

Invasive Aspergillus Animal Models (IAAM)

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at San Antonio

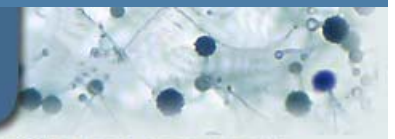
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INVASIVE ASPERGILLOSIS ANIMAL MODELS

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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

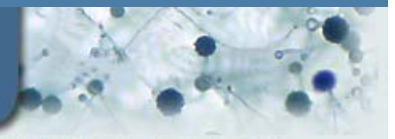
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RFA NIH-NIAID-DMID-03-09:
**New Animal Models for:
Part B Invasive Aspergillosis**

(August 12, 2002)



NIH-NIAID-N01-AI-30041

New Animal Models for

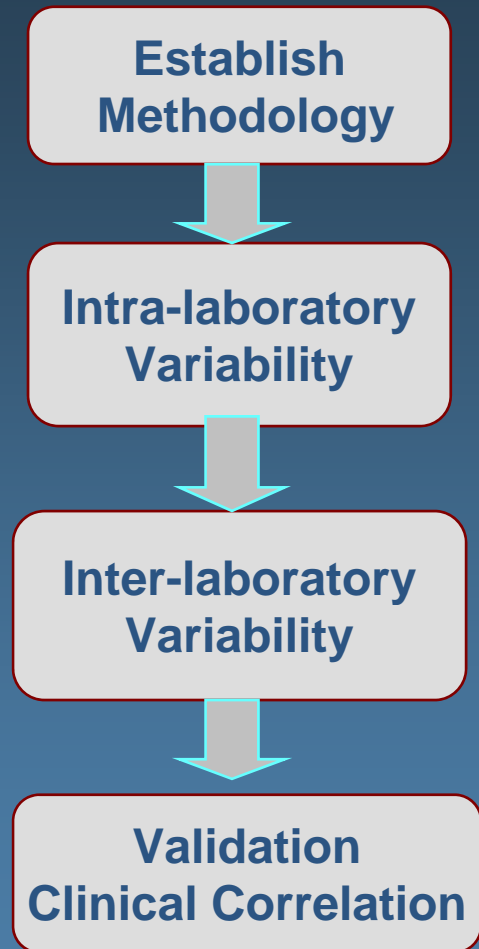
Invasive Aspergillosis

(August 15, 2003-August 14, 2010)

I think....therefore IAAM. Dennis Dixon Sept '03

Need for Reference Standard(s)

- Historical perspective:
Critical needs in antifungal susceptibility
 - Method reproducible
 - Provides reference standard for comparison of other methods
 - Validated for clinical correlation
- Highest priority for *Aspergillus* and new diagnostics
 - Standardized models aimed at identifying new targets for diagnosis & monitoring of disease progression



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SPECIFIC AIMS

- **Establish and standardize animal models of IA**
 - Mouse Model
 - Guinea pig Model
 - Rat Model
- **Develop molecular tools to provide standardized procedures for genetic manipulation of *Aspergillus* strains.**
 - Molecular Toolbox
 - Pathogenesis Toolbox
- **Provide samples (blood, tissues, BAL, urine, etc.) for comparative evaluation of new *Aspergillus* diagnostics and standardization for current approaches**
- **Dissemination of knowledge and skills to qualified scientists and laboratories**
 - Training
 - Website
 - Annual workshops

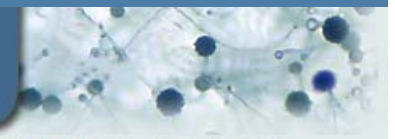
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NIAID/DMID
Project Officer
Rory Duncan
Dennis Dixon



IA Animal Models (IAAM)
Principal Investigator
Tom Patterson
Steering Committee
Denning, Filler, May, Nierman, Walsh
♦ Reviews ♦ Guides
Central Unit
Administrative Core:
Rick Kirkpatrick/Connie LaBeaux



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



**Functional Components
(Working Groups)**
*Patterson, Filler, Sheppard,
Denning, Wickes, Wiederhold, Pollock*
♦ Proposes ♦ Develops
♦ Implements ♦ Delivers

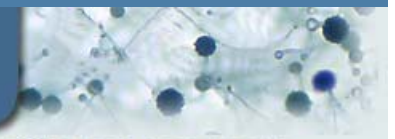
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Animal Models: Key Features

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

■ Neutropenia/non-neutropenic; other immunosuppression	■ Continuous blood sampling for surrogate markers	■ Survival duration allowing for disease progression (4-7 d)
■ Differentiate: exposure/colonization/infection	■ Quantify tissue burden (2 methods)	■ Assess growth dynamics of fungi
■ Standardized	■ Local/disseminated infection	■ <i>A. fumigatus</i> (AF293); suitable for others
■ Telemetry/IR fever curves	■ Genomic approach to molecular diagnosis	■ Gene profiling

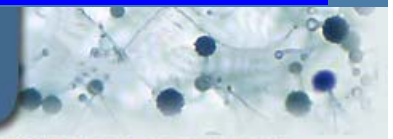
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Guinea Pig & Murine Models of Invasive Pulmonary Aspergillosis

- Inhalational challenge: Madison & acrylic chamber
- Immunosuppression
 - Cyclophosphamide
 - Cortisone acetate
- Extensive pulmonary infection
- Assessment of tissue burden
 - Colony forming units (CFU)
 - Galactomannan
 - qPCR (FKS and multi-copy gene targets)
- Serial assessment of infection
 - Blood
 - Serum
 - BAL
 - Urine
 - Others



Vallor AC, et al. *AAC* 2008;52:2593-8.
Sheppard DC, et al. *AAC* 2006;50:3501-3

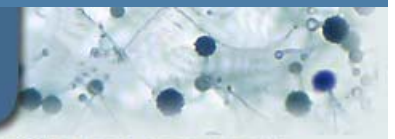
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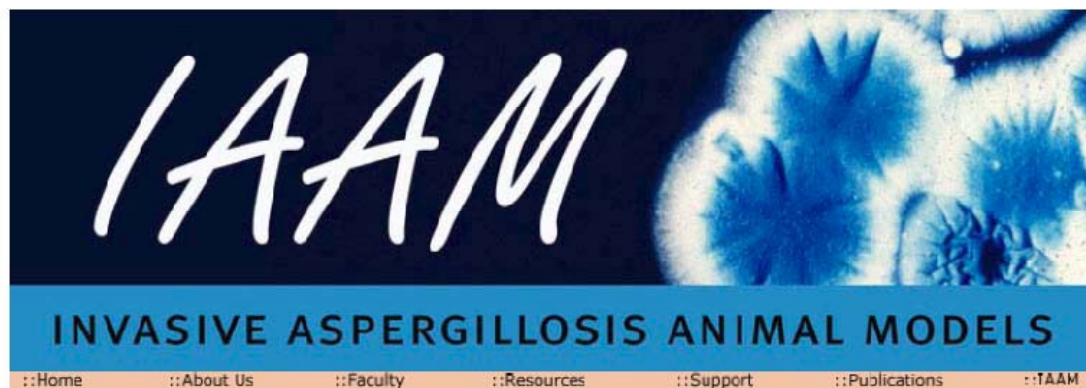
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IAAM: Standard Operating Procedures



IAAM Standard Operating Procedures

Title	File for download
Standard Operating Procedure for Preparation of Aspergillus fumigatus Test Strains for Inhalational Pulmonary Aspergillosis Animal Studies.	PDF File
Standard Operating Procedure for Murine Inhalational Pulmonary Aspergillosis.	PDF File
Standard Operating Procedure for Guinea Pig Inhalational Pulmonary Aspergillosis	PDF File
Standard Operating Procedure for Animal Tissue Homogenization.	PDF File
Standard Operating Procedure for Processing Animal Tissue Samples for PCR, Galactomannan and Storage.	PDF File
Standard Operating Procedure for Aspergillus spp. DNA Extraction for Quantitative Real-time Polymerase Chain Reaction.	PDF File
Standard Operating Procedure for the Determination of Tissue Fungal Burden Utilizing Quantitative Real Time Polymerase Reaction (qPCR).	PDF File

www.sacmm.org/iaam.html

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INVASIVE ASPERGILLOSIS ANIMAL MODELS

Key Questions

- Qualified investigator
 - Researcher with interest in *Aspergillus*
 - Trained to safely perform requested research
 - Qualifications: Principal investigators; Trainees (Post-doctoral fellows, students); Industry researchers
- Key Questions
 - Gene/gene product as diagnostic target
 - Evaluation of surrogate marker(s)
 - Effects of therapy on diagnostic markers
 - Role of virulence determinants in diagnosis
 - Others

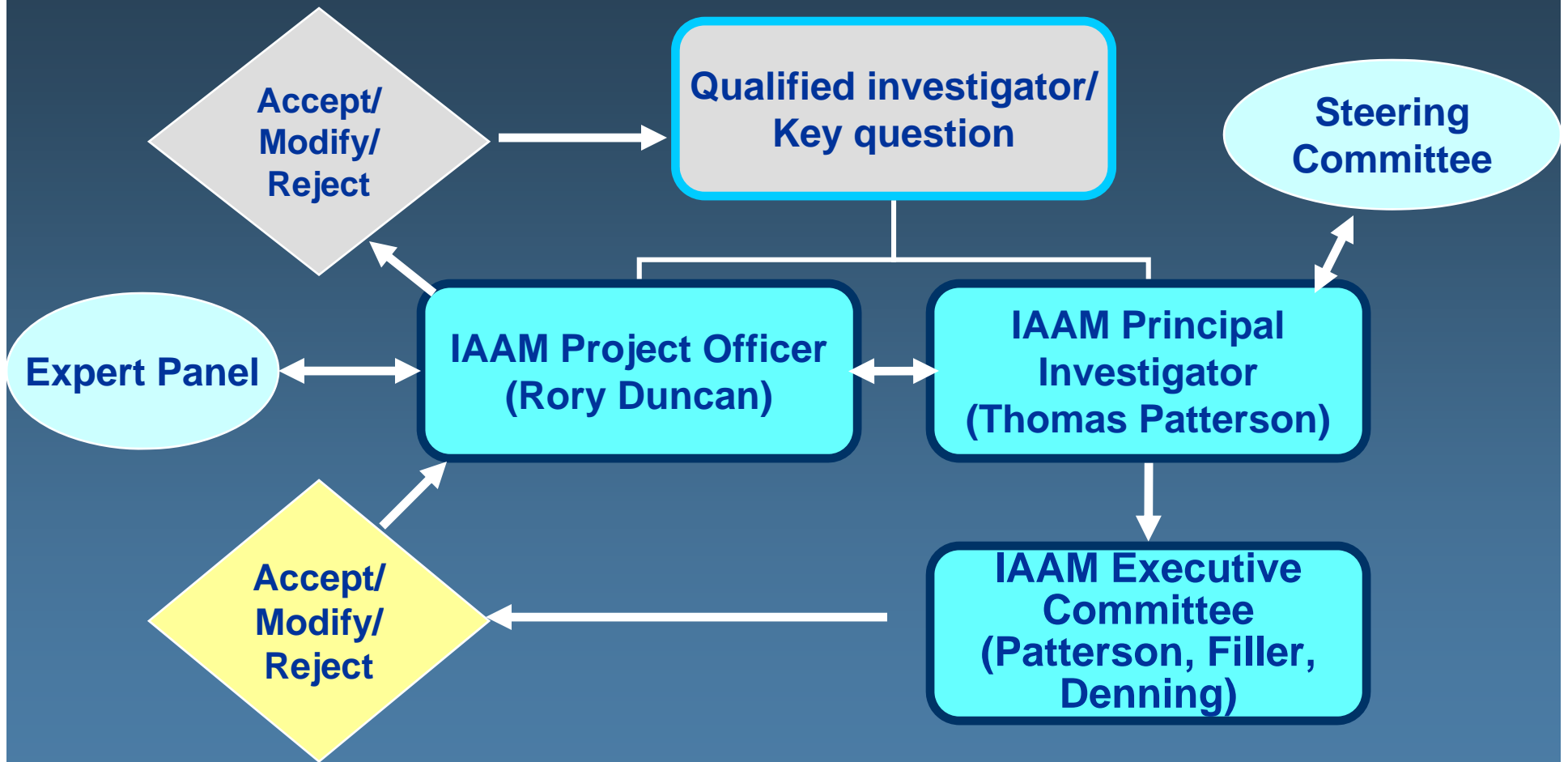
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Key Questions



Key Questions

- Prioritization of key questions
 - High likelihood of commercialized diagnostic product
 - Data to support development or clinical utility of diagnostic product
 - Pilot studies to test theoretical diagnostic target
 - NIH funded research
 - Preliminary data to support NIH application with favorable priority score on review
 - Pilot studies to evaluate investigator initiated concept
 - Industry sponsored research

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Key Questions

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

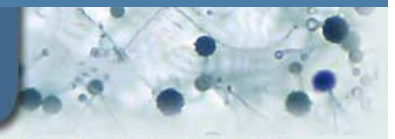
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Key Questions

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

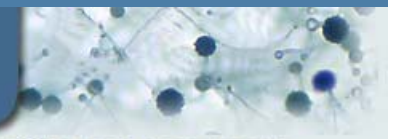
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Key Questions

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

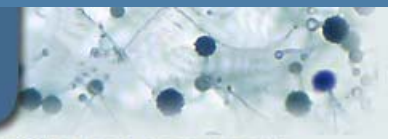
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Future Directions: Invasive Aspergillosis Animal Models (IAAM)

- Deliverables/Model refinement
 - SOPs online
 - Alternative *Af* strains
 - Role of host responses
 - Distinction of colonization vs disease
 - Impact of sample types, collection, storage
- New target development: Innovative Approaches to Target Identification and Assay Development for Fungal Diagnosis (RFA-AI-08-055 <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-08-055.html>)
- Diagnostic development with AsTec
 - Pre-clinical support for diagnostics
 - Industry partners
 - Community awareness/interaction

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