Diagnostics of Invasive Aspergillosis: From Experimental Models to Clinical Evaluation.

Chronic Colonization Model

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Aspergillus Colonization

- Common in chronic airway disease
- Up to 50% of Cystic Fibrosis patients
- 5-10% develop hypersensitivity (ABPA)
- Yet all pts manifest decline in lung function
- New diagnostics should distinguish colonization from infection
Update

- At last IAAM meeting presented our proof of principle data for a model of colonization
- Have now extended studies to 28 days
- Detailed comparison with controls
- Characterizing the inflammatory response
- Testing for hypersensitivity
Colonization model

- Agar bead encapsulated conidia
- Intratracheal injection
- C57BL/6J
- Histology
- GM assay
Histopathology of lungs

Uninfected airways

Sterile beads

A. fumigatus beads
Pulmonary Galactomannan Content

![Graph showing relative fungal burden over days 14, 21, and 28 for AF conidia and AF beads.]

IAAM
INVASIVE ASPERGILLOSIS ANIMAL MODELS

AsTeC
ASPERGILLUS TECHNOLOGY CONSORTIUM
Cellular Inflammation (BAL)

- Total Cell Count
- % Neutrophils

A. fumigatus beads • Sterile beads • A. fumigatus only

A. fumigatus beads • Sterile beads • A. fumigatus only
Cytokines

- Assayed cytokine profile in lung homogenates and BAL fluid at 14, 21 and 28 days
- Inflammatory cytokines assayed using Luminex cytometric bead array (20 cytokines and chemokines)
Inflammatory Markers (d14)

![Graph showing concentration of inflammatory markers. The x-axis represents various cytokines and chemokines: IFN-gamma, IL-12, IL-17, IL-2, IL-1 alpha, IL-1 beta, IP-10, MIG, MIP-1 alpha, TNF-alpha. The y-axis represents concentration (pg/mL) from 0 to 2000. Different bars indicate different conditions: Bead, AF only, Uninfected, AF bead. The graph highlights differences in concentration levels among these conditions.]

Cytokines/chemokines:
- IFN-gamma
- IL-12
- IL-17
- IL-2
- IL-1 alpha
- IL-1 beta
- IP-10
- MIG
- MIP-1 alpha
- TNF-alpha

IAAM: INVASIVE ASPERGILLLOSIS ANIMAL MODELS
AsTec: ASPERGILLUS TECHNOLOGY CONSORTIUM
No other significant increase in cytokines including:
- IL-10, IL-4, IL-5, IL-6, IL-13
- GM-CSF, VEGF

Slight induction of KC

BAL specimens mirrored these results but with lower absolute levels detected

Only significant at d14 - ? Too late
IgE

![IgE graph]

- **Uninfected**
- **Beads alone**
- **A. fumigatus conidia**
- **A. fumigatus Beads**

<table>
<thead>
<tr>
<th>Days</th>
<th>IgE concentration (ng/mL)</th>
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<tbody>
<tr>
<td>Day 14</td>
<td>100</td>
</tr>
<tr>
<td>Day 21</td>
<td>800</td>
</tr>
<tr>
<td>Day 28</td>
<td>400</td>
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</tbody>
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**Day 14**: 
- Uninfected: 100 ng/mL
- Beads alone: 200 ng/mL
- A. fumigatus conidia: 100 ng/mL
- A. fumigatus Beads: 400 ng/mL

**Day 21**: 
- Uninfected: 800 ng/mL
- Beads alone: 200 ng/mL
- A. fumigatus conidia: 200 ng/mL
- A. fumigatus Beads: 600 ng/mL

**Day 28**: 
- Uninfected: 400 ng/mL
- Beads alone: 200 ng/mL
- A. fumigatus conidia: 200 ng/mL
- A. fumigatus Beads: 400 ng/mL
Future Plans

- Inflammatory markers at D7
- Evaluate existing serum markers
  - Serum GM
  - ß-d-glucan course
- Pulmonary function and airway hyper-reactivity