Non-neutropenic animal models of IPA – RAT

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Basic Parameters of the Rat Model

✓ 250-300g Male Sprague Dawley Rats

✓ Housed in autoclaved HEPA filter cages with sterile food and water
Basic Parameters of the Rat Model

- 250-300g Sprague Dawley Rats
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Basic Parameters of the Rat Model

- 250-300g Male Sprague Dawley Rats
- Housed in autoclaved HEPA filter cages with sterile food and water
- Administered Baytril (enrofloxacin) prophylaxis in drinking water at 5ppm starting on day -5
- Infection by aerosol on day 0 with A. fumigatus A1163
- Endpoints include weight loss (>25%), respiratory distress, bloody nasal discharge, hypothermia
Basic Parameters of the Rat Model

<table>
<thead>
<tr>
<th>Days</th>
<th>200mg/kg Cortisone acetate</th>
<th>150mg/kg Cortisone acetate</th>
<th>Infection by aerosol</th>
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</table>

- Antinflammatory Prophylaxis
  - 200mg/kg on day -4
  - 150mg/kg on days -2, 0 and +2
- Antibacterial Prophylaxis in drinking water
Non-Neutropenic Rat Model of IPA

Survival non-neutropenic rats

Number of survivors

Days post infection

- Posaconazole 5mg/kg
- Vehicle
- Uninfected
Non-Neutropenic Rat Model of IPA

Weight Change non-neutropenic rats

Average Weight (g)

Day of Infection

-6 -4 -2 0 2 4 6 8 10

Posaconazole 5mg/kg
Vehicle
Uninfected
Non-Neutropenic Rat Model of IPA
The lung pathology following infection in non-neutropenic hosts is dominated by white cell recruitment resulting in loss of lung function.
Lung Burden Progression (qPCR) (Neutropenic vs Non-Neutropenic)

Average Log CE/gm

Lung (NT)

Average Log CE/gm

Lung (NON)

Hours Post-Infection

4h 24h 48h 72h 96h
BAL Burden Progression (qPCR) (Neutropenic vs Non-Neutropenic)

Average Log CE/ml BAL (NT)

Average Log CE/ml BAL (NON)

Hours Post-Infection

4h 24h 48h 72h 96h
GMI (Neutropenic Vs Non-Neutropenic)

Days Post-Infection

GMI

GMI (NT)

GMI (NON)
Summary

• The non-neutropenic model is characterised by white cell recruitment and low levels of tissue invasion.

• 100% mortality in untreated rats (>5 x 10^8 cfu/ml)

• Large numbers of *Aspergillus* can be recovered in BAL

• It is possible to monitor disease progression using galactomannan and qPCR as a surrogate marker but levels remain low

• Posaconazole is effective but amphotericin and caspofungin are ineffective