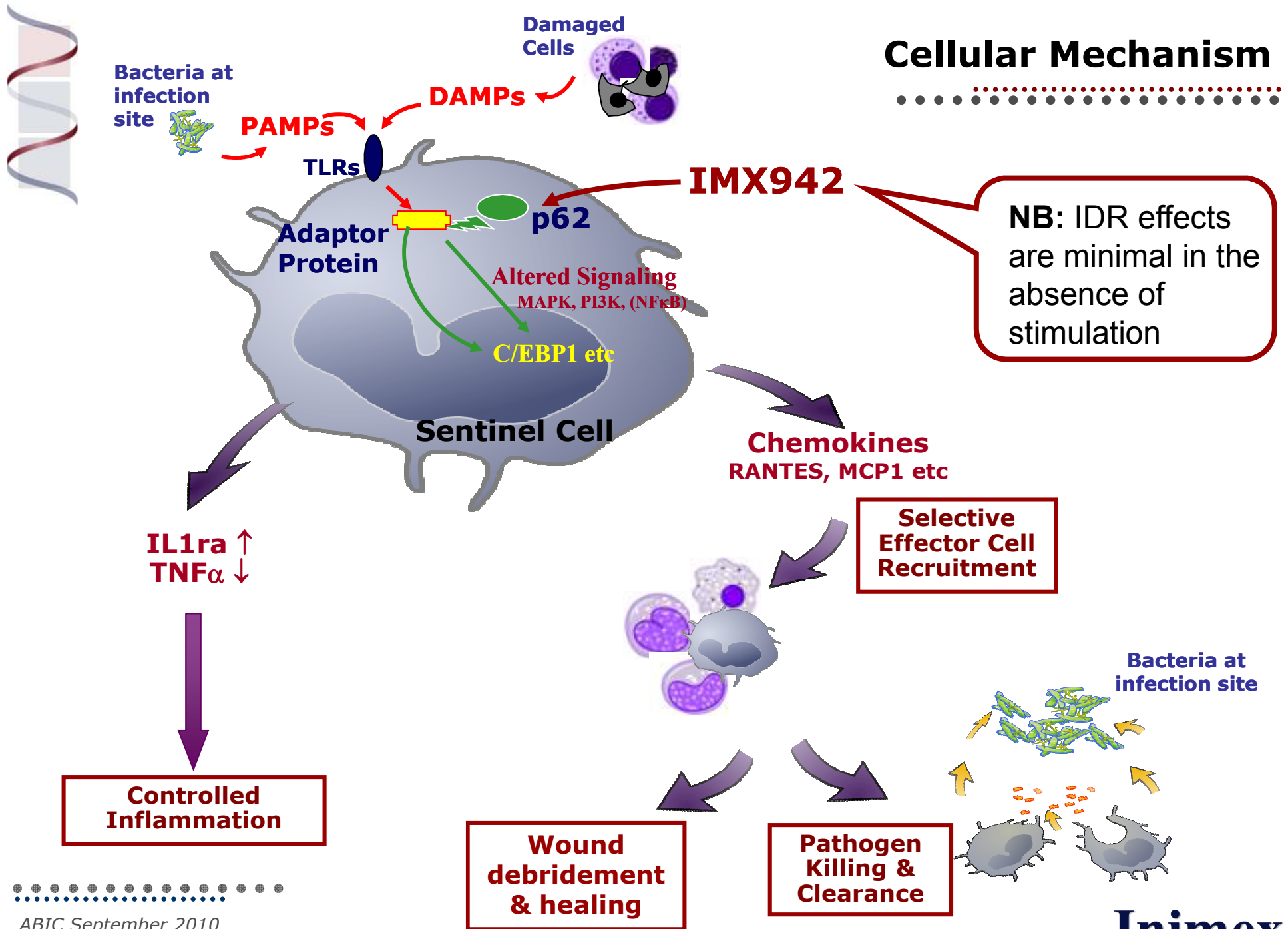




# Mechanism of Action

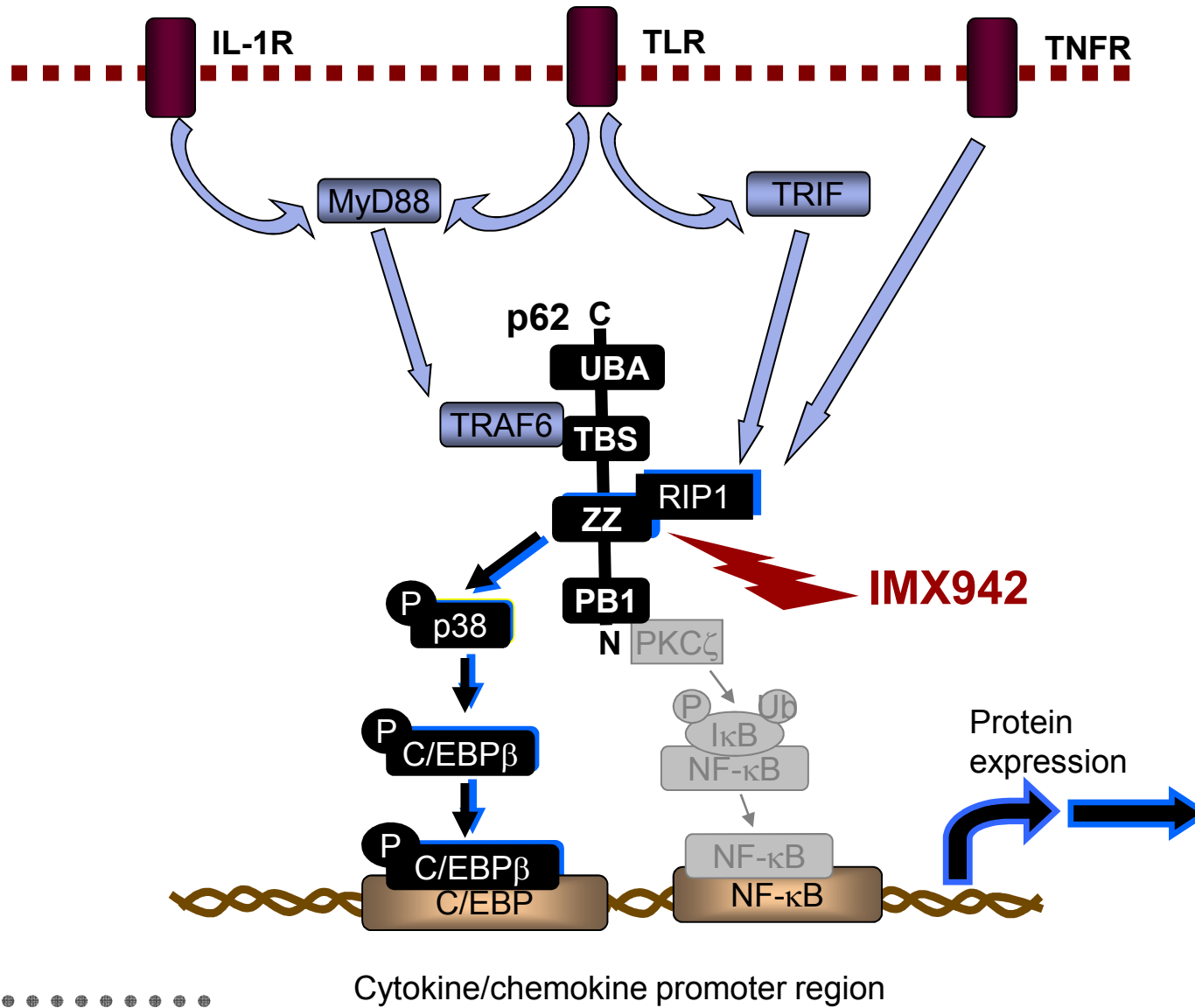


# Cellular Mechanism



**NB: IDR effects are minimal in the absence of stimulation**

# IDR/p62 Molecular Mechanism of Action



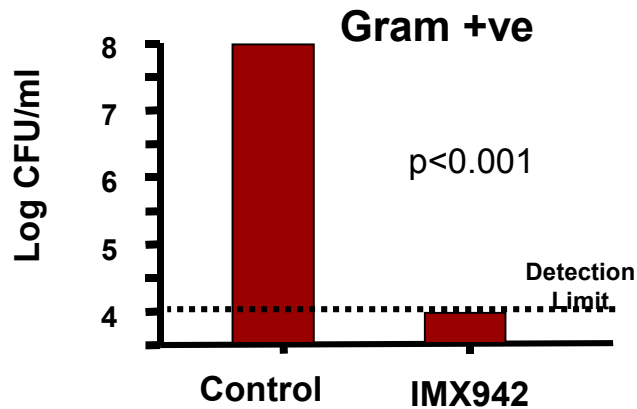


# Effectiveness in Animal Models

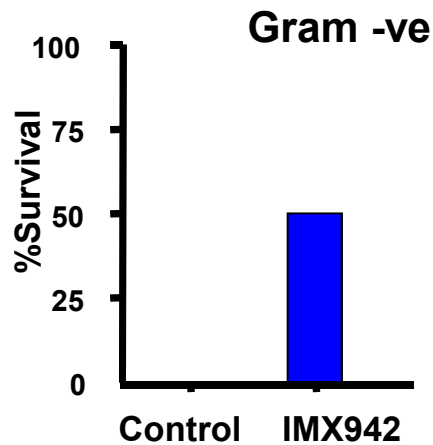




# Broad Spectrum Anti-Infectives

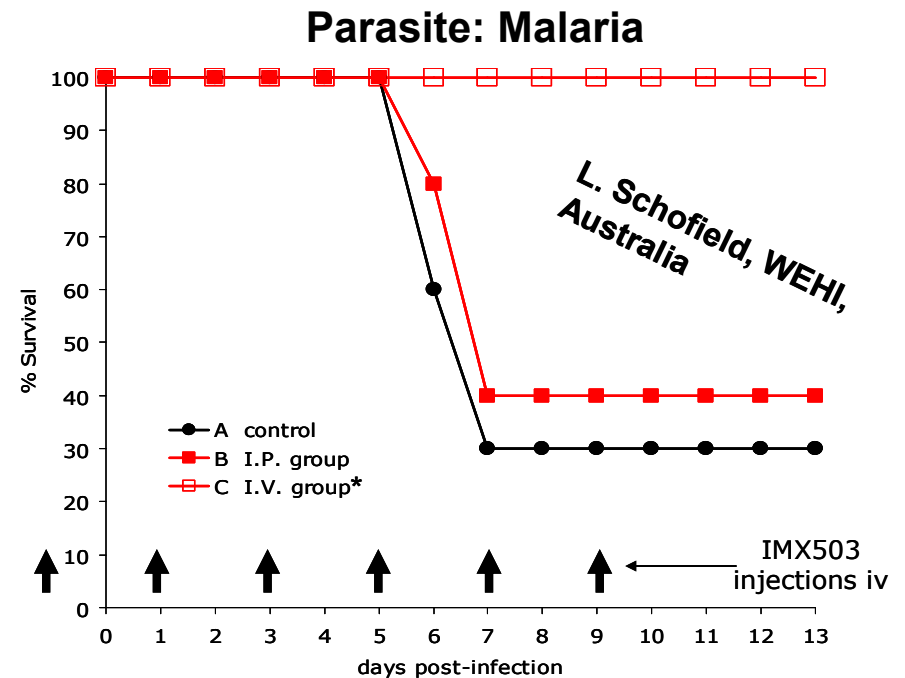


9.5 mg/kg IMX942 IP, 4 h after *S. aureus* IP infection; Peritoneal bacteria counted at 24 h; 8 mice/group.

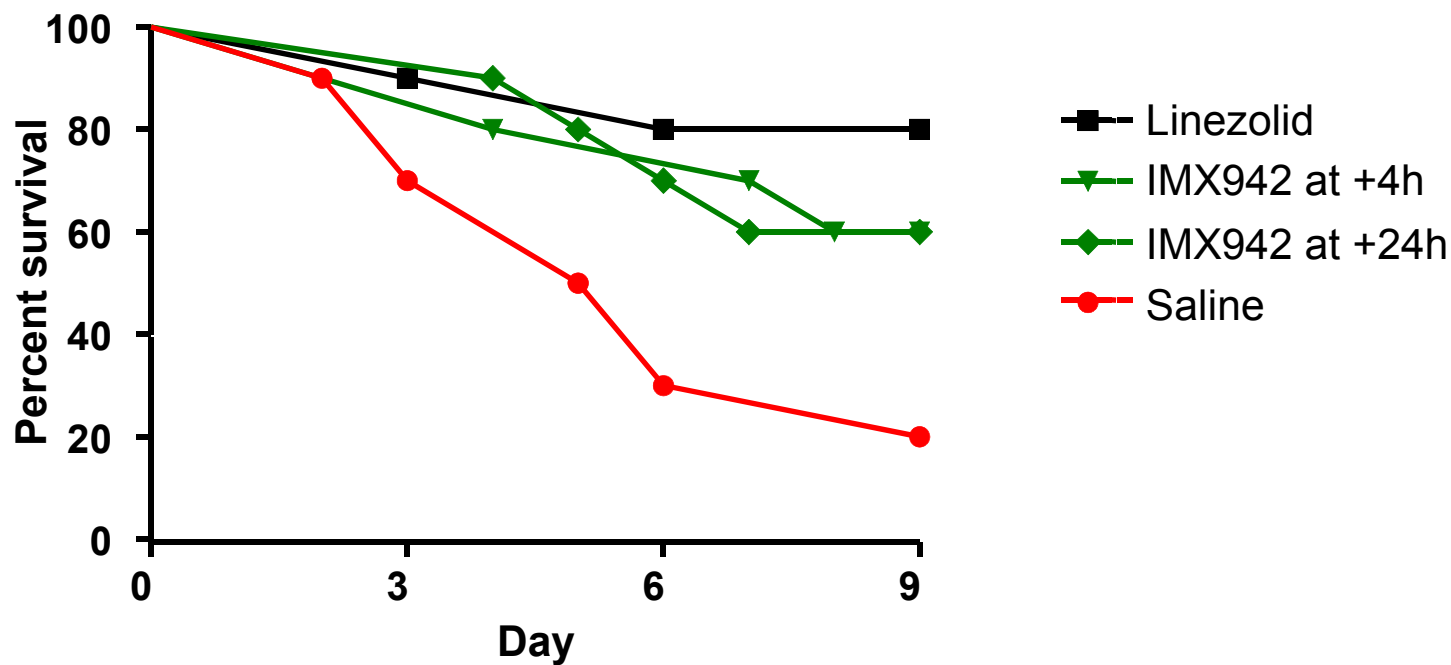


24 mg/kg IMX942 IP 24 h before *Klebsiella* IP infection; survival at 24 h; 8 mice/group.

- IDRs are effective against a wide range of pathogens;
- “Disease-modifying”, not directly anti-pathogen;
- A single dose has a prolonged effect – at least 72 h.



# MRSA Bacteremia – Therapeutic Dosing



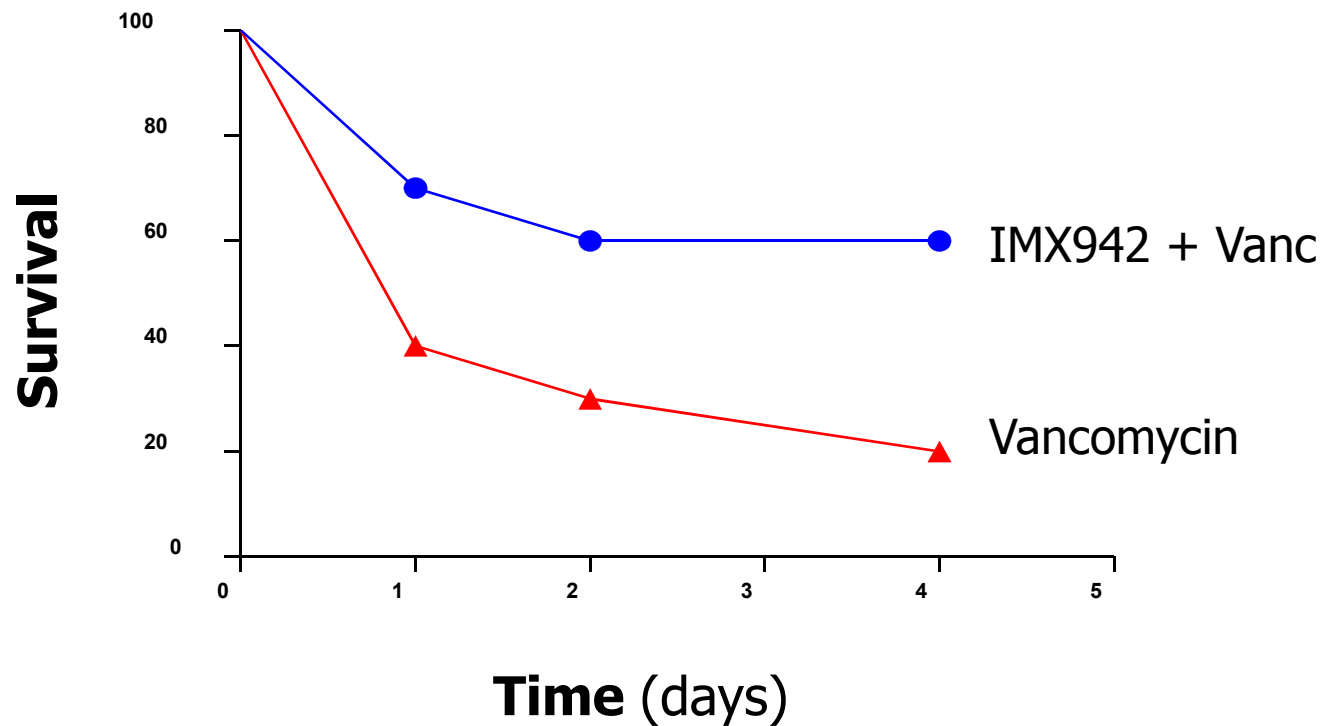
1.6x10<sup>7</sup> MRSA was administered IV to female BALB/c mice (N=12 Saline, N=10 all other groups). Saline and IMX942 were given IV at the times shown; Linezolid was given orally immediately after infection. Survival monitored for 9 days.

- CONCLUSION: Therapeutic window of 24h in this model.





# IMX942 Complements Antibiotics against MRSA

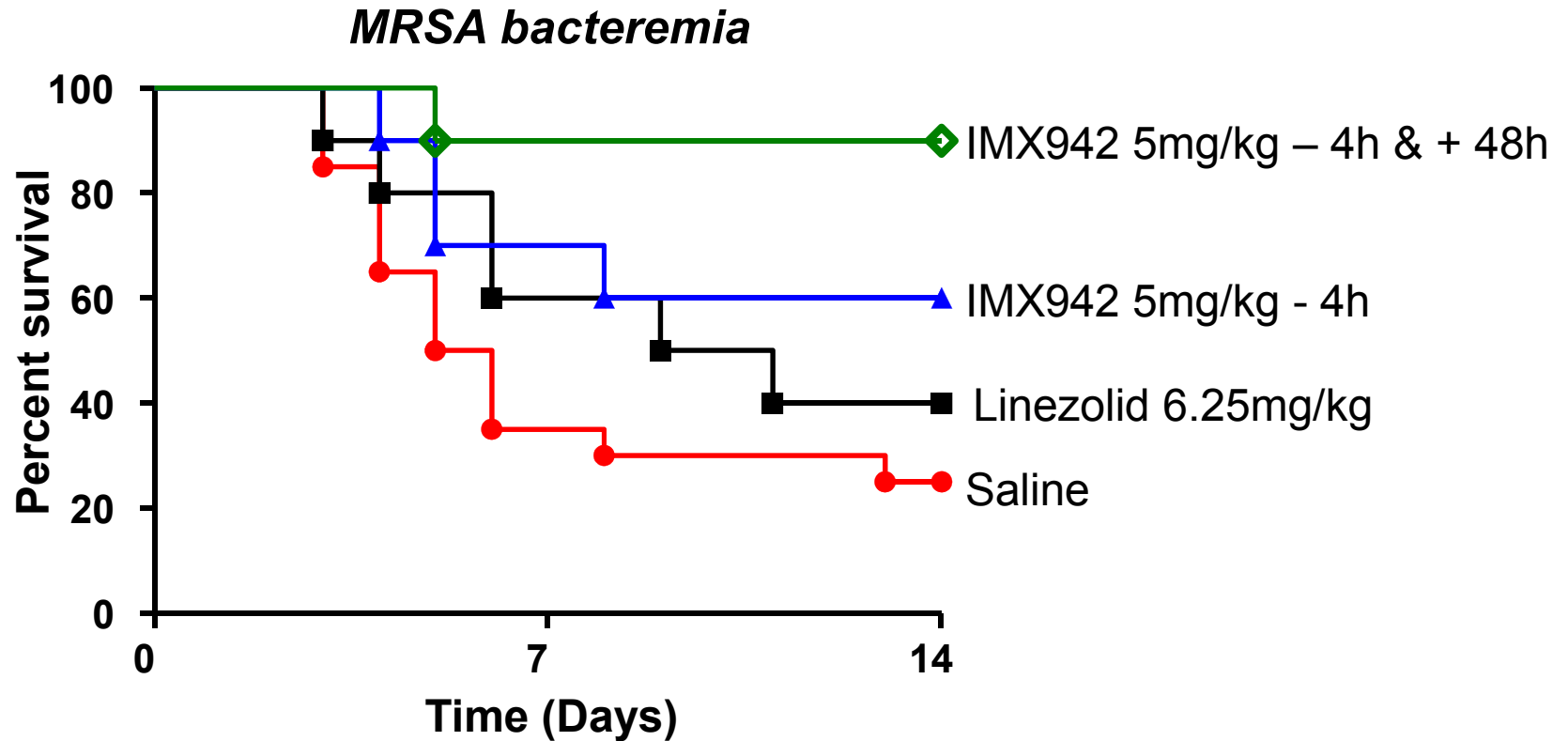


IMX942 (50 mg/kg) or saline treatment was administered IV **48 h prior** to inoculation with MRSA (UC6685,  $8.2 \times 10^7$ ) to female CF-1 mice (N=10/group). Vancomycin treatment (3 mg/kg) was administered SC, 1 and 5 h after infection. Survival was monitored once daily for 5 days.





# Optimization of Treatment

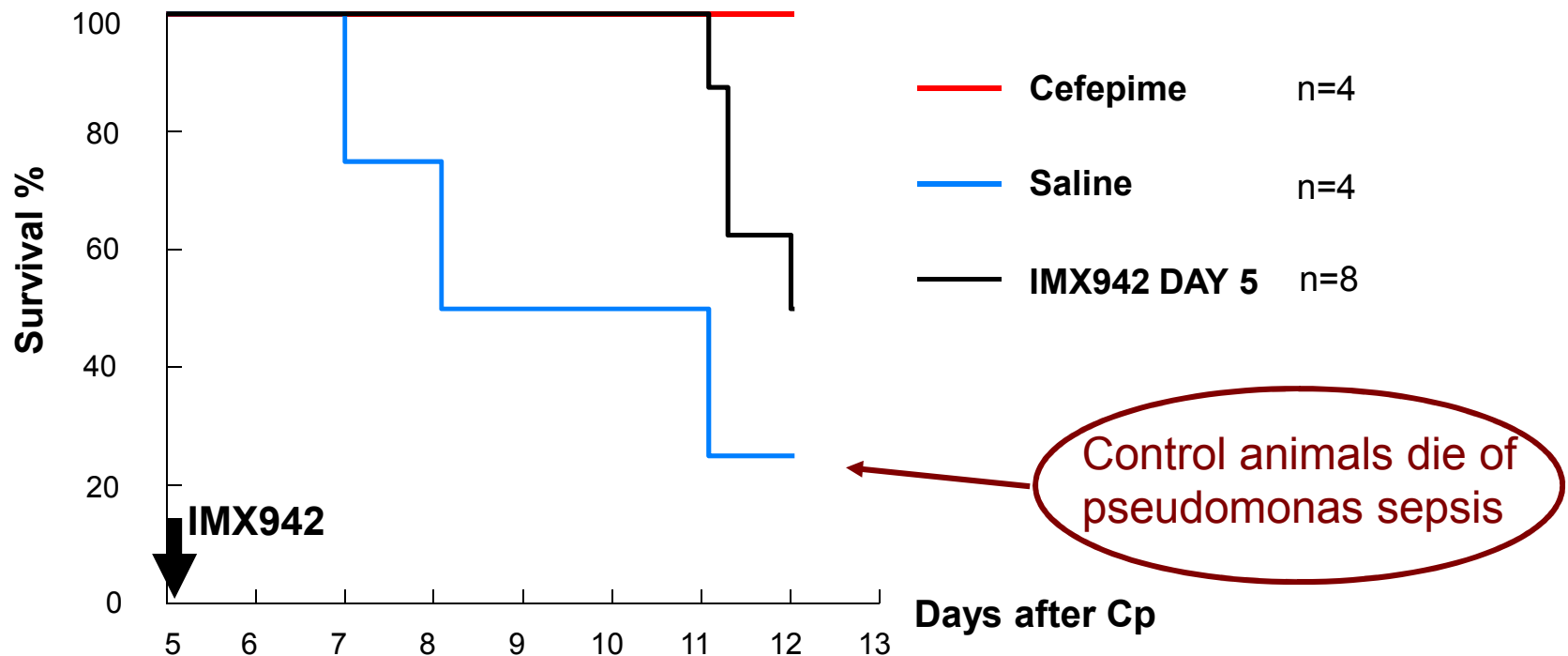


1.6x10<sup>7</sup> MRSA USA300 was administered IV to female BALB/c mice (N=20 Saline, N=10 all other groups). Saline was administered IV 4 hours prior to bacterial challenge. IMX942 was administered either 4 hours prior to, or 4 hours prior to and 48 hours after, bacterial challenge. Linezolid was administered IV immediately after bacterial challenge. Survival was monitored for 14 days.





# IMX942 Improves Neutropenic Rat Survival



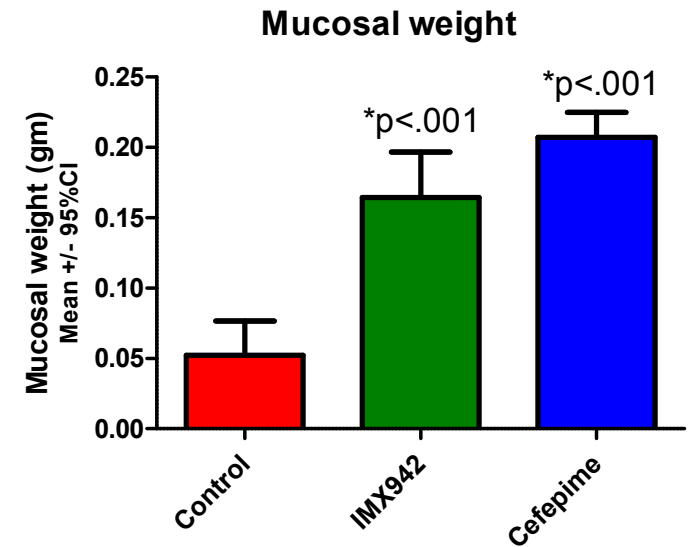
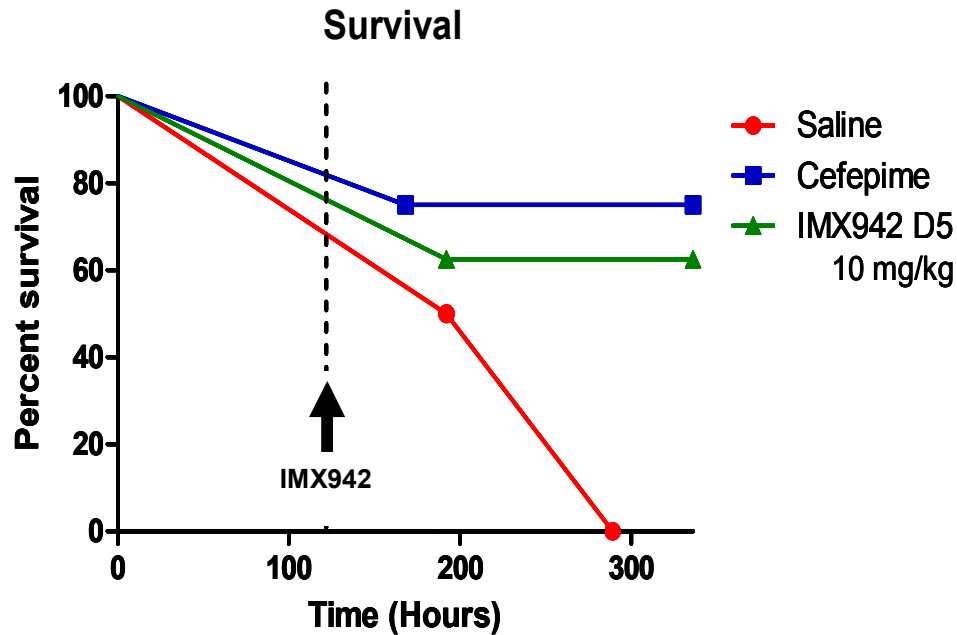
Opal et al.: Female Sprague-Dawley rats were treated with IM cefamandole 4 days prior to day 0 to disrupt their GI flora. On day 0 rats were treated with 75 mg/kg cyclophosphamide IP and challenged with oral *P. aeruginosa*. Cyclophosphamide treatment was repeated on day 2 and *P. aeruginosa* challenge was repeated on days 2 and 4.

In one group of rats, 10 mg/kg IMX942 was administered IV on **day 5**, while other animals received saline or 40 mg/kg cefepime IM daily for 3 days.





# Mucosal Protection / Reduced Infection



## Summary:

- IMX942-enhanced survival (green), correlates with protection of the GI barrier (increased mucosal weight);
- Data support both Mucositis and Febrile Neutropenia as potential IMX942 indications.

## 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:  $1 \times 10^6$  CFU/ml *P. aeruginosa* by orogastric feeding (pathogen repopulation of the gut)
- Day 5 (Start of fever): IV IMX942 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).





# Skin Damage & Infection

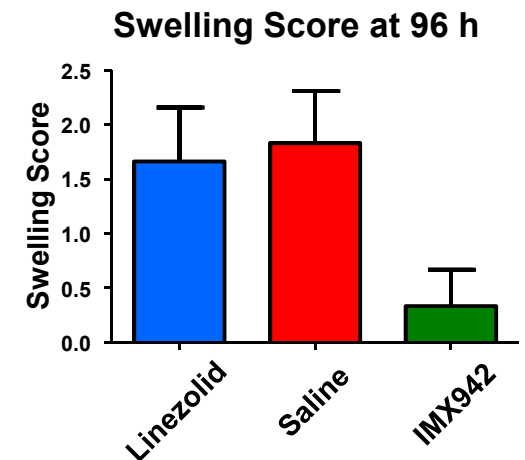
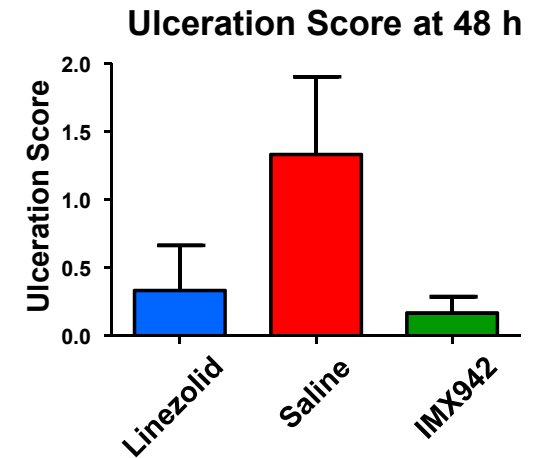
Linezolid (12mg/kg) administered PO at 0 and 24h after infection



Saline administered IV 4 hrs prior to infection



IMX942 (25mg/kg) administered IV 4 hrs prior to infection



## Summary:

- IMX942 significantly reduced ulceration and swelling of the epithelial barrier.

## STUDY DESIGN:

Day -1: remove fur; Day 0 -4h: IMX942 or saline IV; Day 0 0h: Tape strip & infect (MRSA USA 300); Day 0 & 1 & 2: Linezolid treatment; Day 2 & 4: Photographs. No effect was observed on bacterial counts in biopsies with either IMX942 or antibiotic Tx (N=6/group).





# Side Effect of Cancer Therapies



- **Mucositis**—Damage done to mucosa by anticancer therapies (chemo, radiation);
- Affects 500,000 people in the US per year—40% of chemo patients;
- Very painful—can lead to infection, sepsis, need for parenteral nutrition and narcotic analgesia;
- Can lead to dose reductions in cancer treatment which can lower efficacy.



# Pathobiology of Mucositis

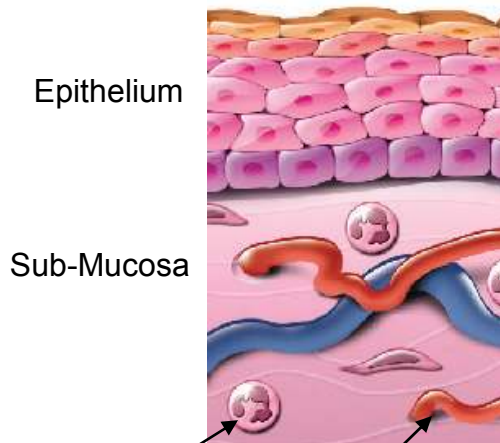
Ref: S. Sonis 2004



Radiation



Normal Epithelium



Epithelium

Sub-Mucosa

Basal Cell

Blood Vessel

Chemotherapy



Innate response to  
Damage-Associated  
Molecules

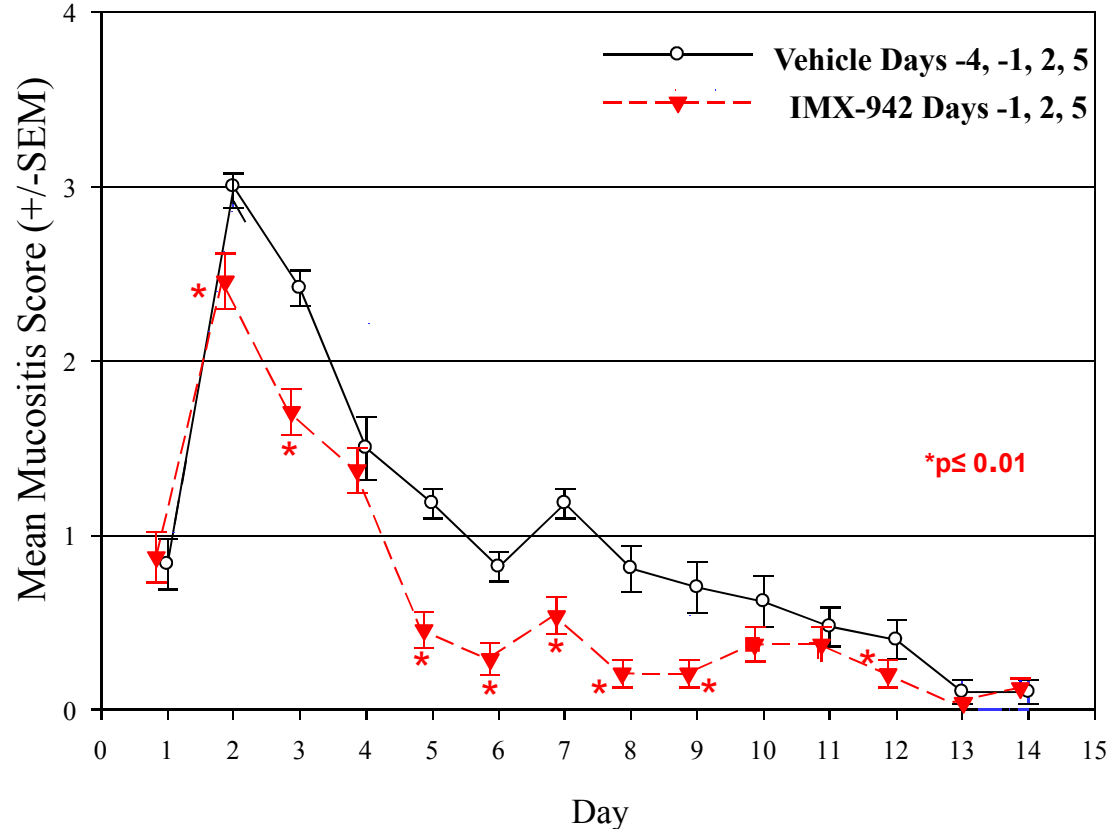
Inflammatory Cell



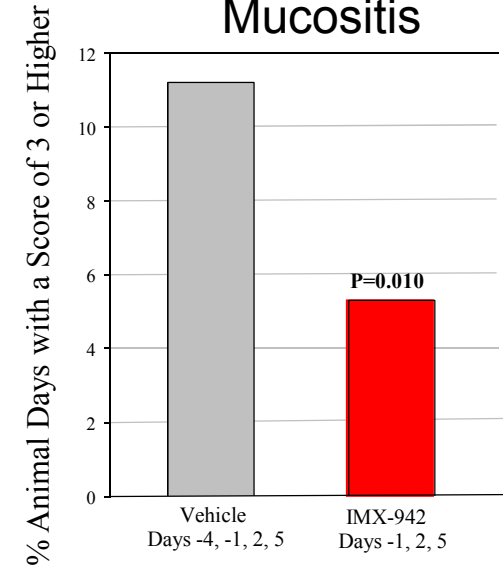
# IMX942 in Chemo-induced Mucositis



## Oral Mucositis Score by Day



## Duration of Severe Mucositis



### Summary:

Statistically significant improvement ( $p \leq 0.01$ ) in oral mucositis scores on 7 of 14 days AND the duration of mucositis was decreased by 50%.

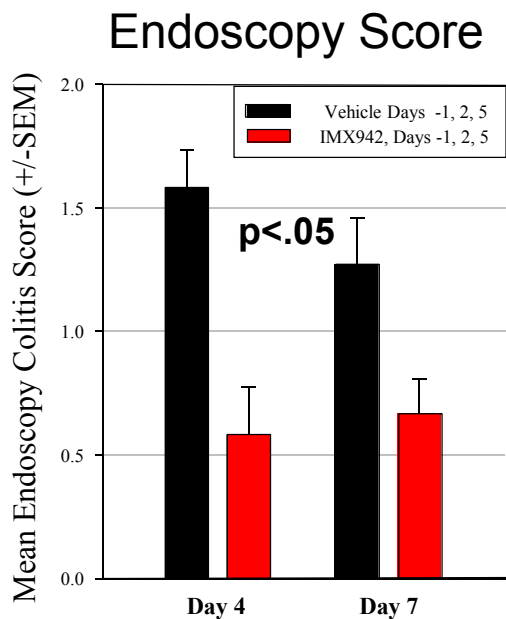
### STUDY DESIGN:

• C3H/H3N Crl mice; N=12/grp; Day -4 & -2: 60mg/kg 5FU IP; Day 0: Chemical burn (4x4 mm sq paper soaked in 50% acetic acid applied for 1 min); Days 1-14: monitor: oral muco score; body wt; blood in stool; clinical obs.; Days 4 & 7: endoscopy

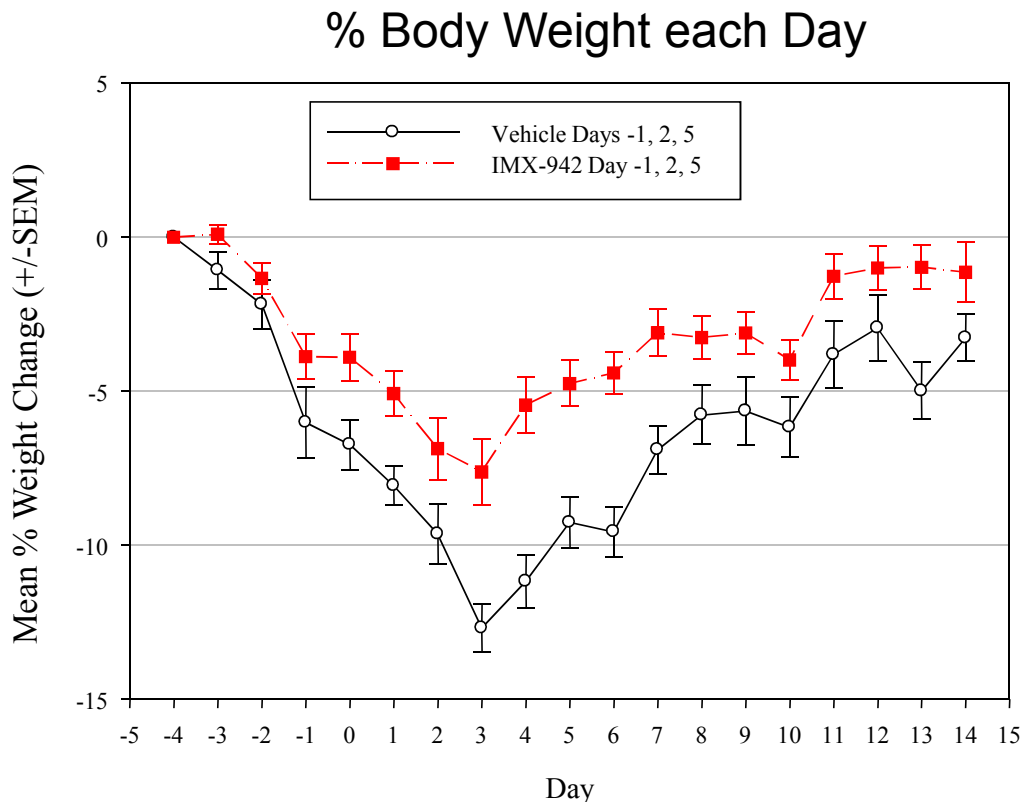




## IMX942 in Mucositis: Study #2



IMX942 TREATMENT:  
Day -1, 2, 5



### Summary:

Trends in clinical endoscopy scores and body weight are consistent with oral mucositis scores. Body weight changes in the IMX942-treated animals show statistically significant differences from vehicle.

### STUDY DESIGN:

• C3H/H3N Crl mice; N=12/grp; Day -4 & -2: 60mg/kg 5FU IP; Day 0: Chemical burn (4x4 mm sq paper soaked in 50% acetic acid applied for 1 min); Days 1-14: monitor: oral muco score; body wt.; blood in stool; clinical bservations; Days 4 & 7: endoscopy.





# Clinical Development





# IMX942 Phase 1 Synopsis



## Single Ascending Dose in healthy volunteers:

- 18-55 years; Target 30% females, non-childbearing potential;
- All cohorts: 6 active and 2 placebo. Blinded / randomised.
- PK and PD sampling;
- Six dose levels planned and completed (0.15 – 8 mg/kg);
- ***Drug well tolerated***

## Multiple Ascending Dose:

- 7- daily doses;
- Cohorts of 6, each with 2 placebo. Blinded / randomised;
- PD & PK evaluations;
- Five cohorts planned and completed (0.5 – 6.5 mg/kg x7);
- ***Drug well tolerated***





## Phase 2 Proof of Concept



### Planning Framework:

- Small (<100 patients) trial to establish PoC for therapeutic impact of IMX942 on innate defense responses in Man;
- Prophylactic setting ideal but need high incidence to keep trial size small;
- Clinical setting to be consistent with preclinical data.





Patients at high risk of severe mucositis:

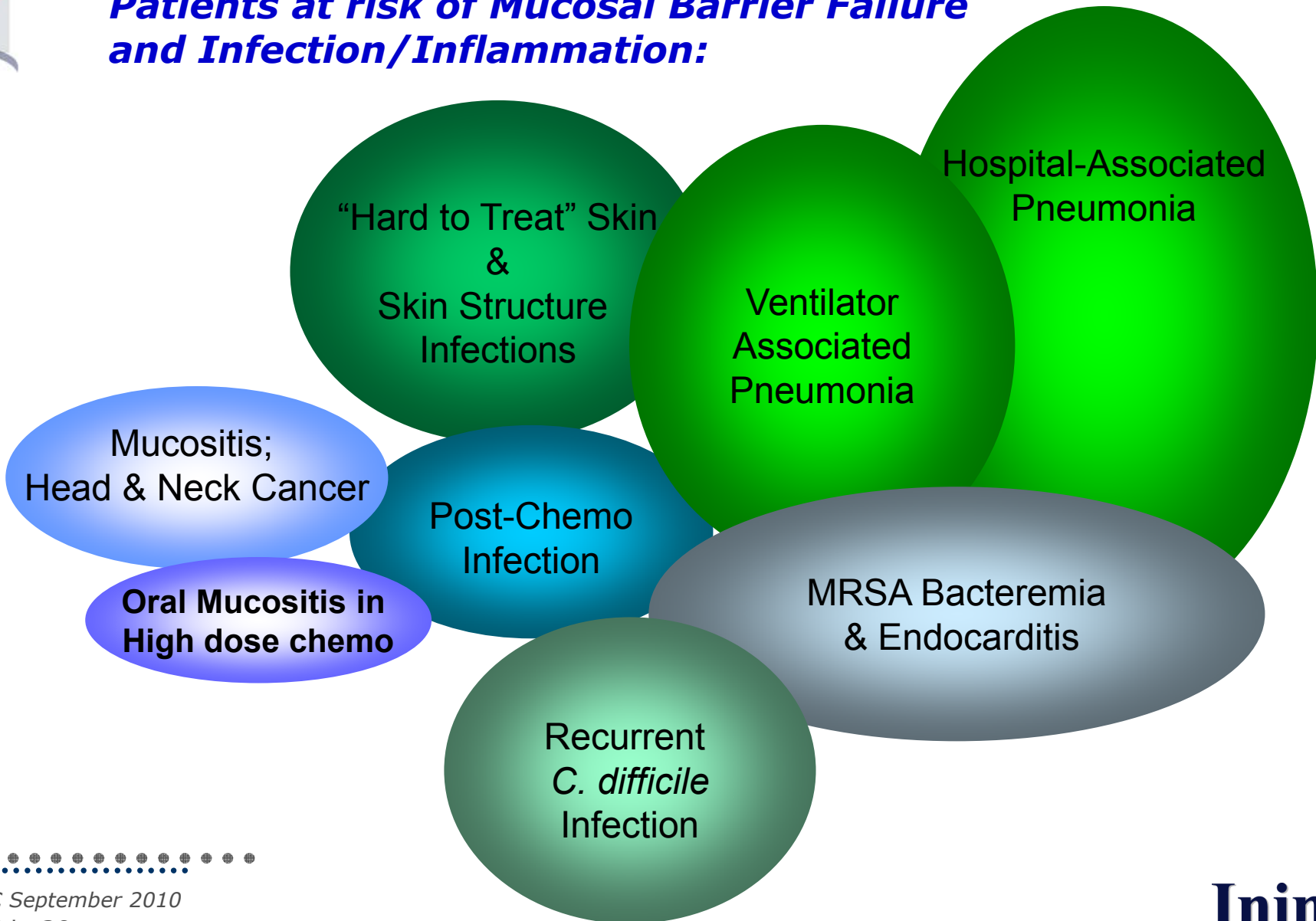
- Autologous SCT with high dose chemo/radiation
- Head & Neck cancer patients receiving chemo/radiation therapy



# IMX942 - Clinic to Market Strategy:



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





# Medical Implications of Innate Defense Regulation



## Scope:

- Control antibiotic-resistant infections
- Inflammation control
- **Patients at high risk of infection:**
  - Recurrent infections *e.g. C.Difficile*
  - Cancer / Stem Cell Transplant
  - Intensive Care Units / Infectious Disease Management
  - Elderly Patients with Immune Senescence
  - High risk infections; *e.g. Biodefense; Malaria*
- **Inflammation:**
  - Control of inflammation while reducing susceptibility to infectious disease





# Inimex

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***Thank You***

