AsTeC and IAAM Project overview

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IAAM
INVASIVE ASPERGILLOSIS ANIMAL MODELS

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Invasive Aspergillus Animal Models (IAAM)

NIH-NIAID-N01-AI-30041

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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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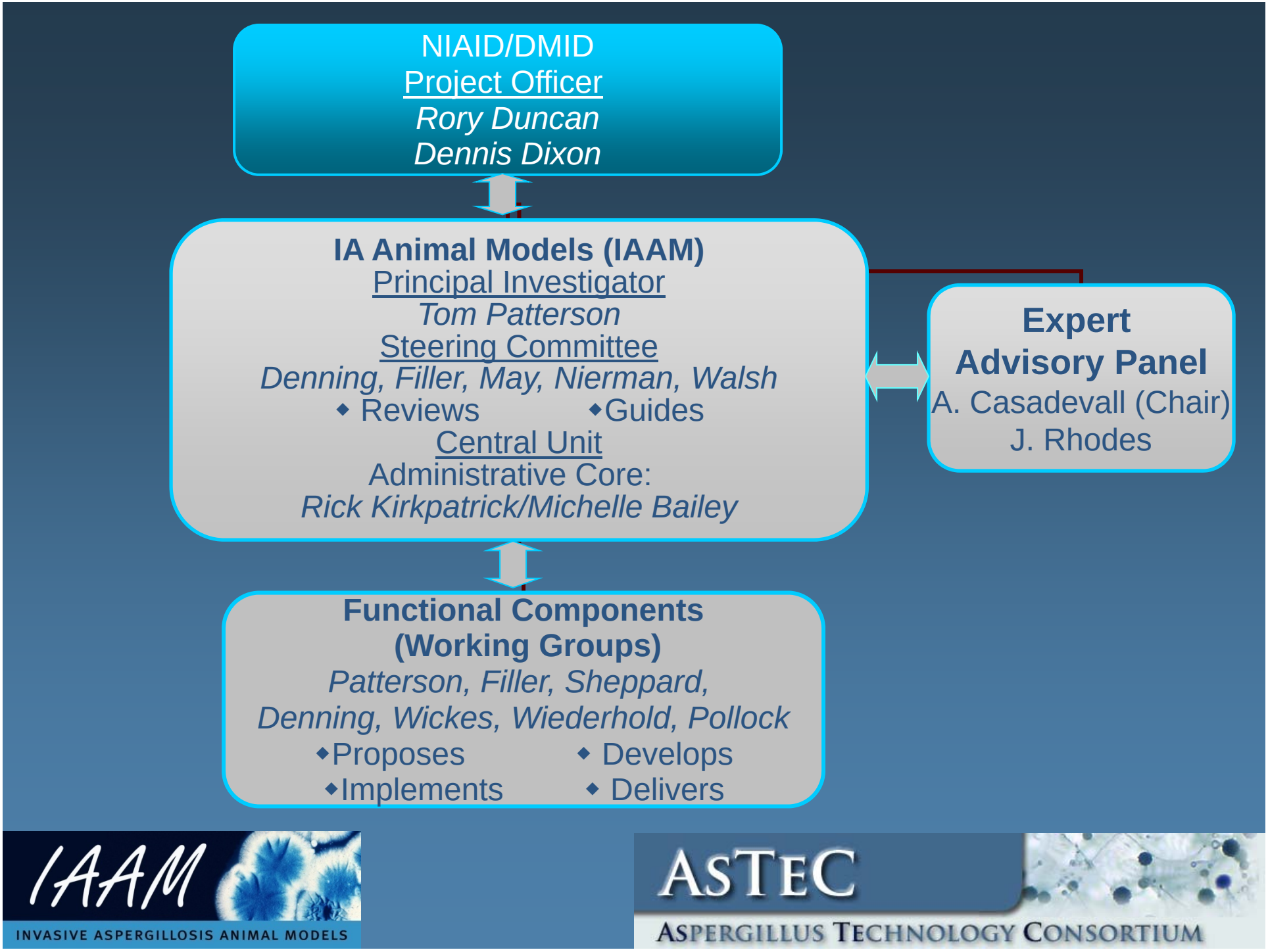
NIAID/DMID
Project Officer
Rory Duncan
Dennis Dixon
IA Animal Models (IAAM)
Principal Investigator
Tom Patterson
Steering Committee
Denning, Filler, May, Nierman, Walsh
◆ Reviews
◆Guides
Central Unit
Administrative Core:
Rick Kirkpatrick/Michelle Bailey
Expert
Advisory Panel
A. Casadevall (Chair)
J. Rhodes
Functional Components
(Working Groups)
Patterson, Filler, Sheppard,
Denning, Wickes, Wiederhold, Pollock
◆Proposes
◆ Develops
◆Implements
◆ Delivers
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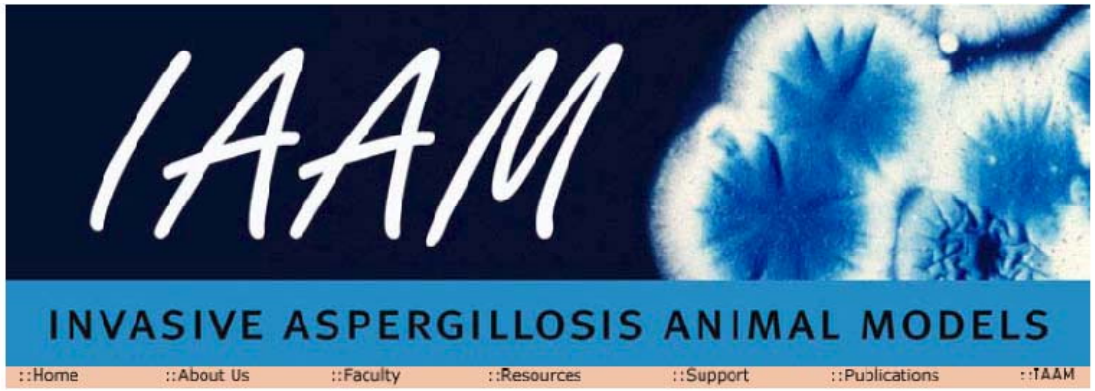
Animal Models: Key Features

- Mice & larger animals: guinea pigs/rats
  - 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	▪*A. fumigatus* (AF293)*;* suitable for others
▪Telemetry/IR fever curves	▪Genomic approach to molecular diagnosis	▪Gene profiling

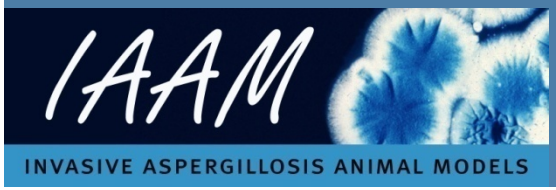
IAAM: Standard Operating Procedures



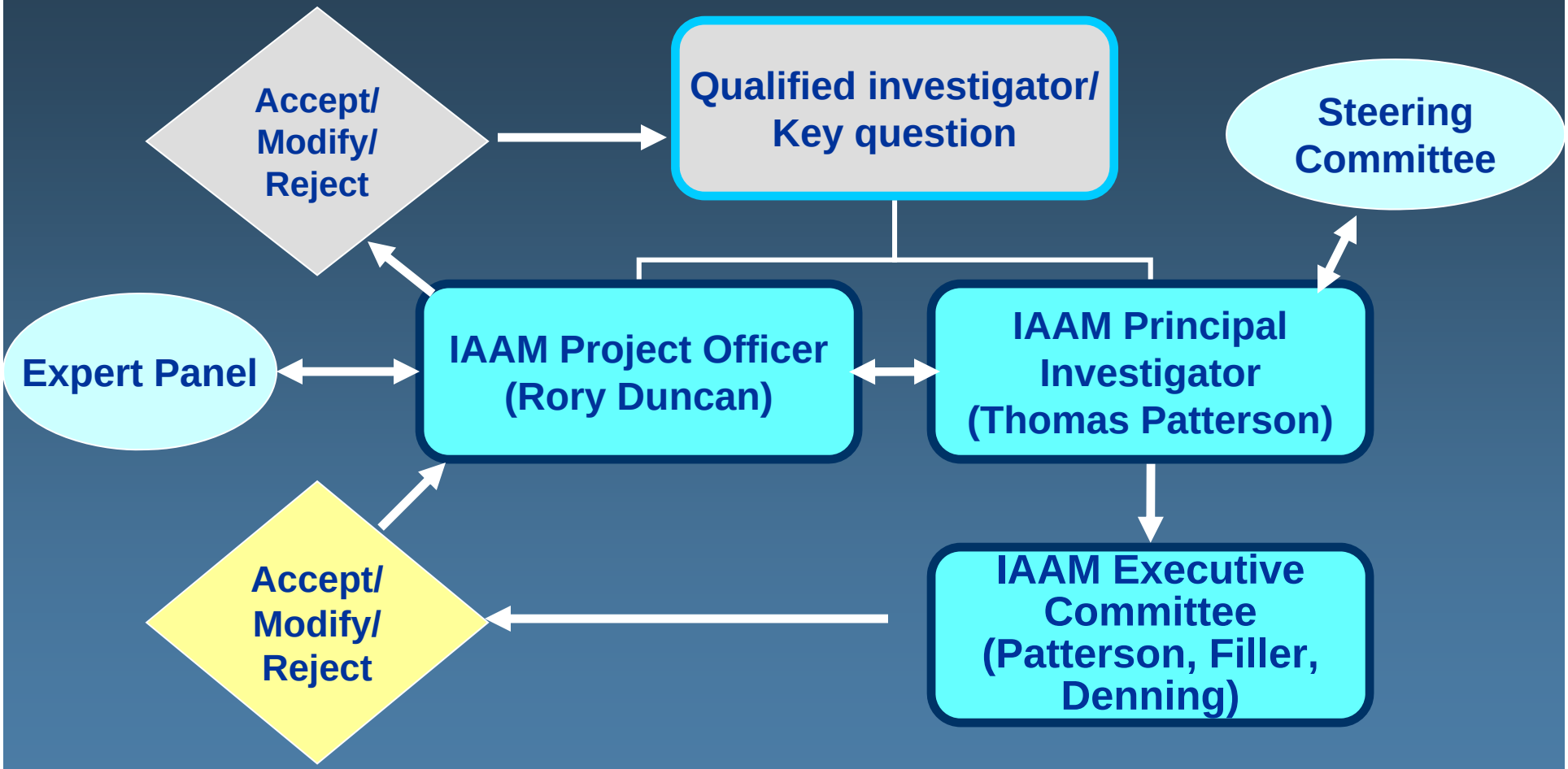
IAAM Standard Cperating Procedures

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 Inhalaticnal 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



Key Questions



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Key Questions

W. Steinbach	Calcineurin pathway in IA	Duke
R. Cramer	Role of *gliP* in gliotoxin synthesis	Duke
B. Miller	*Aspergillus* virulence determinants	U Idaho
N. Wiederhold	Genome-wide expression to echinocandins for *Af*	UTHSCSA
C. Clancy	*In vivo* gene expression of *Af*	U Florida
S. Harris	Polarized Hyphal Growth in *Af*	U Nebraska
R. Akins / J. Sobel	Microfluidic device for rapid pathogenic fungal diagnosis	U Michigan
A. Zaas	Genetic determinants of *Af* susceptibility	Duke
R. Calderone	Germination in *Af*	Georgetown
M. Momany	Rho GTPases in polar growth of *Af*	U Georgia
B. Segal	Development of *Aspergillus* vaccine	SUNY / Buffalo
D. Perlin	New Diagnostics for *Af*	New Jersey
C. Selitrennikoff	Prophylactic and therapeutic Aspergillus vaccines	MycoLogics, Inc, Aurora, CO
C. Douglas	QPCR for diagnostics of A. fumigatus	Merck and Co., Inc, Rahway, NJ
J. Loeffler	QPCR for diagnostics of A. fumigatus	University of Wuerzburg, Germany
G. Ramage	Real-Time PCR assay to detect A. fumigatus	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 A. fumigatus	McGill University, Montreal Canada
B. Wickes	PCR diagnostics in A. fumigatus	UTHSCSA
S. Filler / D. Sheppard	Host response to invasive aspergillosis	UCLA - Harbor / McGill University
S. Baker	Proteomics approach to A. fumigatus detection	Pacific Northwest National laboratory, Richland, WA
R. Cramer	Metabolomics approach to A. fumigatus 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 *Aspergillus* 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 A. fumigatus	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 A. fumigatus	University of Wuerzburg, Germany
A. Caliendo	Fungal DNA Stability	AsTeC - Emory University
A. Caliendo	Extraction methods for PCR diagnostics of A. fumigatus	AsTeC - Emory University
S. Bauman	Antigen detection for Aspergillus diagnosis	Immuno-Mycologics Inc.
V. Slepnev	Multiplexed PCR for Aspergillus diagnosis	Primera Biologics
S. Glickman	pulsed laser optoacousticspectroscopy	UTHSCSA
J. Schuster	GC / Mass spec	Teotten Diagnostics
D. Himsworth/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
  - Role of host responses
  - Distinction of colonization vs disease
  - Development of DNA standard for calibration
  - 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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Clinical Laboratory Diagnostics for Invasive Aspergillosis

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Barbara Alexander, MD
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HHSN266200700023C
5/31/07-5/30/14

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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

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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

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AsTeC Project

Project Officers

Alec Ritchie

C. Gale Auguste

Dennis Dixon

Scientific Working Group

David Hillyard

Sally Selepak

Paul Verweij

NIH/NIAID: #N01-AI-70023

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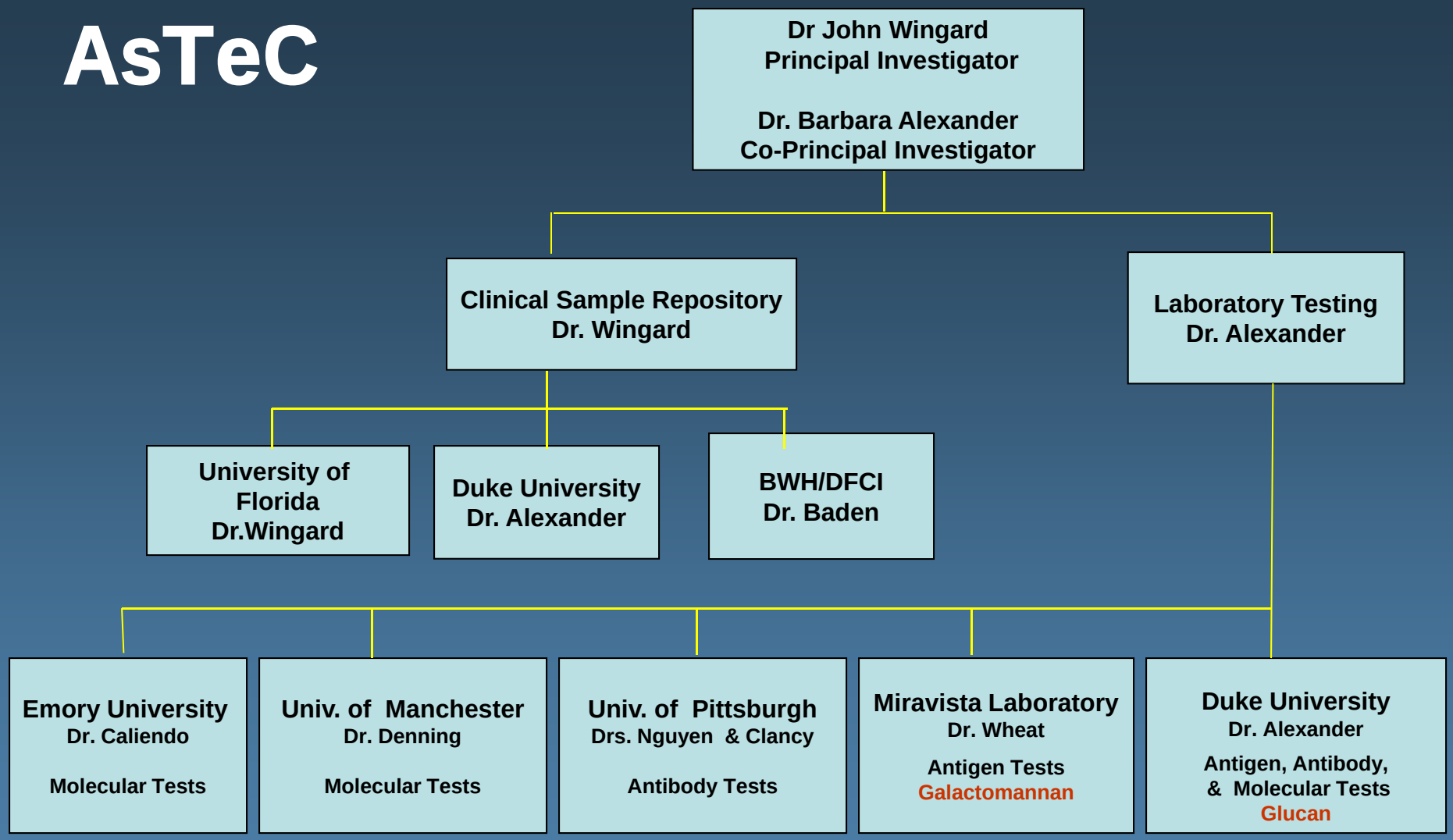

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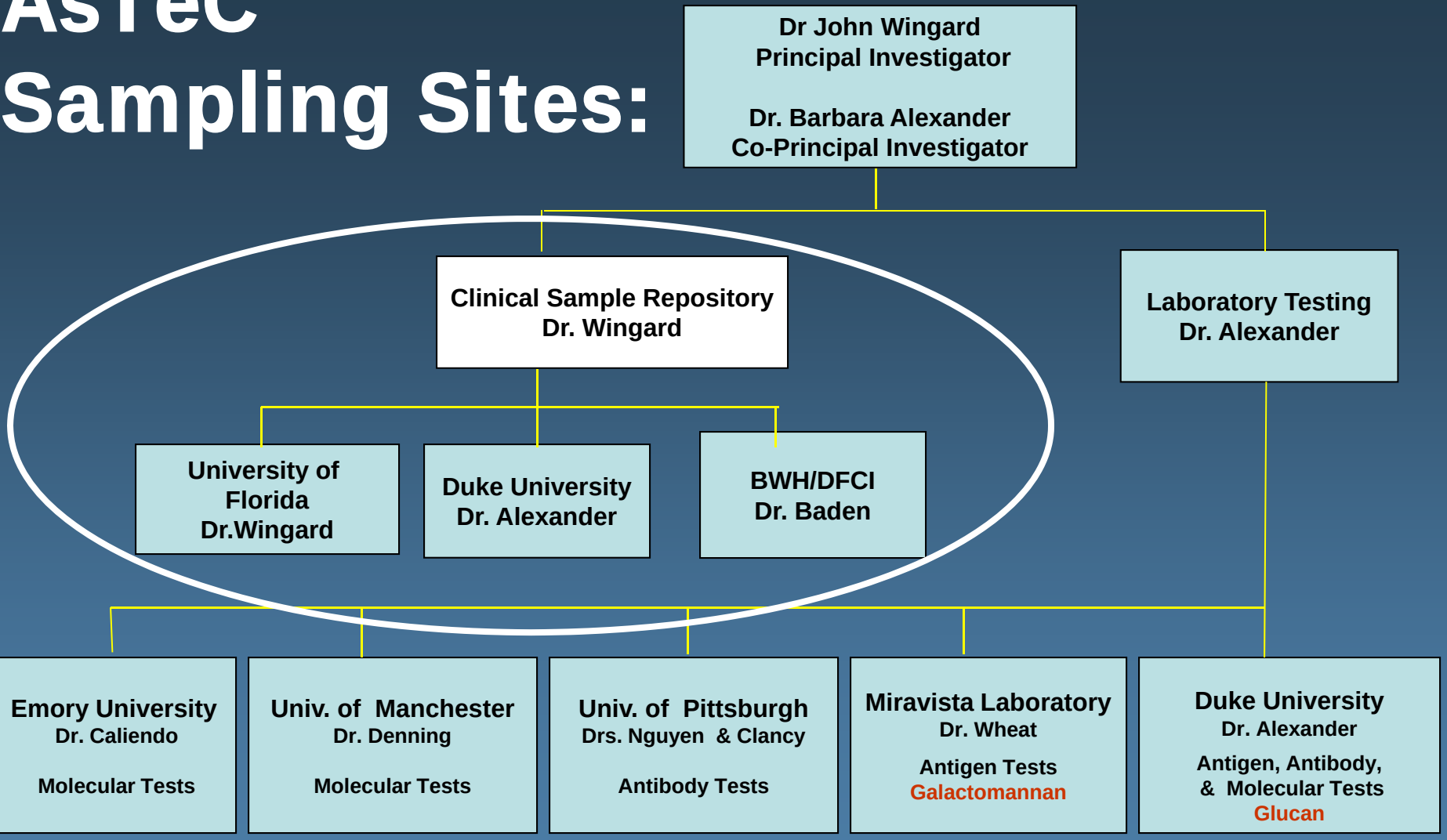
AsTeC Sampling Sites:



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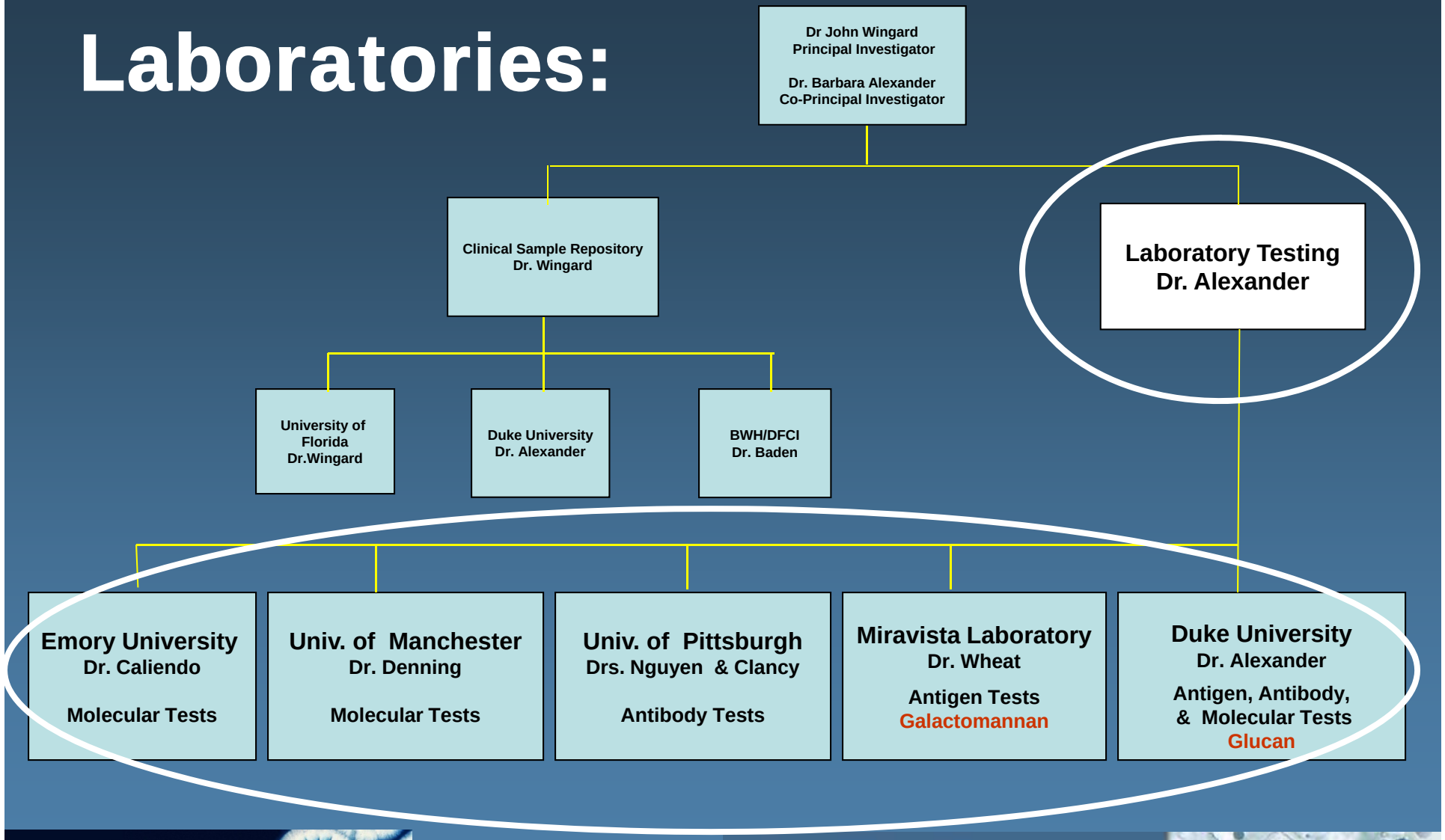
AsTeC Laboratories:



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Interactions between AsTeC & IAAM

- 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

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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

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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

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