Diagnostic Imaging in Experimental Invasive Pulmonary Aspergillosis
Introduction

• Invasive pulmonary aspergillosis is an important cause of morbidity and mortality in immunocompromised patients.

• CT scan technology has greatly enhanced our capability for early diagnosis and for monitoring of therapeutic response.

• We have applied CT scan technology to the monitoring of therapeutic response in experimental pulmonary aspergillosis.
Objectives

- Review basic concepts in CT imaging (CTI)
- Illustrate application of CTI
  - Pathophysiology
  - Monitoring of therapeutic response to AFT
  - Single agent
  - Combination therapy
  - Pathogenesis: *A. fumigatus* vs *A. terreus*
- MDVI
- Application to human IPA
- Future directions
Relationship to Pulmonary Pathophysiology

- Pulmonary infiltrates in neutropenic hosts with invasive aspergillosis are caused by vascular invasion and hemorrhagic infarction.
- CT scan imaging may provide an objective parameter by which to serially measure organism-mediated tissue injury.
- We therefore have monitored the course of pulmonary infiltrates by serial ultrafast computerized tomography (UFCT) in persistently granulocytopenic rabbits with experimental invasive pulmonary aspergillosis.
Ultrafast High Resolution CT Scan

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Ultrafast High Resolution CT Scan: Principles

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Bronchopneumonia with irregular boundaries caused by invasive pulmonary aspergillosis involving the right middle lobe and right lower lobe.

Normal lung tissue

Nodular pulmonary infiltrate

Contour of the heart
Rabbit Models of Invasive Pulmonary Aspergillosis

- Central silastic venous catheter permits atraumatic venous access
- Ara-C induction of profound and persistent neutropenia
- Further immunomodulation with CsA and methylprednisolone, where applicable
- Intensive supportive care with broad spectrum antibacterial antibiotics, twice daily monitoring, and 24/7 on-call schedule
Real time Therapeutic Monitoring of Invasive Pulmonary Aspergillosis in Persistently Neutropenic Rabbits

Antigen, metabolite, and PCR
e.g. galactomannan antigenemia

Serial CT and MRI scans
Correlation with Pulmonary Infarct Scores
Dose Response Relationships to Amphotericin B Formulations
Echinocandin-Triazole Combination Therapy: Surrogate Markers of Therapeutic Response

CT Pulmonary Infarct Score

Galactomannan Antigenemia
Aspergillus terreus: In vivo Resistance to AmB

Persistence of viable *A. terreus* in lung tissue (log CFU/g)
Experimental IPA: 
*A. fumigatus* and *A. terreus*
Experimental IPA:

A. fumigatus and A. terreus

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Multi-dimensional Volumetric Imaging of Pulmonary Infiltrates
CT volume used in the analysis software to generate a volume measurement

Transverse plane depicting pulmonary infiltrates in both lower lobes

Sagittal plane depicts a column of infiltrate due to invasive pulmonary aspergillosis

Coronal image depicting irregularly contoured pulmonary infiltrates
Representative maximum intensity projections (MIPs) from untreated control and DAMB-treated rabbits.
The dynamics of the pulmonary infiltrate volume correlate with changes in the pulmonary infiltrate score measured using conventional UFCT.
Volume of pulmonary infiltrates correlate with pulmonary infarct score, total lung weights, residual fungal burden, and galactomannan antigenemia.
MDVI in Patients with Invasive Mycoses
(Pyrgos et al: ICAAC 2007)

7219  (June 8)
29,747 (June 22)
15,101 (June 29)
Summary

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Future Directions

- Further studies in experimental aspergillosis with different classes of antifungal compounds and immunomodulation using MDVI
- Correlation with new molecular and proteomic diagnostic markers
- Genetically modified *Aspergillus* spp.
- PET/CT
- Incorporation of MDVI into clinical trials
- Utility in other infectious causes of pneumonia
Gratitude

- ICHS/NCI
  - Laboratory Animal Facility
    » Vidmantas Petraitis
    » Ruta Petraitiene
    » Robert Schaufele
    » Tin Sein
    » Lora Greene
    » Molly Cotton
  - Host Defense Research Unit
    » Emmanuel Roilides
    » Vasilios Pyrgos
    » Joanne Peter
    » Shmuel Shoham

- Diagnostic Imaging CC/NIH
  - Nilo Avila
  - Jeff Solomon
  - Irwin Feurstein

- Washington Hospital Center
  - Shmuel Shoham
  - Vasilios Pyrgos