ISHAM 2009,Tokyo, JAPAN

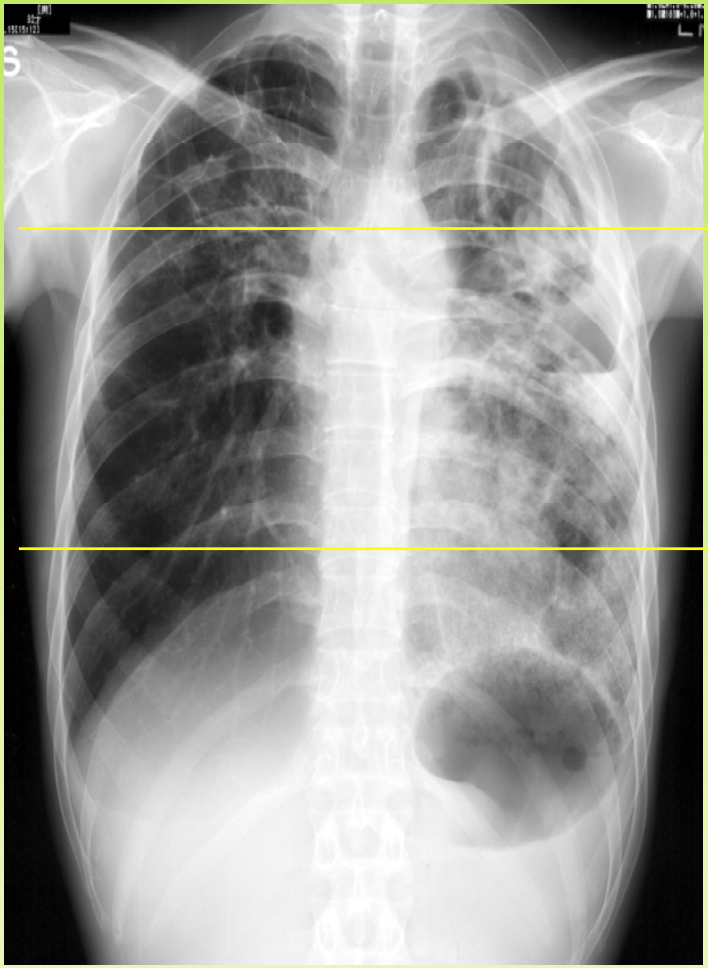
Fungal infections in non-neutropenic patients (CL-02)

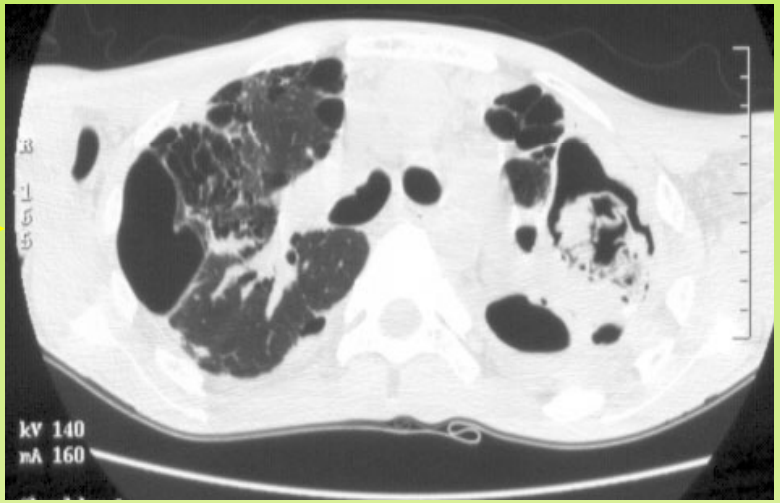
Chronic Pulmonary Aspergillosis

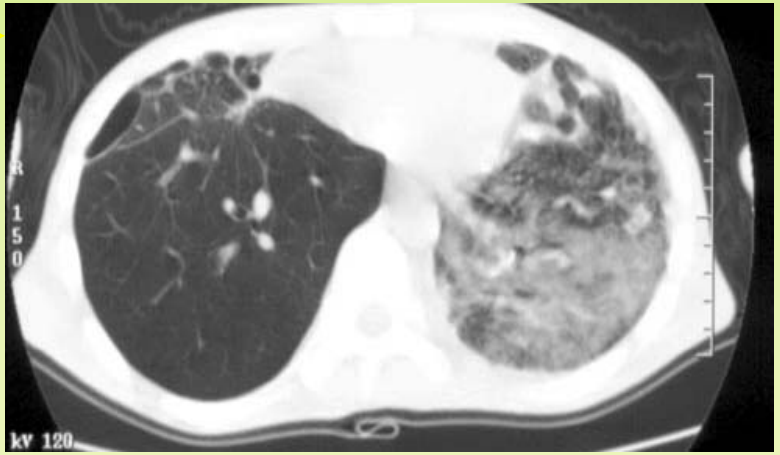
Department of Molecular Microbiology and Immunology
Nagasaki University Graduate School of Biomedical Sciences

Koichi IZUMIKAWA, M.D., Ph.D.

Chronic forms of Pulmonary Aspergillosis





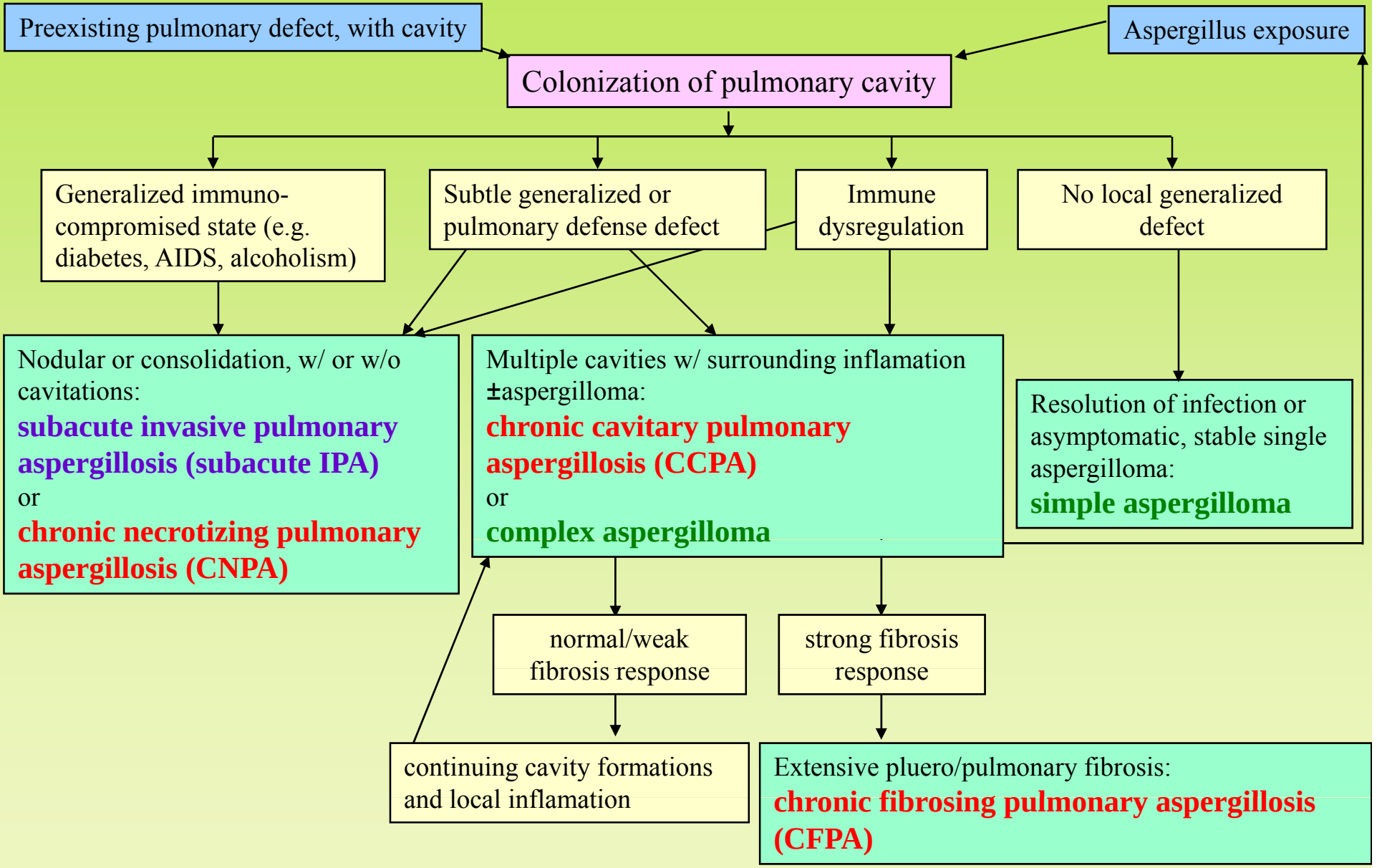


Definition:
slowly progressive inflammatory pulmonary syndrome due to *Aspergillus* spp.

Chronic forms of pulmonary aspergillosis

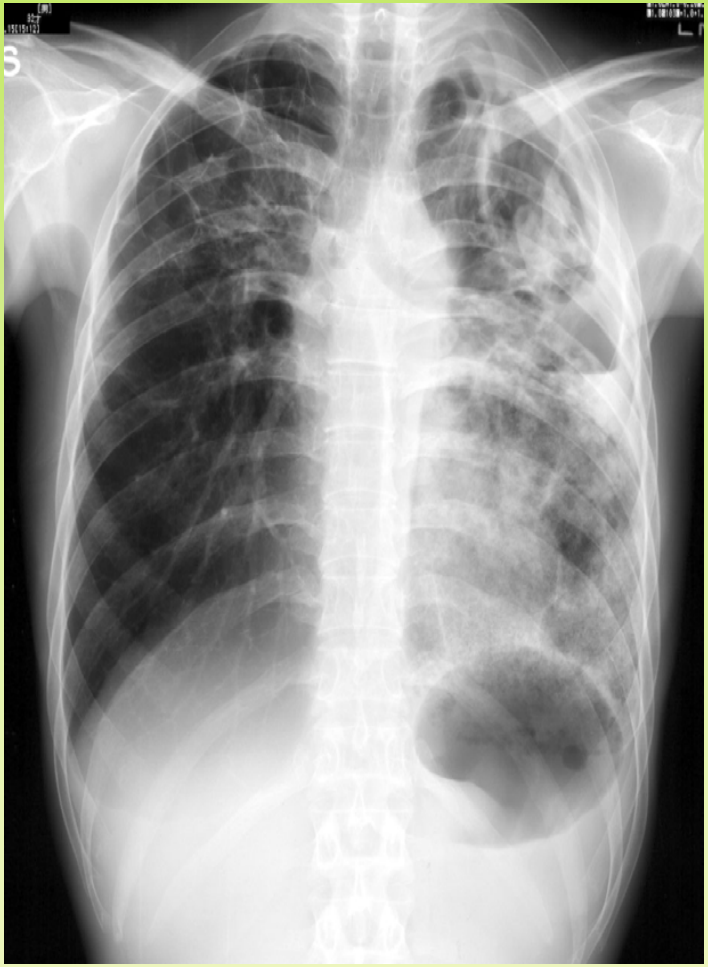
- ✓ Also Known As;
- ✓ Chronic cavitary pulmonary aspergillosis (CCPA)
- ✓ Chronic fibrosing pulmonary aspergillosis (CFPA)
- ✓ Chronic necrotizing puomonary aspergillosis (CNPA)
- ✓ Sub-acute IPA
- ✓ Semi-invasive pulmonary aspergillosis
- ✓ Chronic invasive pulmonary aspergillosis
- ✓ Symptomatic pulmonary aspergilloma
- ✓ Aspergillus pseudotuberculosis
- ✓ Complex aspergilloma
- ✓ Chronic destructive pulmonary aspergillosis

Proposed classification and pathogenesis of chronic pulmonary aspergillosis



Denning et al: Clin Infect Dis 37 Suppl 3: S265-80, 2003

Chronic forms of Pulmonary Aspergillosis



Can you tell?

This is

CNPA?

CCPA?

CFPA?

Complex aspergilloma?

Clinical characters of chronic pulmonary aspergillosis (CPA)

Who at risks;

pre-existing lung diseases; COPD, Tuberculosis sequelae, brochiectais, cystic fibrosis, aspergilloma, post surgery with mild immunocompromising conditions (e.g., HIV infection, leukemia, and chronic granulomatous disease)

Symtoms;

chronic pulmonary or systemic symptoms (duration, 3 months)
weight loss, productive cough, or hemoptysis

Images;

cavitary pulmonary lesion with paricavitary infiltrates, new cavity formation, or expansion of cavity size over time

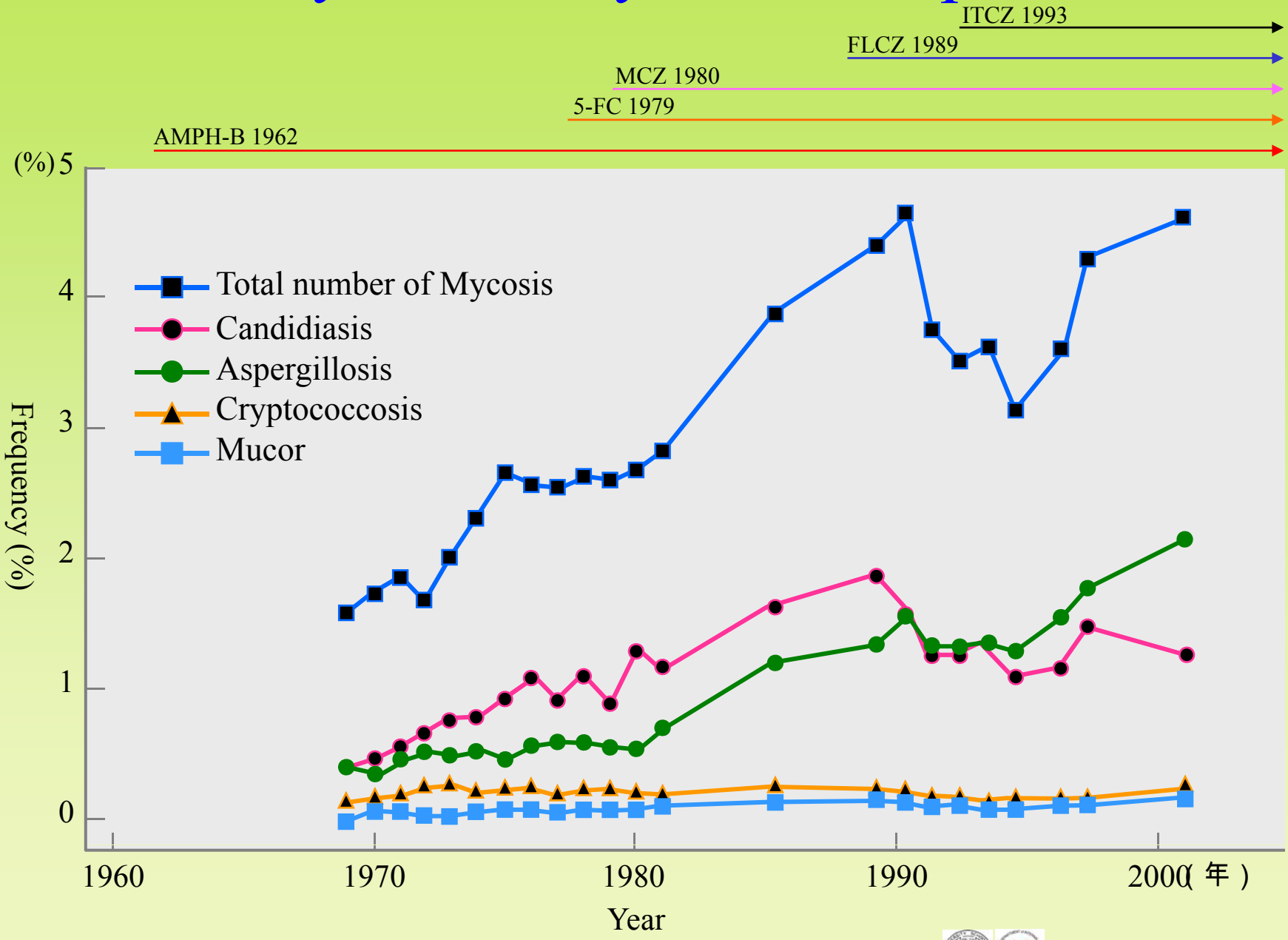
Laboratory findings;

serum *Aspergillus* antibody test
isolation of *Aspergillus* spp. from pulmonary or pleural cavity
elevated levels of inflammatory markers

Others;

Exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests

Systemic Mycosis in Japan



Nippon Ishinkin Gakkai Zasshi. 2006;47(1):15-24.

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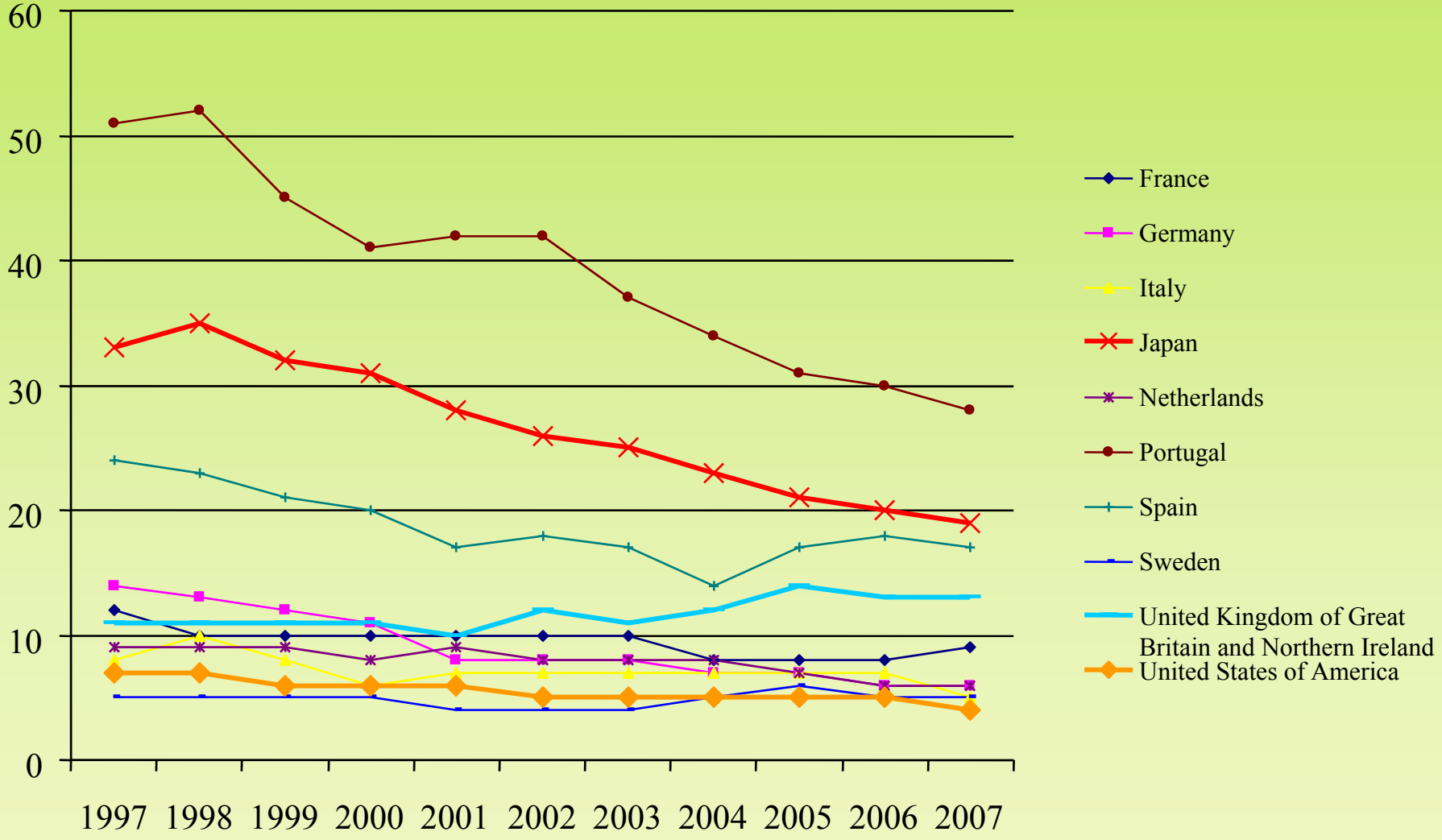
Reported TB cases
New and relapse cases (per 100 000 population)



WHO, Communicable Diseases Report

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Problems in CPA

Definition

→world-wide consensus required

Diagnosis

→precise and rapid detection tests required

→development of maker indicating progression

Treatment

→lack of evidence

Analysis of disease

→in vivo model development

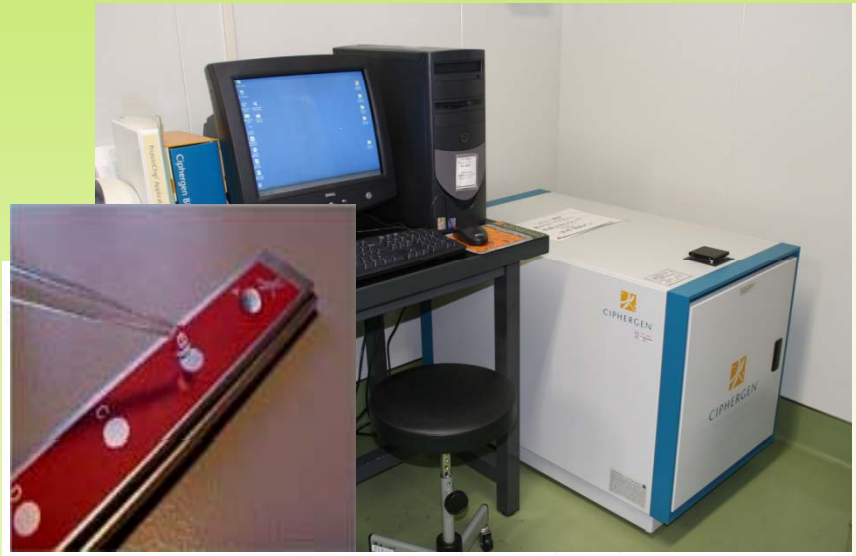
Diagnosing CPA

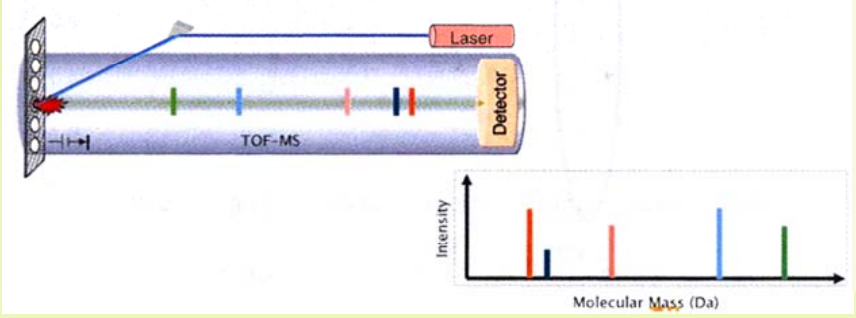
No reliable tests existed yet

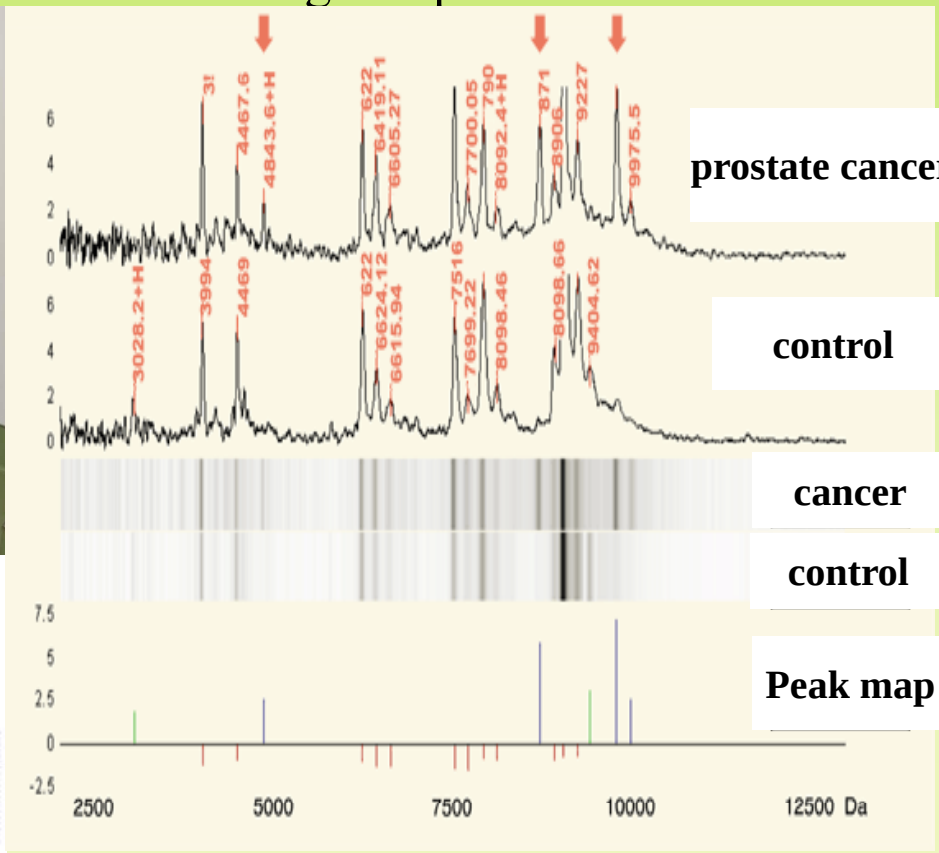
Proteomics for discovering new Aspergillus antigen

Ciphergen ProteinChip® System (SELDI TOF-MS)

Developed for the performing functional analyses such as, expression, interaction, ornamentation or for the refinement/identification of targeted protein



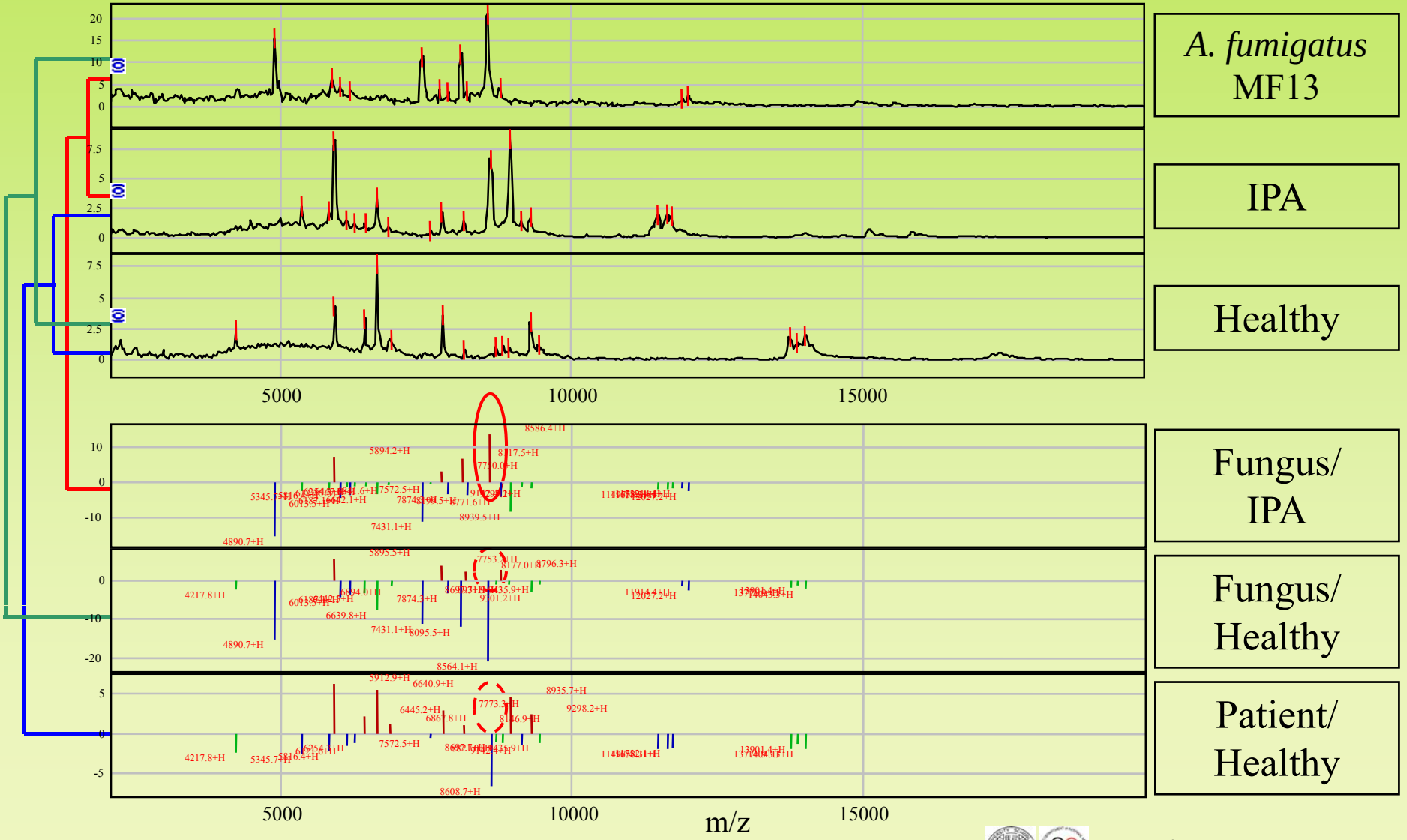




(some images from http://www.ciphergen.co.jp/)

Proteomics for discovering new Aspergillus antigen

Peaks comparison in extracted protein from *A. fumigatus* MF13 and serum of IPA patient and healthy volunteer



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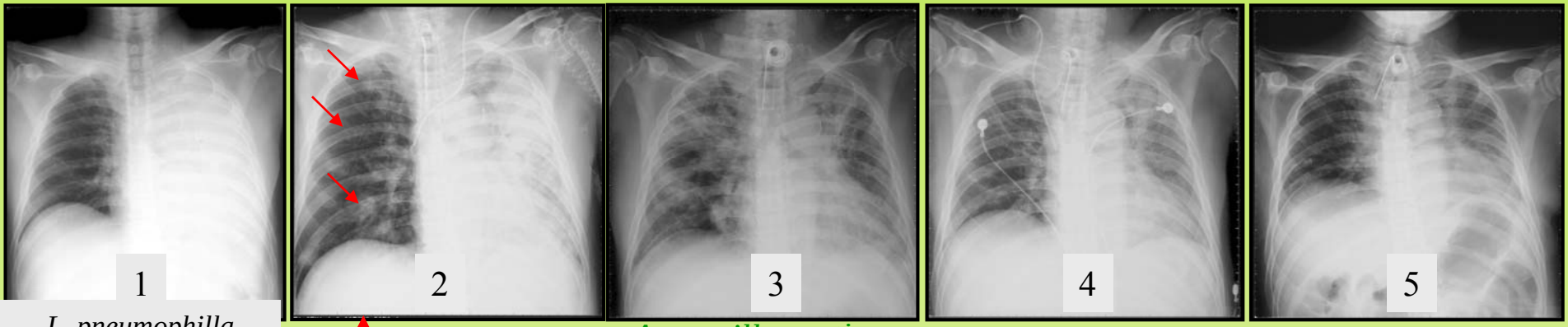
Proteomics for discovering new Aspergillus antigen

Transition of targeted peaks in the course of Legionella and IPA infection case

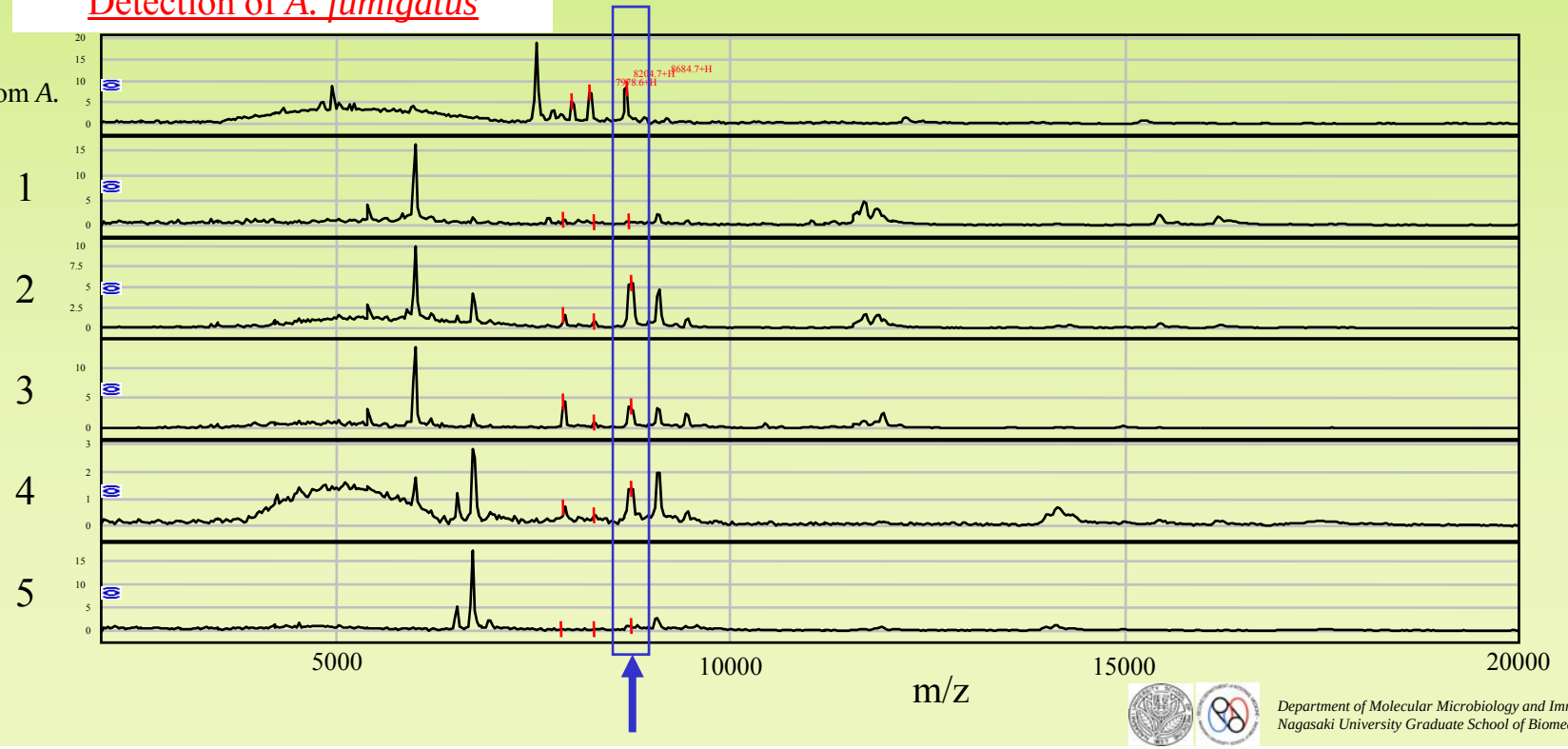


L. pneumophilla pneumonia

1.101 ← *Aspergillus* antigen ELISA → 0.265

Detection of *A. fumigatus*

Extracted protein from *A. fumigatus*



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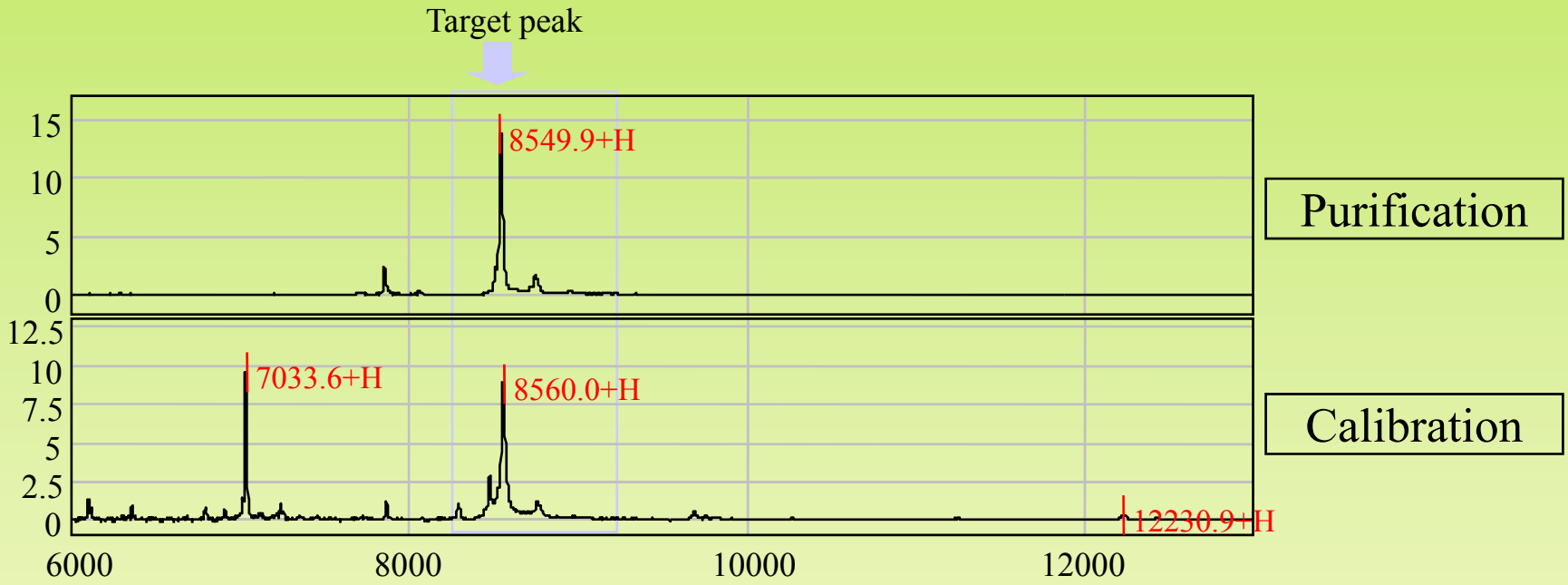
Proteomics for discovering new Aspergillus antigen

Purification and calibration of targeted peak @ 8560 m/z



Proteomics for discovering new Aspergillus antigen

Result of PMF and MS/MS analysis

- PMF

gi|70993888	Mass: 35178	Score: 71	polyubiquitin (UbiD)	[*Aspergillus fumigatus* Af293]
gi|55783587	Mass: 34152	Score: 71	polyubiquitin	[*Aspergillus fumigatus*]
gi|70999548	Mass: 17661	Score: 69	ubiquitin (UbiC)	[*Aspergillus fumigatus* Af293]

- MS/MS

gi|70999548	Mass: 17661	Score: 92	ubiquitin (UbiC)	[*Aspergillus fumigatus* Af293]
gi|55783587	Mass: 34152	Score: 88	polyubiquitin	[*Aspergillus fumigatus*]
gi|70993888	Mass: 35178	Score: 88	polyubiquitin (UbiD)	[*Aspergillus fumigatus* Af293]

Treatment of CPA

No enough data yet

CPA case

ITCZ oral solution treatment case

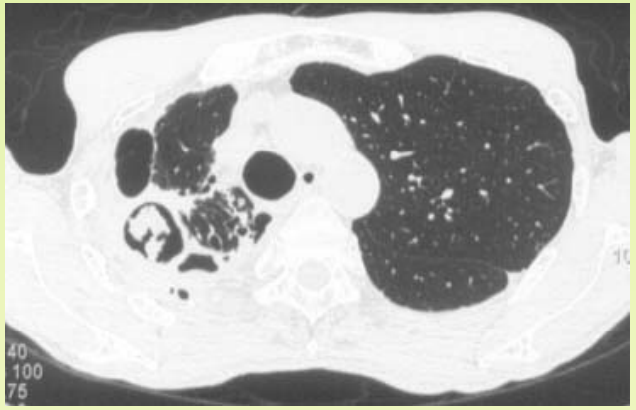
[case]65 Y, Male

[CC] hemosputum, cough

[PH] n.p.

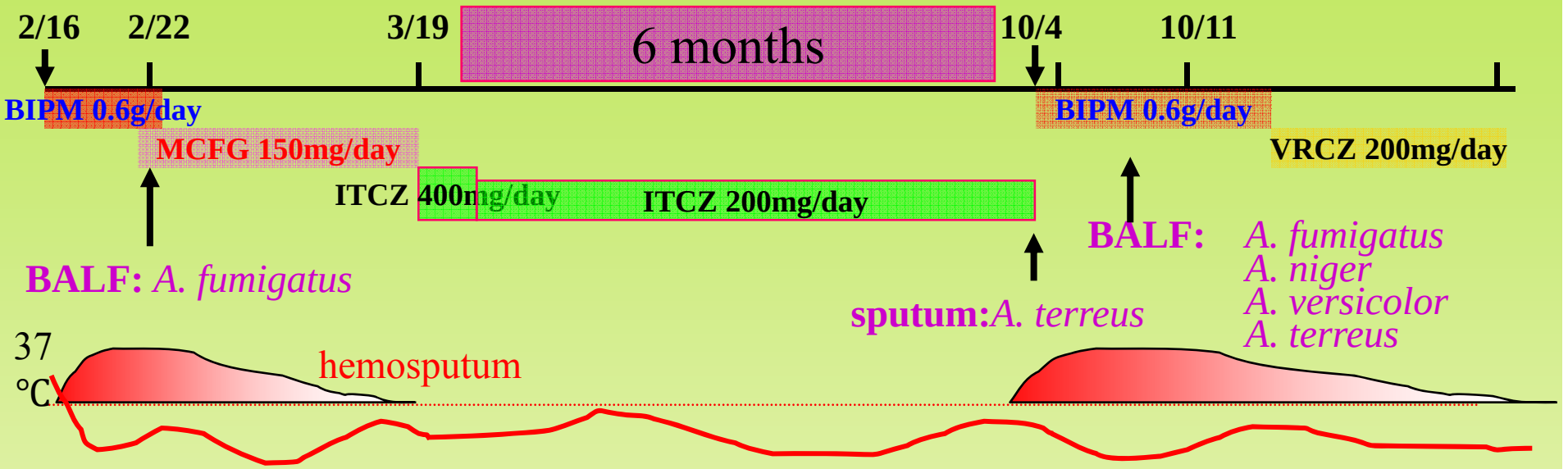
[PI]
1998：right upper lobectomy (Tbc)
2005~：cough, hemosputum
2006~: hemosputum increased
chest CT：fungus ball like shadows in right lower lung.
Platelia EIA: positive, Aspergillus Ab: positive
β-D-gulucan 35.0pg/ml
admission for further treatment

[PE] Height 161cm, Weight 44.3kg, BMI 17.1,
Body temp. 36.8℃, pulse 68/min, regular rhythm



CPA case

ITCZ oral solution treatment



WBC(/μl)

8700 6700 5700 5300 6500 8000 7500 7500

CRP(mg/dl)

1.65 5.70 0.19 0.20 0.93 1.46 3.24 0.72

β-D-glucan(pg/ml)

39.5 117.8 90.9 68.2 47.4 25.9 28.9

Aspergillus antigen (EIA)

0.65 0.976 0.985 1.025 0.441 0.461 0.591 0.517

CPA treatment
IDSA GL

	Treatment		
	Primary	**Alternative**	
CNPA (Subacute IPA)	**VRCZ**	**L-AMB** **ITCZ** **MCFG** **posaconazole** **ABLC** **caspofungin**	Monthly treatment and orally administrative azoles are recommended
CCPA	**ITCZ** **or** **VRCZ**		Innateimmune defects demonstrated Longterm therapy IFN-γ
Aspergilloma	**none** **or** **SURGERY**		The role of medical therapy in treatment of aspergilloma is uncertain

NO RCT existed !!

P.O. first and I.V. is optional

Clin Infect Dis 2008; 46:327-360

CPA treatment strategy

①dividing ACUTE and MAINTENANCE phase

ACUTE：IV (single or combination?)

→possibly shorten the admission period

MAINTENANCE：oral AZOLES

②Initiation with oral AZOLES

③other administrative route of antifungals?

CPA treatment ongoing clinical trial in Japan

Patients：CPA（CNPA+CCPA）, over 100 cases

antifungals：MCFG i.v. v.s. VRCZ i.v.

The 1st RCT in the world

Multicenter study: 35institutes in JAPAN

Another route of antifungal administration

nebulized L-AMB & MCFG IPA murine model

Day-2,0：Cyclophosphamide200mg/kg i.p.+CortisoneAcetate250mg/kg s.c.

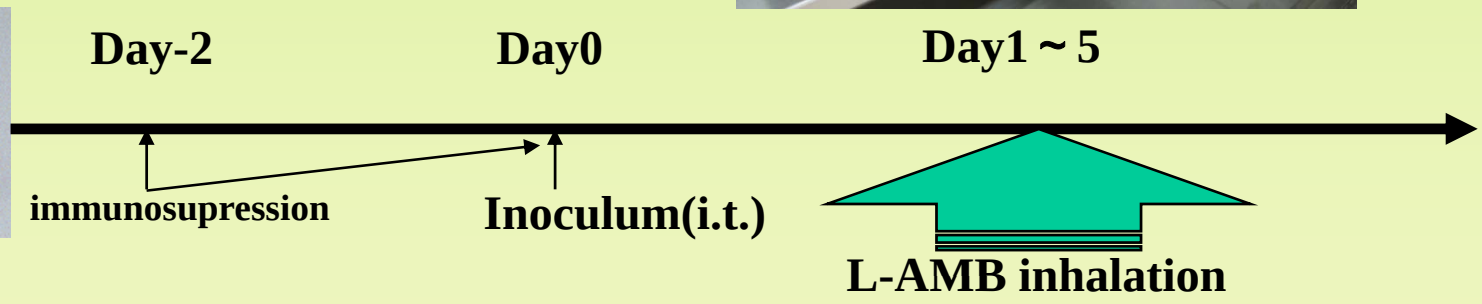
Day0： MF-13 conidia 1×10^8/ml:50μl intratracheal inoculation

Day1～5： L-AMB 1.2mg/ml：8ml nebulize once/day

MCFG 1mg/kg/day intraperitoneal

Group1: nL-AMB + MCFG
Group2: nL-AMB
Group3: MCFG
Group4: Control

ICR,♀,8weeks



Another route of antifungal administration

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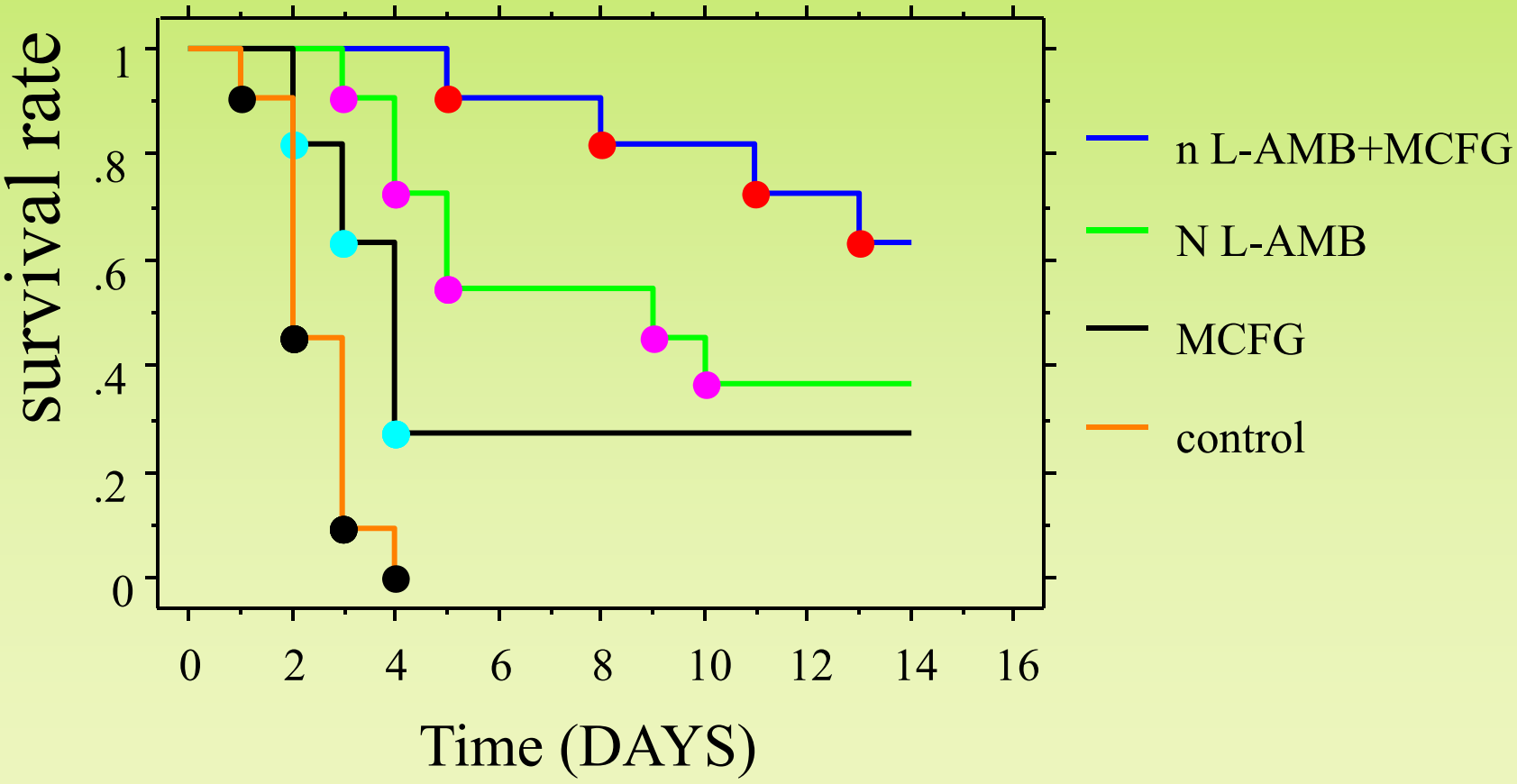

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Challenges against CPA

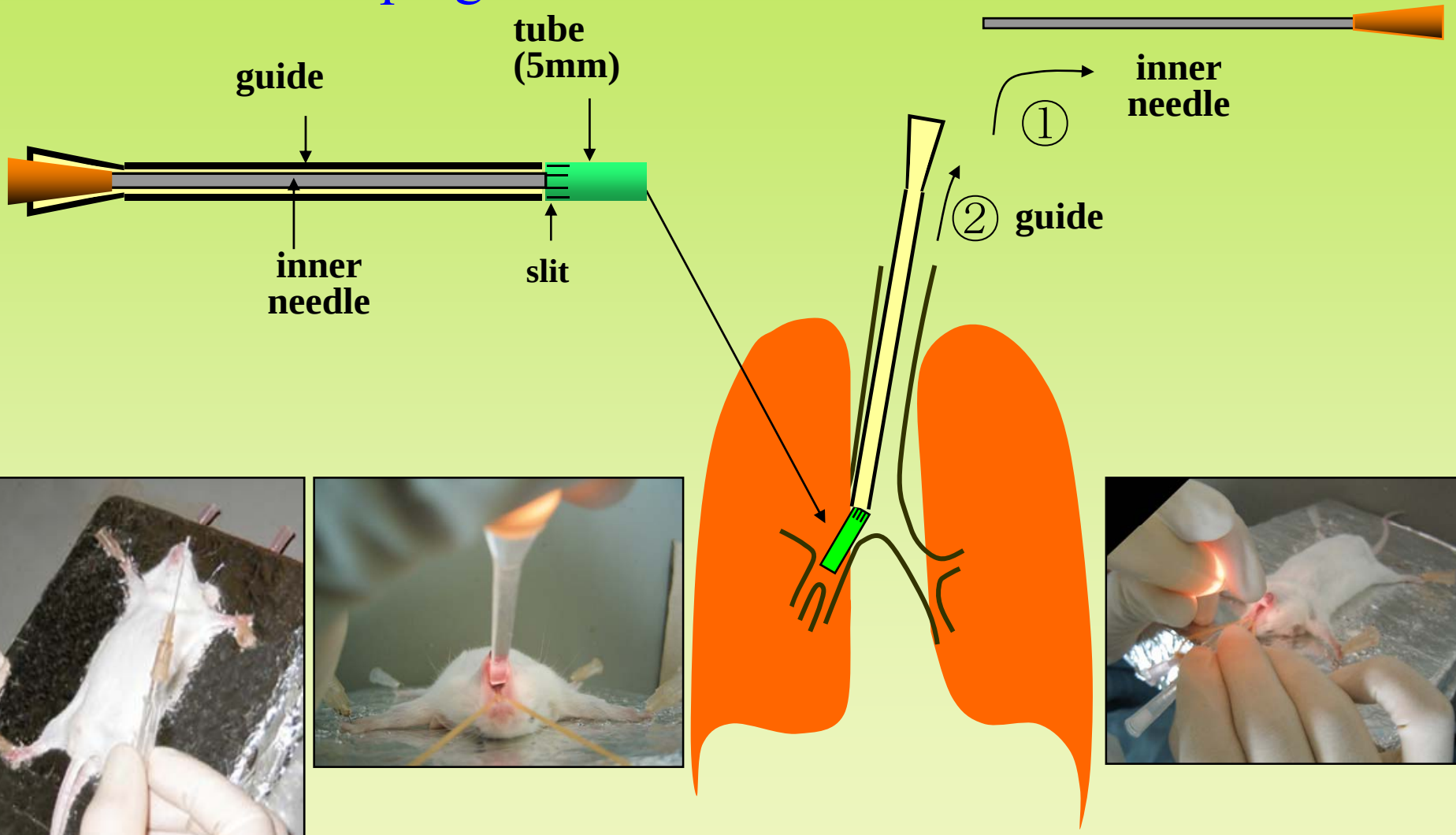
- ✓improve diagnostic rate
- ✓establish the treatment strategy
- ✓evaluate new additional treatment methods

ANALYSIS of CLINICAL FEATURES of CPA

→development of in vivo model is required

CPA mouse model

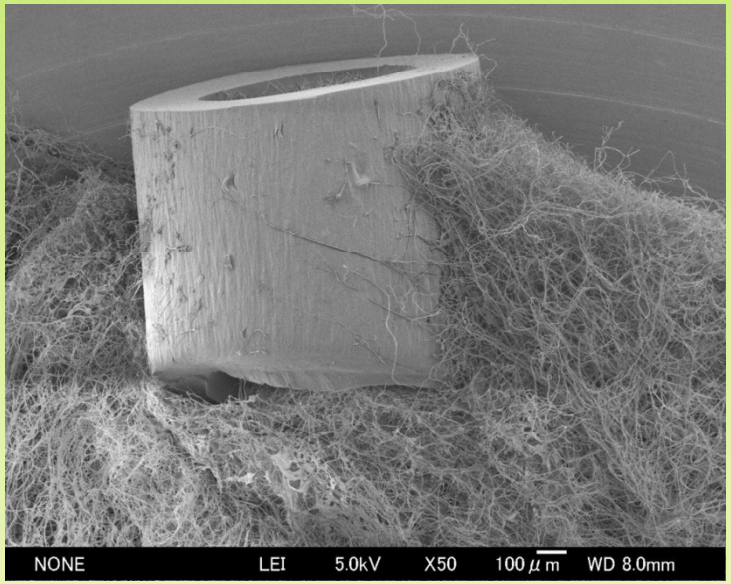
Aspergillus biofilm tube intubation

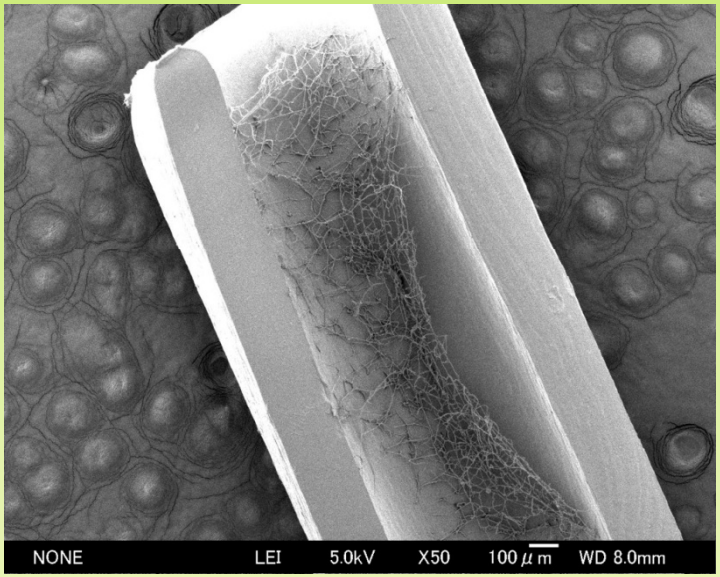


Yanagihara K., et al. Am. J. Respir. Crit. Care Med. 155: 337-342 1997.

CPA mouse model

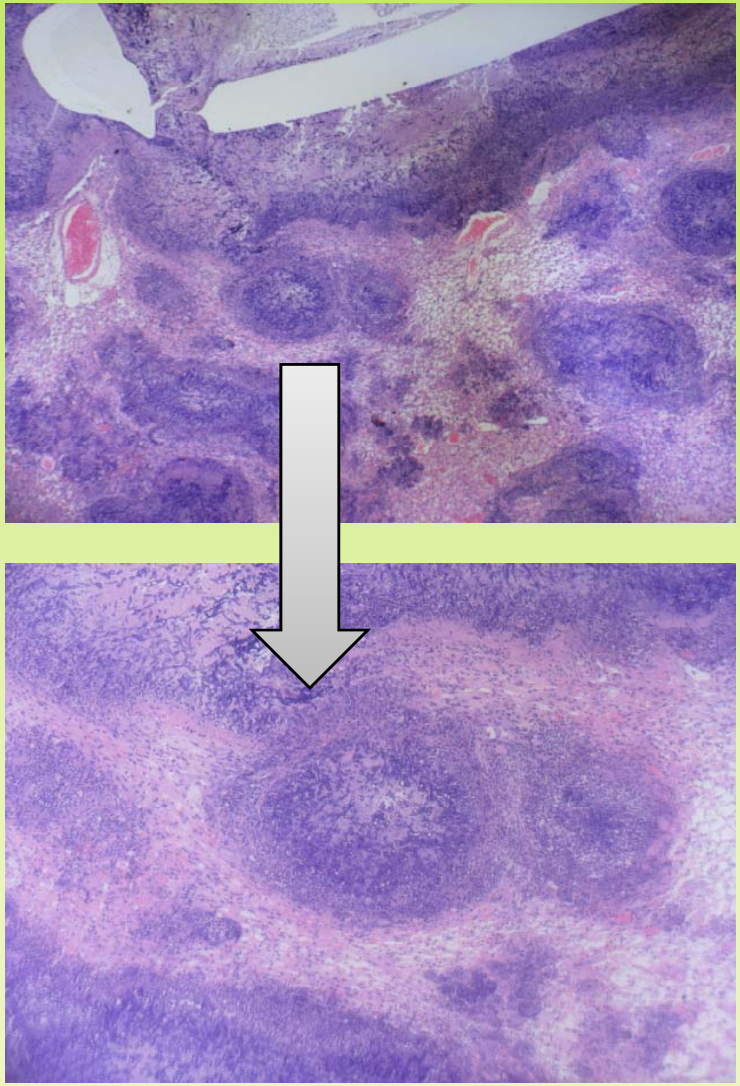
Aspergillus biofilm production

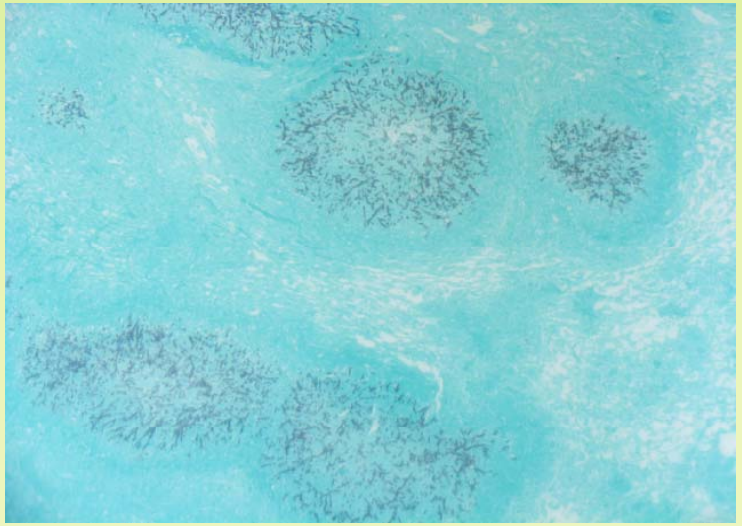




CPA mouse model

A. fumigatus Biofilm tube intubation + immunosupression





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SUMMARY

Definition

→world-wide consensus required

Diagnosis

→precise and rapid detection tests required

→development of maker indicating progression

Treatment

→lack of evidence

→accumulating data about combination therapy

Analysis of disease

→in vivo model development

Acknowledgement

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