AsTeC and IAAM Project overview

Thomas F. Patterson, MD
IAAM PI

John Wingard, MD
AsTeC Co-PI
Invasive Aspergillus Animal Models (IAAM)
NIH-NIAID-N01-AI-30041

Thomas F. Patterson, MD
IAAM Principal Investigator

Professor of Medicine
Chief, Division of Infectious Diseases
Director, San Antonio Center for Medical Mycology
The University of Texas Health Science Center at San Antonio
Invasive Aspergillus Animal Models (IAAM)

- Who are we?
- What do we do?
  - Establishment of standard animal models
  - Address investigator-initiated key questions
  - Service funded by NIAID without cost to investigator
- Key questions for *Aspergillus* diagnostics
  - Pre-clinical evaluation
    - New diagnostic methods or targets
    - Standardization of current diagnostic modalities
  - Collaboration with AsTec
NIAID/DMID
Project Officer
Rory Duncan
Dennis Dixon

IA Animal Models (IAAM)
Principal Investigator
Tom Patterson
Steering Committee
Denning, Filler, May, Nierman, Walsh
- Reviews
- Guides

Central Unit
Administrative Core:
Rick Kirkpatrick/Michelle Bailey

Expert Advisory Panel
A. Casadevall (Chair)
J. Rhodes

Functional Components
(Working Groups)
Patterson, Filler, Sheppard,
Denning, Wickes, Wiederhold, Pollock
- Proposes
- Implements
- Develops
- Delivers
## Animal Models: Key Features

- **Mice & larger animals: guinea pigs/rats**
  - Pulmonary (aerosol) challenge

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tr>
<td>Neutropenia/non-neutropenic; other immunosuppression</td>
<td>Continuous blood sampling for surrogate markers</td>
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<tr>
<td>Differentiate: exposure/colonization/infection</td>
<td>Quantify tissue burden (2 methods)</td>
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<td>Standardized</td>
<td>Local/disseminated infection</td>
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<td>Telemetry/IR fever curves</td>
<td>Genomic approach to molecular diagnosis</td>
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IAAM: Standard Operating Procedures

www.sacmm.org/iaam.html
Key Questions

Accept/Modify/Reject

Qualified investigator/Key question

Steering Committee

Expert Panel

IAAM Project Officer (Rory Duncan)

IAAM Principal Investigator (Thomas Patterson)

IAAM Executive Committee (Patterson, Filler, Denning)
<table>
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<tr>
<th><strong>Key Questions</strong></th>
<th><strong>Calcineurin pathway in IA</strong></th>
<th><strong>Duke</strong></th>
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<td><strong>W. Steinbach</strong></td>
<td><strong>Role of ( glIP ) in gliotoxin synthesis</strong></td>
<td><strong>Duke</strong></td>
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<tr>
<td><strong>R. Cramer</strong></td>
<td><strong>Aspergillus virulence determinants</strong></td>
<td><strong>U Idaho</strong></td>
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<td><strong>B. Miller</strong></td>
<td><strong>Genome-wide expression to echinocandins for ( Af )</strong></td>
<td><strong>UTHSCSA</strong></td>
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<td><strong>N. Wiederhold</strong></td>
<td><strong>In vivo gene expression of ( Af )</strong></td>
<td><strong>U Florida</strong></td>
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<td><strong>C. Clancy</strong></td>
<td><strong>Polarized Hyphal Growth in ( Af )</strong></td>
<td><strong>U Nebraska</strong></td>
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<tr>
<td><strong>S. Harris</strong></td>
<td><strong>Microfluidic device for rapid pathogenic fungal diagnosis</strong></td>
<td><strong>U Michigan</strong></td>
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<td><strong>R. Akins/J. Sobel</strong></td>
<td><strong>Genetic determinants of ( Af ) susceptibility</strong></td>
<td><strong>Duke</strong></td>
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<tr>
<td><strong>A. Zaas</strong></td>
<td><strong>Germination in ( Af )</strong></td>
<td><strong>Georgetown</strong></td>
</tr>
<tr>
<td><strong>R. Calderone</strong></td>
<td><strong>Rho GTPases in polar growth of ( Af )</strong></td>
<td><strong>U Georgia</strong></td>
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<tr>
<td><strong>M. Momany</strong></td>
<td><strong>Development of Aspergillus vaccine</strong></td>
<td><strong>SUNY/Buffalo</strong></td>
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<tr>
<td><strong>B. Segal</strong></td>
<td><strong>New Diagnostics for ( Af )</strong></td>
<td><strong>New Jersey</strong></td>
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<tr>
<td><strong>D. Perlin</strong></td>
<td><strong>Prophylactic and therapeutic Aspergillus vaccines</strong></td>
<td><strong>Mycologics, Inc, Aurora, CO</strong></td>
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<tr>
<td><strong>C. Selitrennikoff</strong></td>
<td><strong>QPCR for diagnostics of ( A. fumigatus )</strong></td>
<td><strong>Merck and Co., Inc, Rahway, NJ</strong></td>
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<tr>
<td><strong>C. Douglas</strong></td>
<td><strong>QPCR for diagnostics of ( A. fumigatus )</strong></td>
<td><strong>University of Wuerzburg, Germany</strong></td>
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<tr>
<td><strong>J. Loeffler</strong></td>
<td><strong>Real-Time PCR assay to detect ( A. fumigatus )</strong></td>
<td><strong>Glasgow Caledonian University, Glasgow, Scotland</strong></td>
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## Key Questions

<table>
<thead>
<tr>
<th>Authors</th>
<th>Research Focus</th>
<th>Institution/Location</th>
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<tr>
<td>C. Cray</td>
<td>Murine model of Pulmonary invasive Aspergillosis</td>
<td>University of Miami Miller School of Medicine, Miami FL</td>
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<tr>
<td>D. Sheppard</td>
<td>GM diagnostics in A. fumigatus</td>
<td>McGill University, Montreal Canada</td>
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<tr>
<td>B. Wickes</td>
<td>PCR diagnostics in A. fumigatus</td>
<td>UTHSCSA</td>
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<tr>
<td>S. Filler / D. Sheppard</td>
<td>Host response to invasive aspergillosis</td>
<td>UCLA - Harbor / McGill University</td>
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<tr>
<td>S. Baker</td>
<td>Proteomics approach to A. fumigatus detection</td>
<td>Pacific Northwest National laboratory, Richland, WA</td>
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<tr>
<td>R. Cramer</td>
<td>Metabolomics approach to A. fumigatus detection</td>
<td>Duke</td>
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<tr>
<td>N. Wiederhold</td>
<td>Chitin assay development for pulmonary aspergillosis</td>
<td>UTHSCSA</td>
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<tr>
<td>N. Wiederhold</td>
<td>Effect of paradoxical effect on diagnosis of IPA during echinocandin therapy</td>
<td>UTHSCSA</td>
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<tr>
<td>A. Vallor</td>
<td>Utility of serum vs whole blood for assessment of fungal burden in IPA</td>
<td>UTHSCSA</td>
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<tr>
<td>S. Filler / D. Sheppard</td>
<td>Effect of different aspergillus isolates on experimental murine IPA</td>
<td>UCLA - Harbor / McGill University</td>
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<tr>
<td>M. Del Poeta</td>
<td>Detection of anti-glucosylceramide antibody in an Invasive Aspergillosis</td>
<td>Medical Univ. Of S. Carolina, Charleston, SC</td>
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<tr>
<td>R. Lewis</td>
<td>Animal models for diagnosis and treatment (Use of SOPs)</td>
<td>MD Anderson, Houston TX</td>
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<tr>
<td>G. Fuji</td>
<td>Viatrode technology for Aspergillus diagnostics</td>
<td>Molecular GPS</td>
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<tr>
<td>M. Moore</td>
<td>Siderophores in invasive aspergillosis</td>
<td>Simon Fraser University, Burnaby, BC, Canada</td>
</tr>
<tr>
<td>T. Sweeney</td>
<td>ABI P in an inhalational model of aspergillosis (Use of SOPs)</td>
<td>Nektar Therapeutics, San Carlos, CA</td>
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### Key Questions

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<tr>
<th>Name</th>
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<td>D. Sheppard</td>
<td>GM diagnostics in A. fumigatus</td>
<td>McGill University, Montreal Canada</td>
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<td>W. Furmaga / A Fothergill</td>
<td>Proteomics Approach to Aspergillus Diagnosis</td>
<td>UTHSCSA</td>
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<tr>
<td>S. Kleiboeker</td>
<td>Proprietary qPCR approach to Aspergillus diagnostics</td>
<td>ViraCorp</td>
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<tr>
<td>N. Wiederhold</td>
<td>Serum Beta-Glucan as a Diagnostic Tool</td>
<td>UTHSCSA</td>
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<tr>
<td>C. O'Sullivan</td>
<td>Mass Spectrometry to detect and diagnose Aspergilosis</td>
<td>Barts and the London NHS Trust, London UK</td>
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<tr>
<td>C. Thornton</td>
<td>Lateral flow device for the rapid serodiagnosis of IA</td>
<td>University of Exeter, UK</td>
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<tr>
<td>P. Donneley / J. Loeffler</td>
<td>Extraction methods for PCR diagnostics of A. fumigatus</td>
<td>University of Wuerzburg, Germany</td>
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<tr>
<td>A. Caliendo</td>
<td>Fungal DNA Stability</td>
<td>AsTeC - Emory University</td>
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<td>Extraction methods for PCR diagnostics of A. fumigatus</td>
<td>AsTeC - Emory University</td>
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<td>S. Bauman</td>
<td>Antigen detection for Aspergillus diagnosis</td>
<td>Immuno-Mycologics Inc.</td>
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<tr>
<td>V. Slepnev</td>
<td>Multiplexed PCR for Aspergillus diagnosis</td>
<td>Primera Biologics</td>
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<tr>
<td>S. Glickman</td>
<td>pulsed laser optoacoustic spectroscopy</td>
<td>UTHSCSA</td>
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<tr>
<td>J. Schuster</td>
<td>GC / Mass spec</td>
<td>Teotten Diagnostics</td>
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<tr>
<td>D. Himsworth / T. Bright</td>
<td>Fungal Pathogen Detection Panel</td>
<td>Luminex Molecular Diagnostics</td>
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<tr>
<td>N. Clancey</td>
<td>Aspergillus Diagnostics</td>
<td>AsTeC - U. Pittsburgh</td>
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Future Directions: Invasive Aspergillosis Animal Models (IAAM)

- Deliverables/Model refinement
  - SOPs online
  - Role of host responses
  - Distinction of colonization vs disease
  - Development of DNA standard for calibration
  - Impact of sample types, collection, storage
- Diagnostic development with AsTec
  - Pre-clinical support for diagnostics
  - Industry partners
  - Community awareness/interaction
Clinical Laboratory Diagnostics for Invasive Aspergillosis

John Wingard, MD
AsTeC Principal Investigator
Barbara Alexander, MD
AsTeC Co-PI

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HHSN266200700023C
5/31/07-5/30/14
Goals of AsTeC Project

- Establish & maintain repository of clinical samples from pts at high risk for &/or infected with Invasive Aspergillosis

- Establish a network of laboratories compliant with Good Laboratory Practices to assess new diagnostic assays for Invasive Aspergillosis

IA = Invasive Aspergillosis
Why is this important?

- Mortality from IA is substantial
- Making the diagnosis is difficult
  - Diagnosis not confirmed by DRC in 26% of pts in large IA treatment trial
  - Cultures negative in half of histologically proven cases
- Other pathogens produce similar clinical syndromes
- Current diagnostics have limitations
- Starting treatment early is associated with better outcomes
- Evaluating treatment responses is difficult
AsTeC Project

Project Officers
Alec Ritchie
C. Gale Auguste
Dennis Dixon

Scientific Working Group
David Hillyard
Sally Selepk
Paul Verweij

NIH/NIAID: #N01-AI-70023
AsTeC
Sampling Sites:

Dr. John Wingard
Principal Investigator

Dr. Barbara Alexander
Co-Principal Investigator

Clinical Sample Repository
Dr. Wingard

University of Florida
Dr. Wingard

Duke University
Dr. Alexander

BWH/DFCI
Dr. Baden

Laboratory Testing
Dr. Alexander

Emory University
Dr. Caliendo
Molecular Tests

Univ. of Manchester
Dr. Denning
Molecular Tests

Univ. of Pittsburgh
Drs. Nguyen & Clancy
Antibody Tests

Miravista Laboratory
Dr. Wheat
Antigen Tests
Galactomannan

Duke University
Dr. Alexander
Antigen, Antibody,
& Molecular Tests
Glucan

IAAM
INVASIVE ASPERGILLLOSIS ANIMAL MODELS

AsTeC
ASPERGILLUS TECHNOLOGY CONSORTIUM
AsTeC
Laboratories:

Dr. John Wingard
Principal Investigator
Dr. Barbara Alexander
Co-Principal Investigator

Clinical Sample Repository
Dr. Wingard

University of Florida
Dr. Wingard

Duke University
Dr. Alexander

BWH/DFCI
Dr. Baden

Laboratory Testing
Dr. Alexander

Emory University
Dr. Caliendo
Molecular Tests

Univ. of Manchester
Dr. Denning
Molecular Tests

Univ. of Pittsburgh
Drs. Nguyen & Clancy
Antibody Tests

Miravista Laboratory
Dr. Wheat
Antigen Tests
Galactomannan

Duke University
Dr. Alexander
Antigen, Antibody, & Molecular Tests
Glucan

IAAM
INVASIVE ASPERGILLLOSIS ANIMAL MODELS

AsTeC
ASPERGILLUS TECHNOLOGY CONSORTIUM
Interactions between AsTeC & I AACAM

- Divided responsibilities for testing diagnostics
  - Early work with manufacturers: IAAM
  - Preparatory for licensure: AsTeC
- IAAM will provide standards for repeatability and reproducibility testing
- Regular conference calls
- Coordinated meetings
Interactions between AsTeC & IAAM

- Interactive work to date
  - Validation of storage conditions
  - Contamination testing of collection vials
  - Calibrator development
Websites

- IAMM
  - www.sacmm.org/iaam.html
- AsTeC
  - www.astecdiagnostics.org
What we hope to accomplish today

- Discuss animal model developments
- Describe selected promising new diagnostic targets
- Discuss potential of genomic expression for diagnosis
- Describe progress to date
- Ask for your input & suggestions
- Convey how you can access the resources of these two projects