Combination Therapy with SCY-078 and Isavuconazole for Treatment of Experimental Invasive Pulmonary Aspergillosis

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Invasive Aspergillosis

Major cause of morbidity and mortality in patients with

- **Profound / prolonged neutropenia (< 500 µL / > 10 d)**
- **Qualitative defects of phagocytic functions**
  - **Glucocorticosteroid therapy**
  - **Graft-vs-host disease**
  - **Acute graft rejection**
  - **Chronic granulomatous disease**

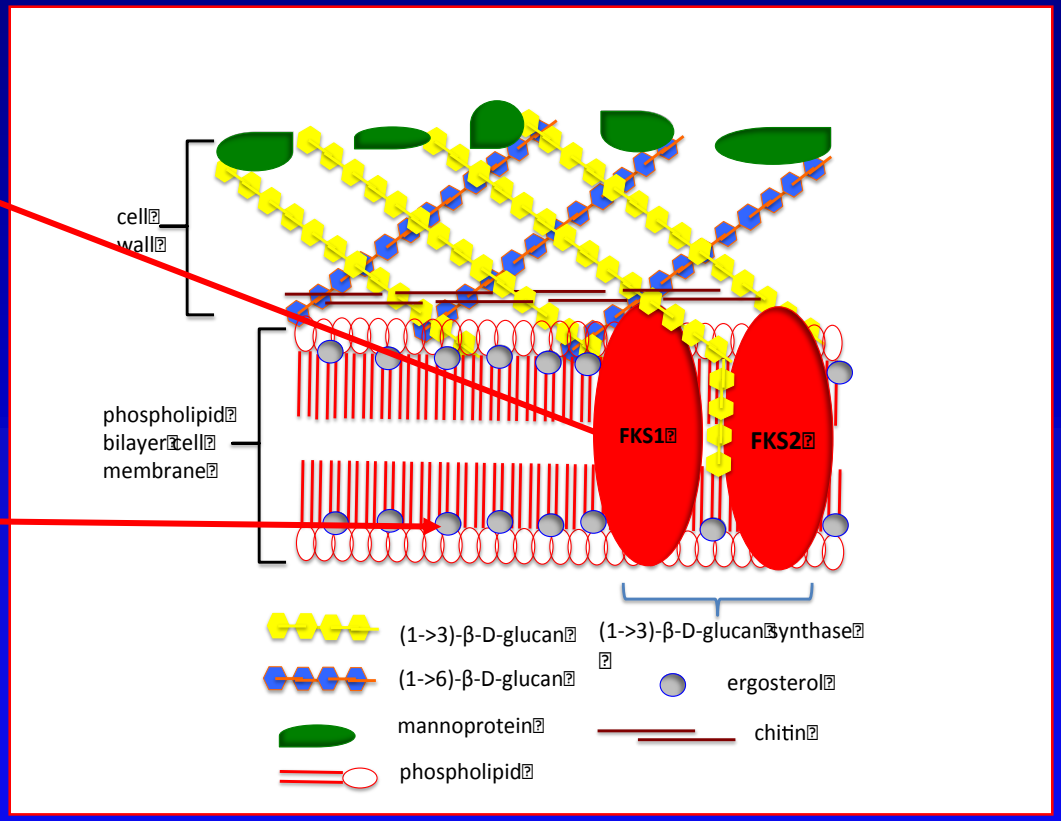
Current Treatment of Invasive Pulmonary Aspergillosis

- Mortality rates of IPA in cancer patients have varied between 13% and 100% depending on the recovery from neutropenia.
- Current treatment of IPA immunosuppressed hosts relies on the administration of antifungal triazoles; however, the overall therapeutic response rate is estimated to be approximately 50-70%.
- Clearly new strategies are needed for more effective treatment of IPA.

Key Targets of Therapy for Aspergillosis

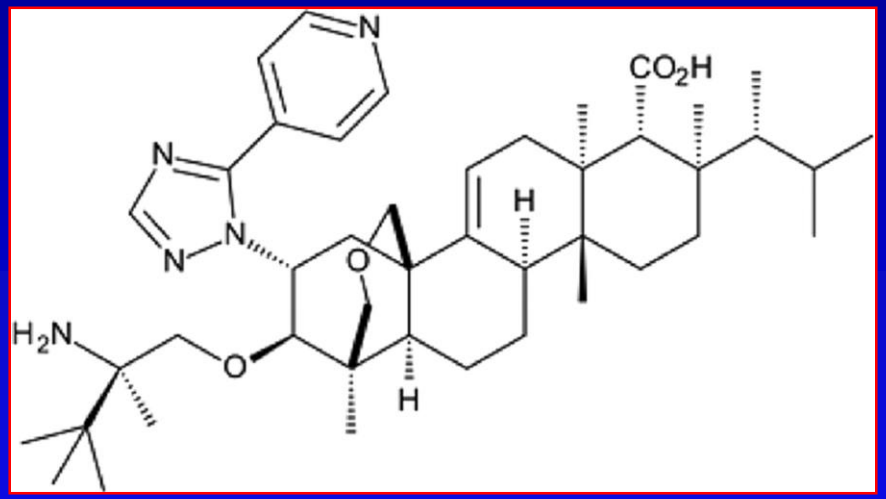
- **Echinocandins** inhibit (1→3)-β-D-glucan synthesis in the fungal cell wall

- **Triazoles act by inhibition of cytochrome p450 14-α-demethylase, blocking synthesis of cell membrane-stabilizing ergosterol**



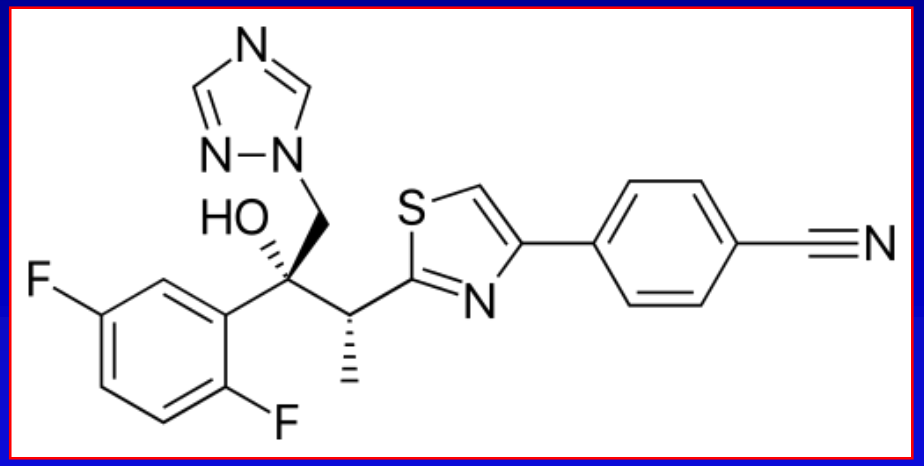
SCY-078

- **SCY-078 is a semisynthetic triterpenoid derivative of the natural product enfumafungin, a** potent inhibitor of fungal (1→3)-β- **D-glucan synthases**
- **This compound is structurally different from the echinocandins**
- **Represents a new class of antifungal agent suitable for oral and IV administration**
- **Even though it has the same molecular target as the echinocandins, it is structurally distinct and potentially effective against echinocandin-resistant strains**



Isavuconazole

- **Active agent – Isavuconazole**
- **Inhibits fungal cell membrane biosynthesis through inhibition of ergosterol formation at the level of lanosterol C14-demethylase**
- **Wide** *in vitro* **and** *in vivo* **antifungal activity, including** *Candida* **spp. and** *Aspergillus* **spp.**



Combination Therapy of IPA

- **Based on previous combination studies between echinocandins and antifungal triazoles we hypothesized that this combination may result in a synergistic interaction *in vivo*.**

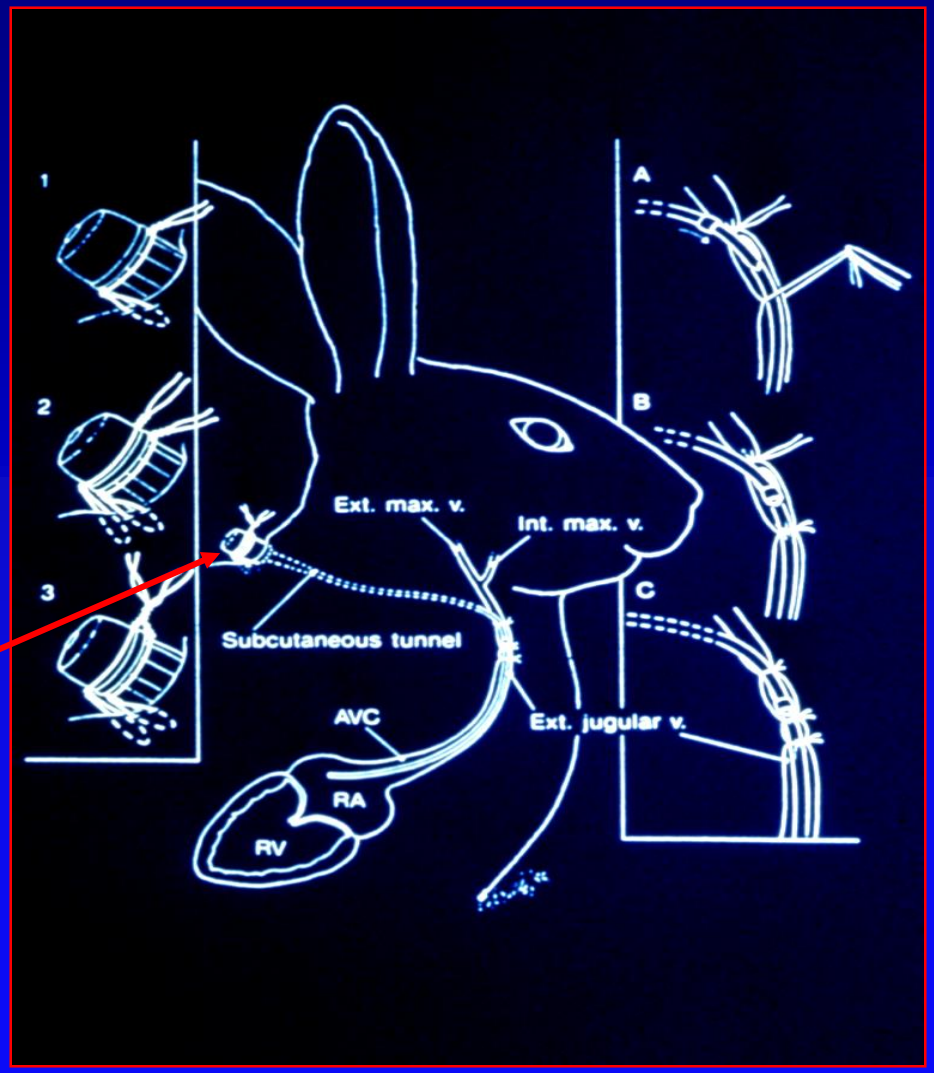
Combination Therapy of IPA

- **We, therefore studied the *in vivo* efficacy of the new extended-spectrum antifungal SCY-078 in combination with isavuconazole in treatment of experimental IPA in persistently neutropenic rabbits.**

- **The data from this study would provide an experimental rationale and establish a foundation for further clinical evaluation.**

Well Described Persistently Neutropenic Rabbit Model of IPA

- Female New Zealand white rabbits weighing 2.8 to 3.6 kg at the time of inoculation were used in this study.
- Atraumatic vascular access was established in each rabbit by the surgical placement of a Silastic tunneled central venous catheter.



Materials and Methods

- *Aspergillus fumigatus* **- NIH isolate 4215 (ATCC No. MYA-1163)**
- **Endotracheal inoculation, which was performed on day 2 of the experiments**
- **Inoculum of 1.25 x 10^8 conidia of** *A. fumigatus* **(250 to 350 µL)**
- **Induction and maintenance of neutropenia**
  - **Cytarabine (Ara-C) 525 mg/m^2 - (days 1-5)**
  - **Cytarabine (Ara-C) 484 mg/m^2 - (days 8-9,13-14)**
  - **Methylprednisolone - 5 mg/kg (days 1 and 2)**

Materials and Methods

- **Antibiotics**
  - **ceftazidime (75 mg/kg given IV twice daily)**
  - **gentamicin (5 mg/kg given IV every other day)**
  - **vancomycin (15 mg/kg given IV daily)**
  - **were administered daily from day 4 of chemotherapy until study completion for prevention of opportunistic bacterial infections during neutropenia.**

- **All rabbits received 50 mg/L of vancomycin in drinking water to prevent antibiotic associated diarrhea due to *Clostridium spiriforme*.**

- **White blood cell counts**
  - **total leukocyte counts were measured by Coulter counter twice weekly.**

Experimental Study Groups

- **Untreated Controls (UC)**
- **SCY-078:** **- 2.5 mg/kg/day IV (SCY2.5)**
  - 7.5 mg/kg/day IV (SCY7.5)
- **Isavuconazole (ISA):** **- 40 mg/kg/day PO (ISA40)**
- **Combination:** **- SCY2.5+ISA40**
  - SCY7.5+ISA40

✧ **Antifungal therapy was initiated 24 h after inoculation and continued throughout the course of the experiment for 12 days.**

Panel of Outcome Variables

- **Survival**
- **Pulmonary lesion scores**
- **Lung weights**
- **Residual fungal burden (quantitative cultures)**
- **Serum galactomannan antigenemia (GMI) detected by the double sandwich enzyme-linked immunosorbent assay (ELISA)**
- **(1→3)-β-D-glucan levels detected by *Limulus* amebocyte lysate assay**

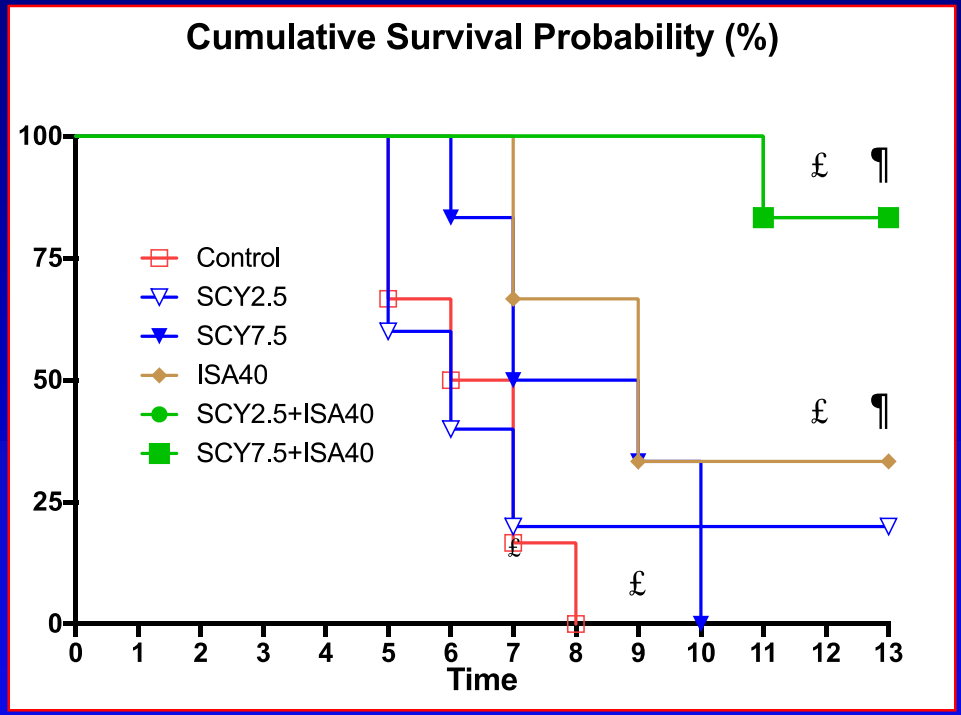
Statistical Analysis

- Comparisons between the groups were performed by analysis of variance (ANOVA) with Bonferroni's correction for multiple comparisons or the Mann-Whitney U-test, as appropriate.
- Survival was plotted by Kaplan-Meier analysis. Differences in survival of treatment groups and untreated controls were analyzed by log-rank test.

Results

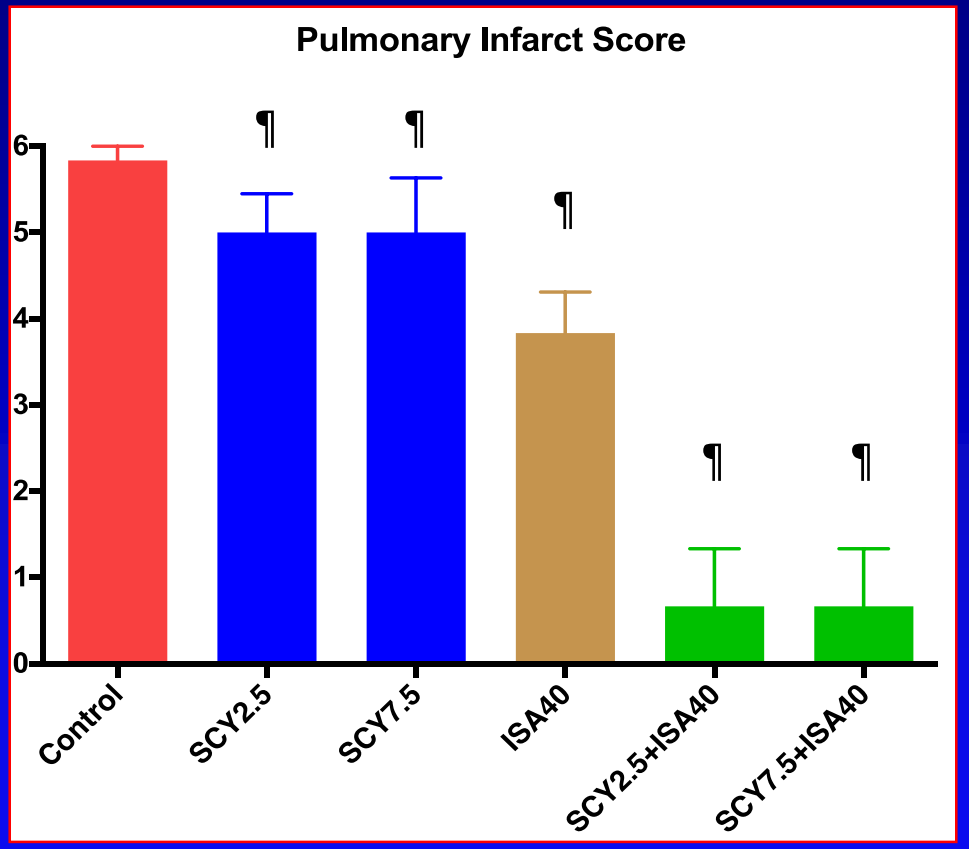
Survival Probability

- ¶, p<0.05, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40
- £, p<0.01, prolonged survival of rabbits treated with SCY2.5+ISA40, SCY7.5+ISA40, ISA40 alone in comparison to that of UC



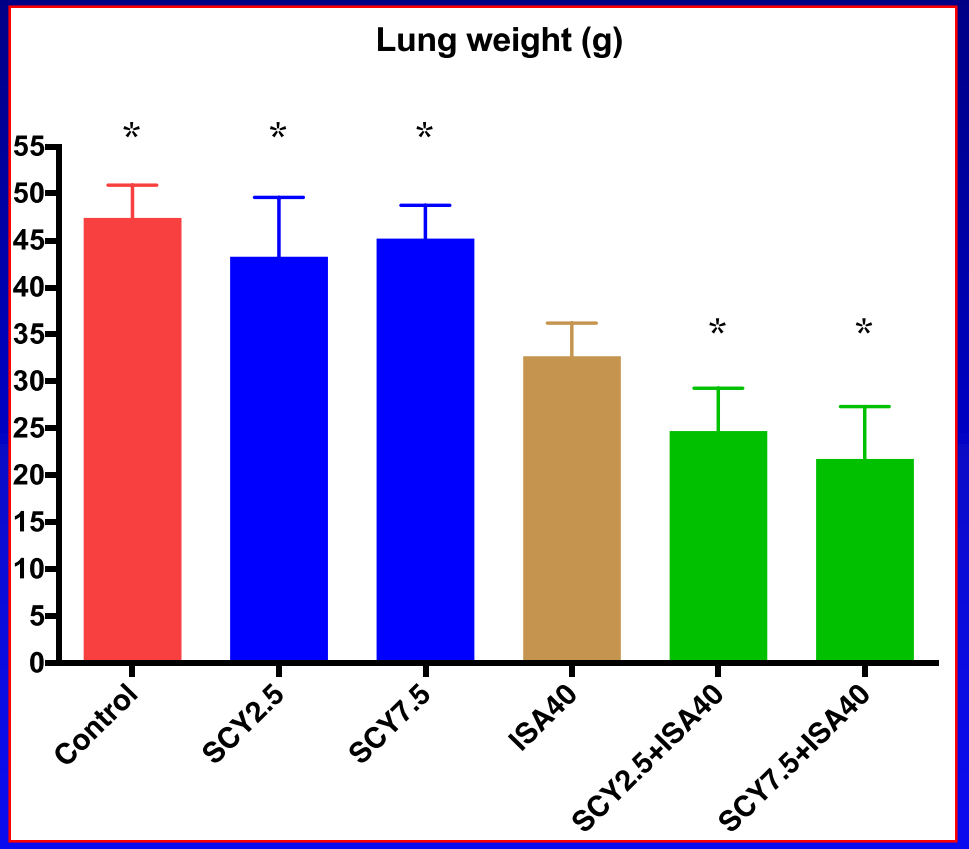
Pulmonary Infarct Score

- ¶, p<0.01, decreased infarct scores in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40



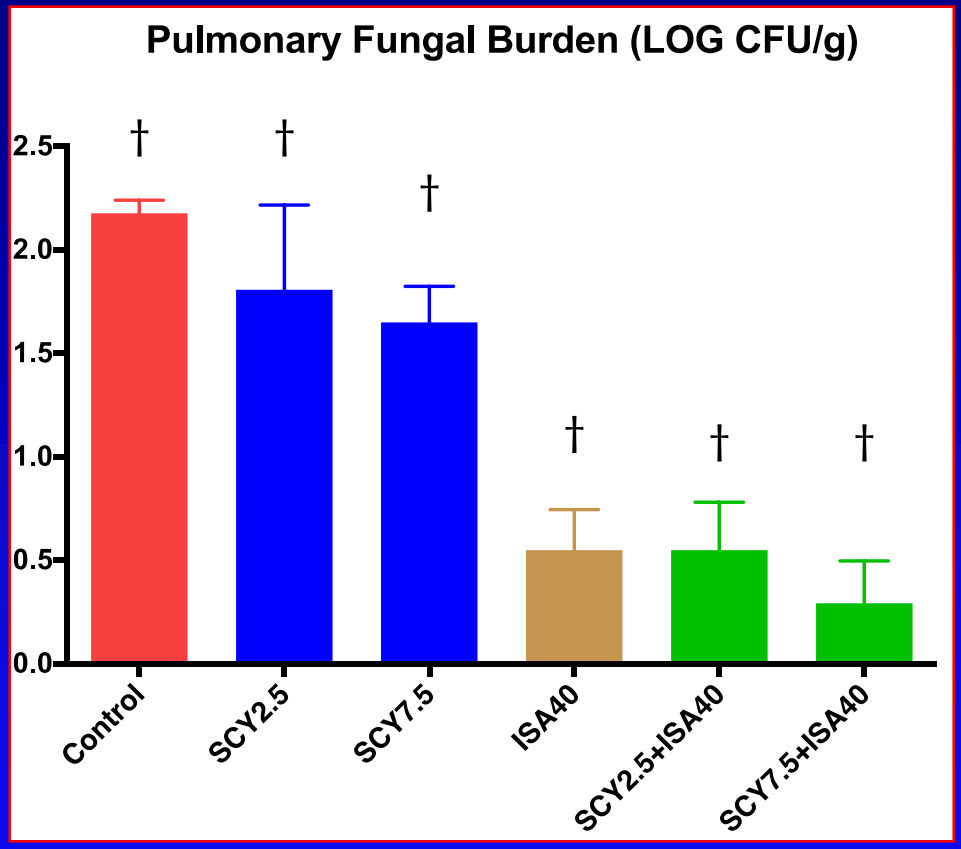
Lung Weight

- *, p<0.05, decreased lung weights in SCY2.5+ISA40 and SCY7.5+ISA40 -treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and untreated controls



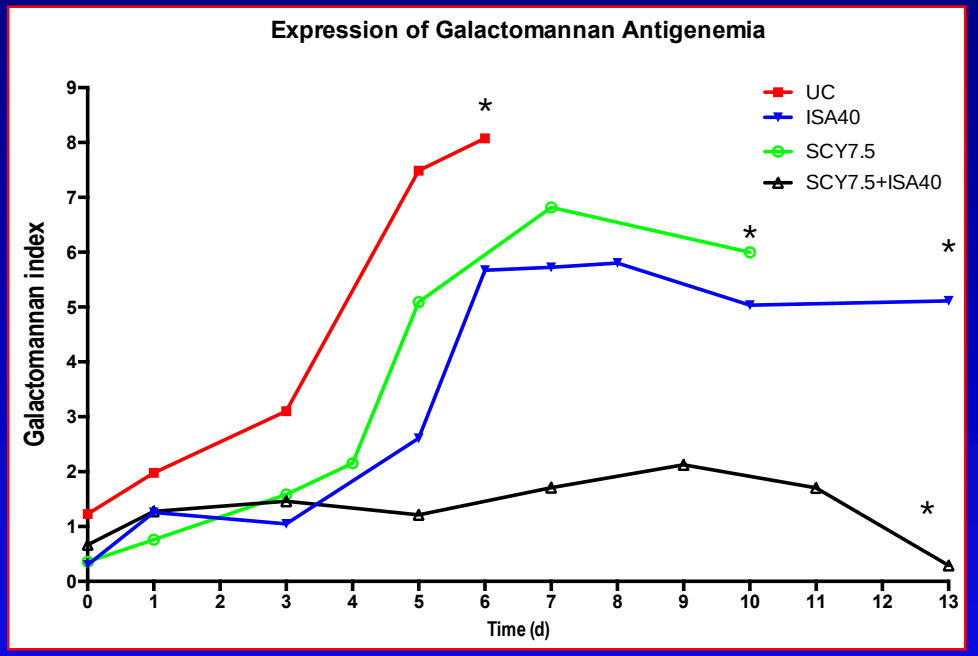
Residual Fungal Burden (log CFU/G)

- †, p<0.01, decreased residual **fungal burden in SCY2.5+ISA40 and SCY7.5+ISA40, and ISA40 - treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and untreated controls**



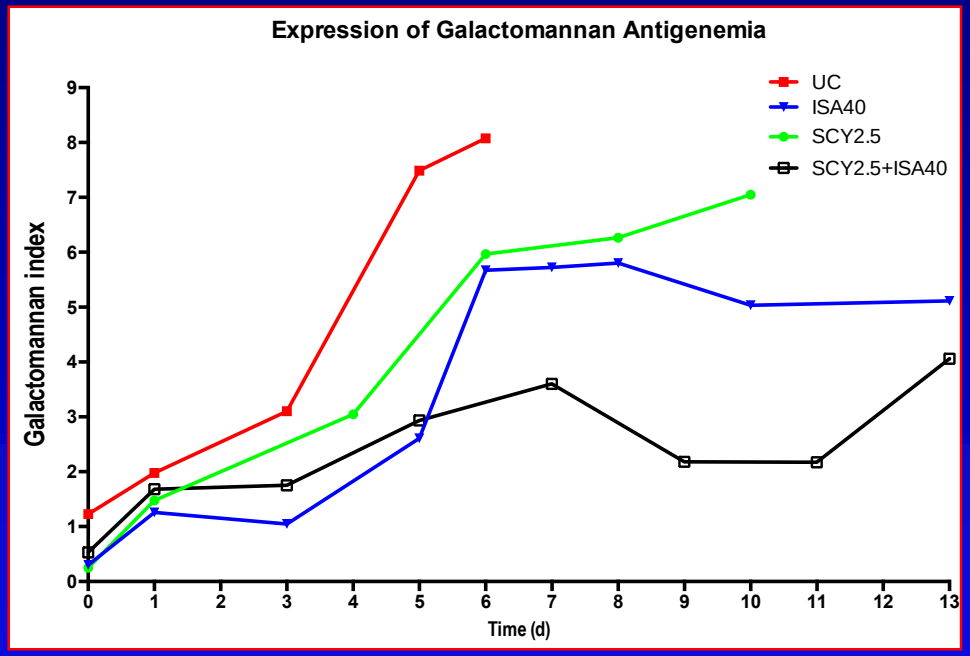
Expression of Galactomannan Antigenemia

- *p<0.05; lower GMI in rabbits treated with combination regiment of SCY7.5+ISA40 in comparison to that of single therapy of SCY7.5, ISA40, and untreated controls



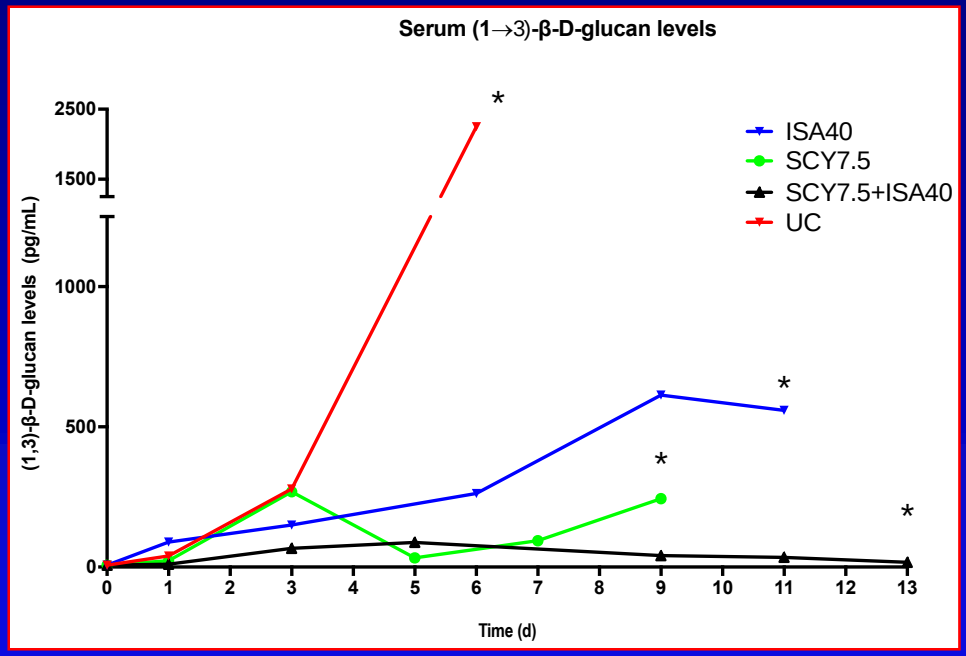
Expression of Galactomannan Antigenemia

- There was lower GMI in rabbits treated with combination regiment of SCY2.5+ISA40, but did not reach significant differences in comparison to that of single drug therapy



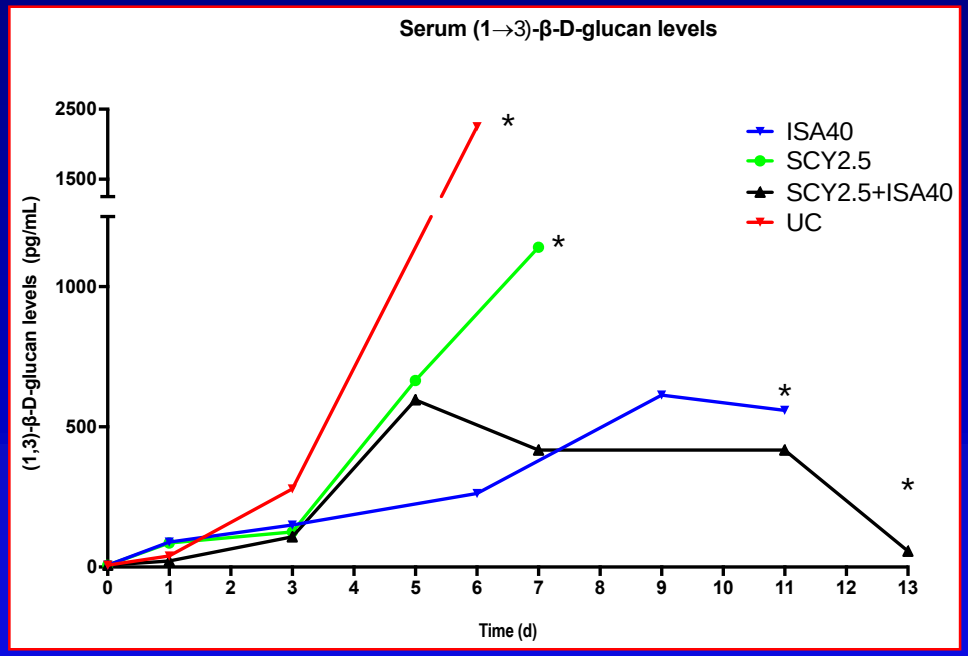
Serum (1→3)-β-D-glucan Levels

- ***p<0.05; decrease of serum (1→3)-β-D-glucan levels in SCY7.5+ISA40, SCY7.5, or ISA40 -treated rabbits in comparison to that of untreated controls**



Serum (1→3)-β-D-glucan Levels

- ***p<0.05; decrease of serum (1→3)-β-D-glucan levels in rabbits treated with combination regiment of SCY2.5+ISA40 in comparison to that of single therapy of SCY2.5 and untreated controls**



Conclusions

- Rabbits treated with the combination of SCY plus isavuconazole demonstrated
  - prolonged survival,
  - decreased pulmonary injury,
  - reduction of residual fungal burden, and
  - lower serum GMI

  in comparison to those of single therapy of SCY and/or isavuconazole
- These findings provide an experimental rationale and establish a foundation for clinical evaluation of the combination of SCY-078 and isavuconazole for treatment of IPA

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