

Cryptococcosis and solid organ transplantation

Olivier Lortholary

Université Paris Descartes

Service des Maladies Infectieuses et Tropicales,

Hôpital Necker-Enfants malades

Centre d'Infectiologie Necker-Pasteur

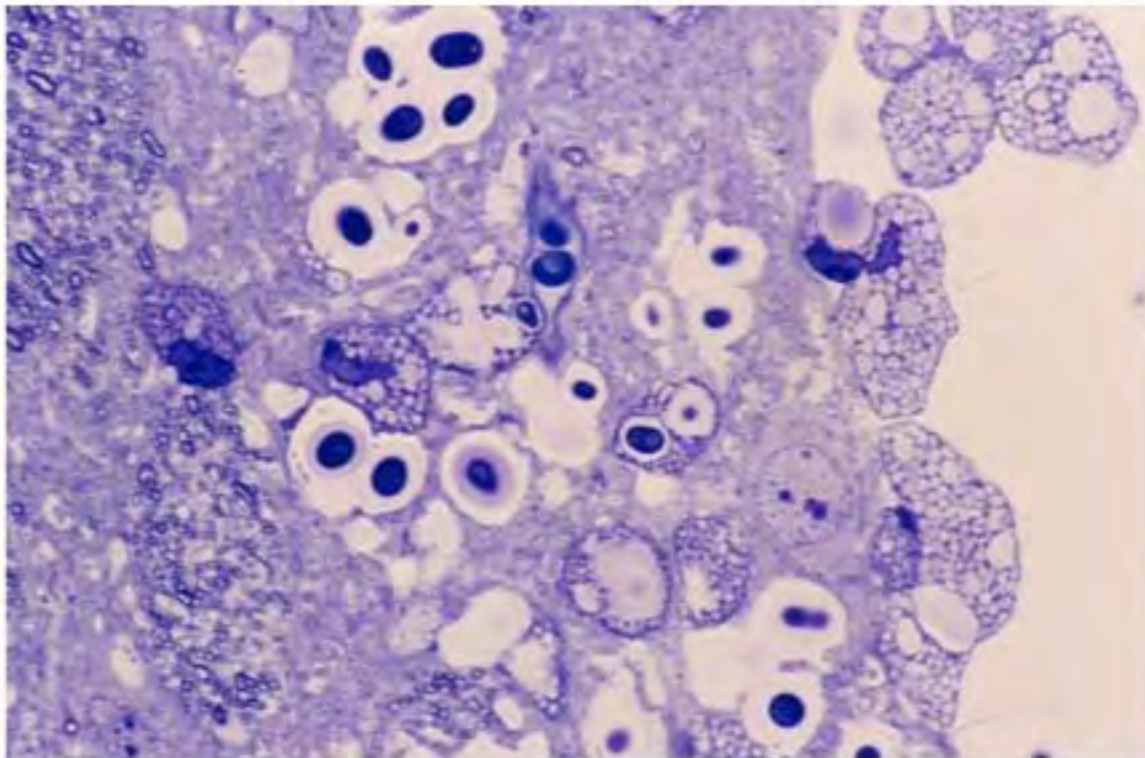
Centre National de Référence Mycologie et Antifongiques,

Unité de Mycologie Moléculaire, CNRS URA3012, Institut Pasteur, Paris

Cryptococcus neoformans

- ✓ **Levure capsulée présente dans l'environnement (pigeons ++)**
- ✓ **Cosmopolite mais de répartition géographique différente selon les sérotypes :**
 - A cosmopolite *C. neoformans* var. *grubii*
 - D européen (France) *C. neoformans* var. *neoformans*
 - B et C tropicaux (*C. gattii*)
- ✓ **Génome : \approx 23 Mb, séquençage achevé**
- ✓ **Cycle sexué, mais population majoritairement clonale avec peu de recombinaisons génétiques**

Probablement intra-cellulaire facultatif



Virulence de *C. neoformans* et hôte

(Casadevall et al. Curr. Opin. Microbiol. 2003;6:332 – Steenbergen & Casadevall Microbes & infection 2003; 5:667)

- ✓ **Mélanine** : résistance au killing oxydatif, aux antifongiques, à la phagocytose, tropisme cérébral
- ✓ **Phospholipase, protéase** : croissance intracellulaire, lésions tissulaires
- ✓ **Croissance à 37°C**
- ✓ **Mating type**
- ✓ **Uréase**

- ✓ **Et surtout la capsule polyosidique**

Capsule polyosidique de *C. neoformans*



Photo S. Varadaradjalou
(Faculté de Pharmacie de Paris)



Cerveau de souris infectée expérimentalement
(état frais)

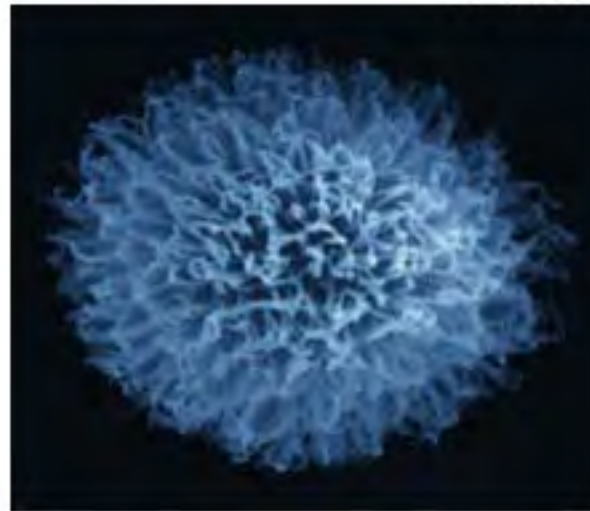
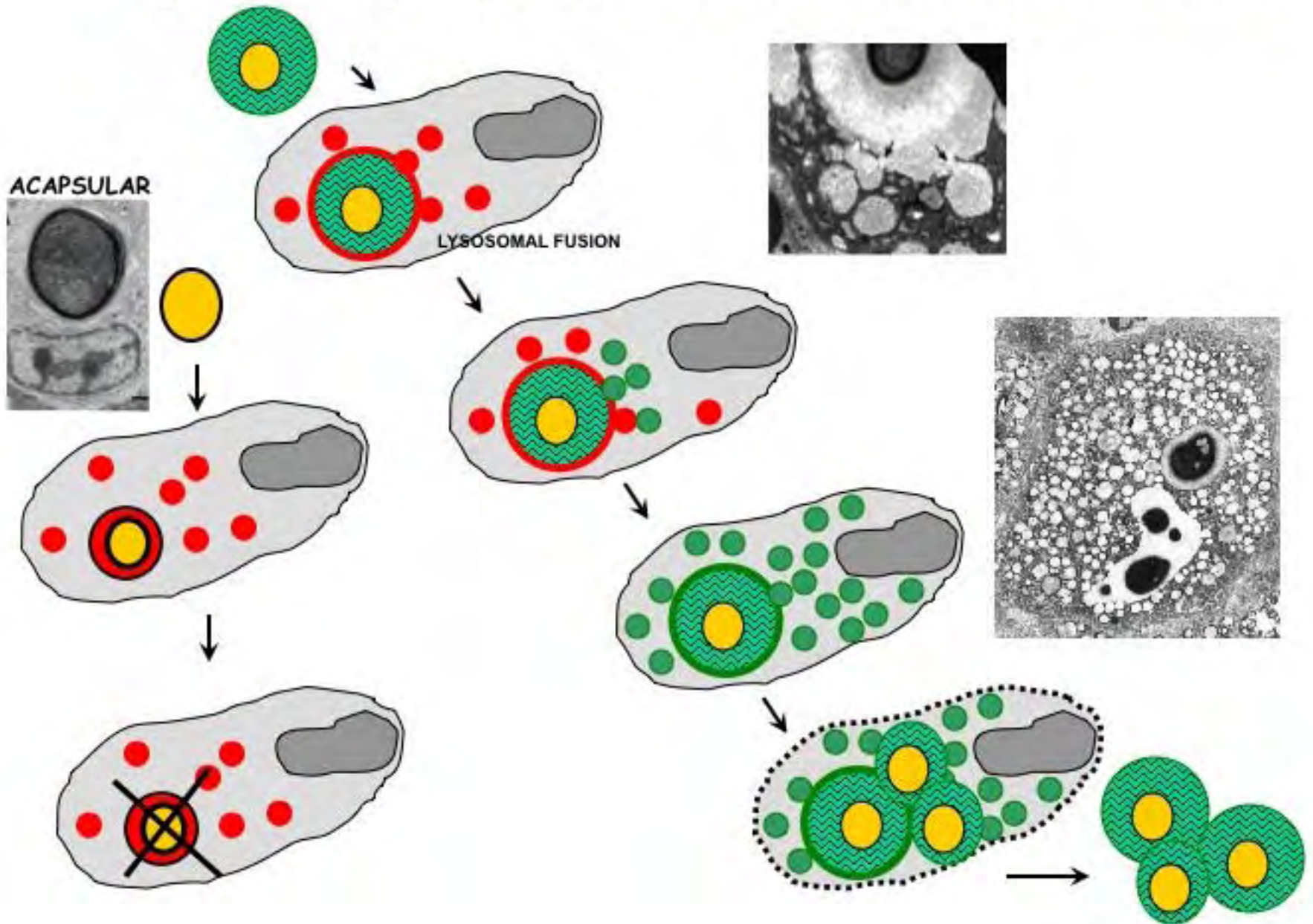


Photo J. Nosanchuk, Albert
Einstein College of Medicine,
Bronx, NY

Capsule et phagocytose/survie intracellulaire



Effets délétères du polyoside capsulaire de *C. neoformans* (1)

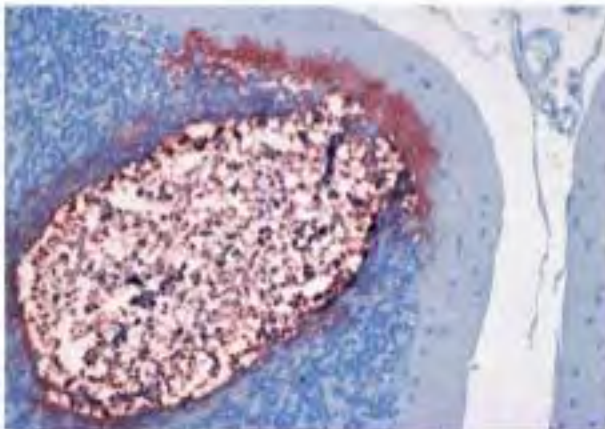
- ✓ **Réduction de la survie chez les souris** (Bennett & Hasenclever, J. Immunol. 1965;94:916)
- ✓ **Œdème cérébral** (Hirano et al., J. Pathol. Bacteriol. 1966;91:149)
- ✓ **Inhibition de la production d'anticorps : ag T-indépendant classe II** (Murphy & Cozad Infect. Immun. 1972;5:896 – Kozel & Cazin, *Infect. Immun.* 1972;5:35 – Dromer et al., Immunogenetics. 1988;28:417)
- ✓ **Masquage des IgG liées à la paroi** (McGaw & Kozel, Infect. Immun. 1979;25:262)
- ✓ **Activation du complément et déplétion** (Macher et al., J. Immunol. 1978;120:1686)

Effets délétères du polyoside capsulaire de *C. neoformans* (2)

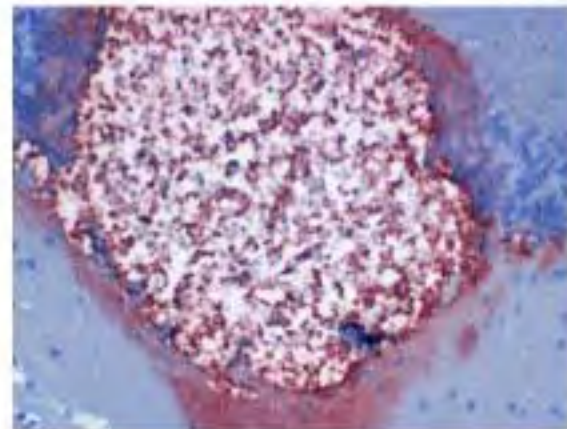
- ✓ **Inhibition de la phagocytose** (Bulmer & Sans, J. Bacteriol. 1968;95:5 – Kozel, Infect. Immun. 1977;16:99)
- ✓ **Induction d' une tolérance immunologique** (Henderson et al., J. Clin. Invest. 1982;69:1185)
- ✓ **Interférence avec la présentation de l' antigène** (Vecchiarelli et al., Clin. Exp. Immunol. 1994;98:217)
- ✓ **Augmentation de l' infection VIH in vitro** (Pettoello-Mantovani et al., Lancet 1992;339:21 – Orendi et al., AIDS 1994;8:423)

Lésions cérébrales entourées de CPS

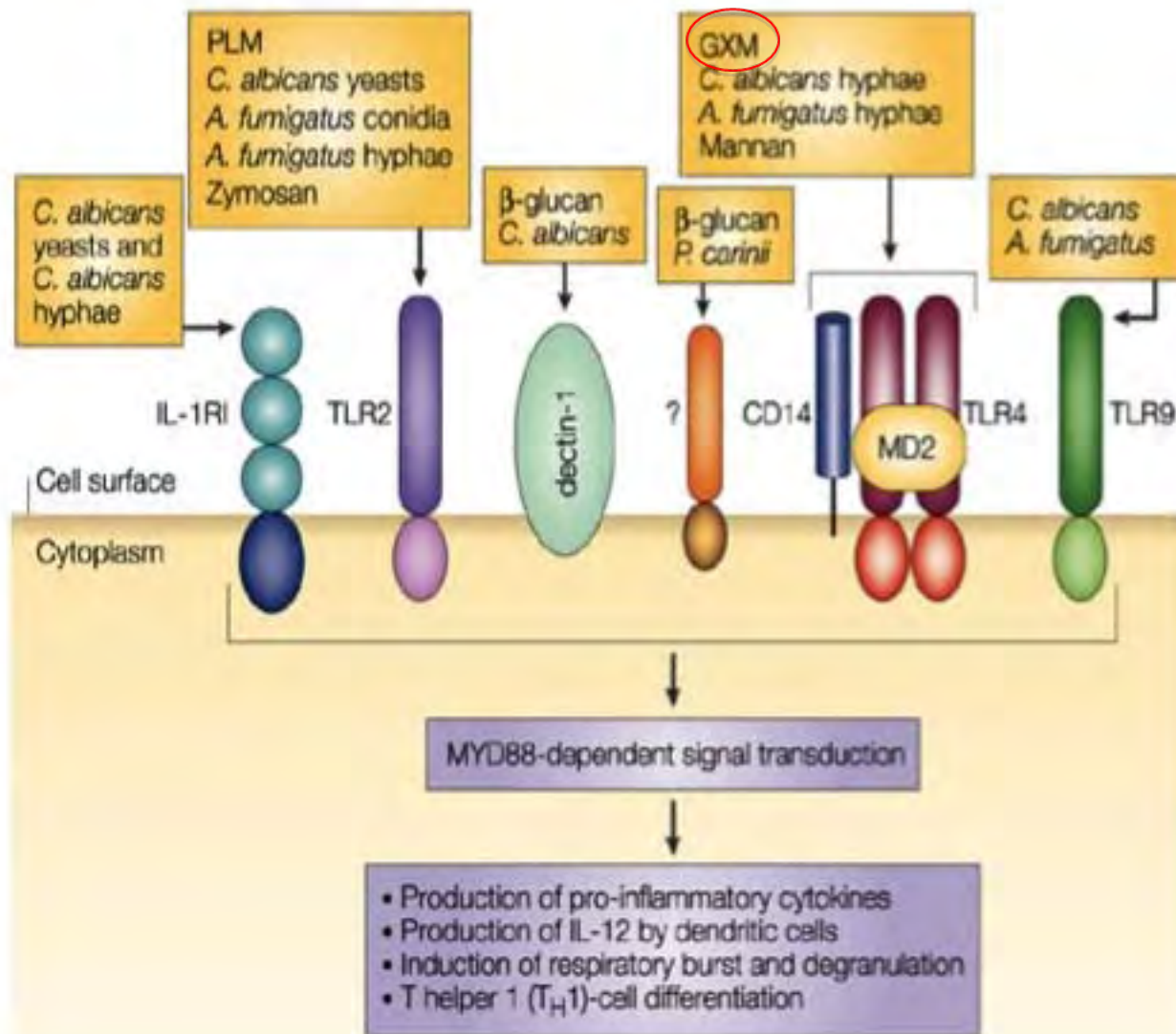
SOURIS



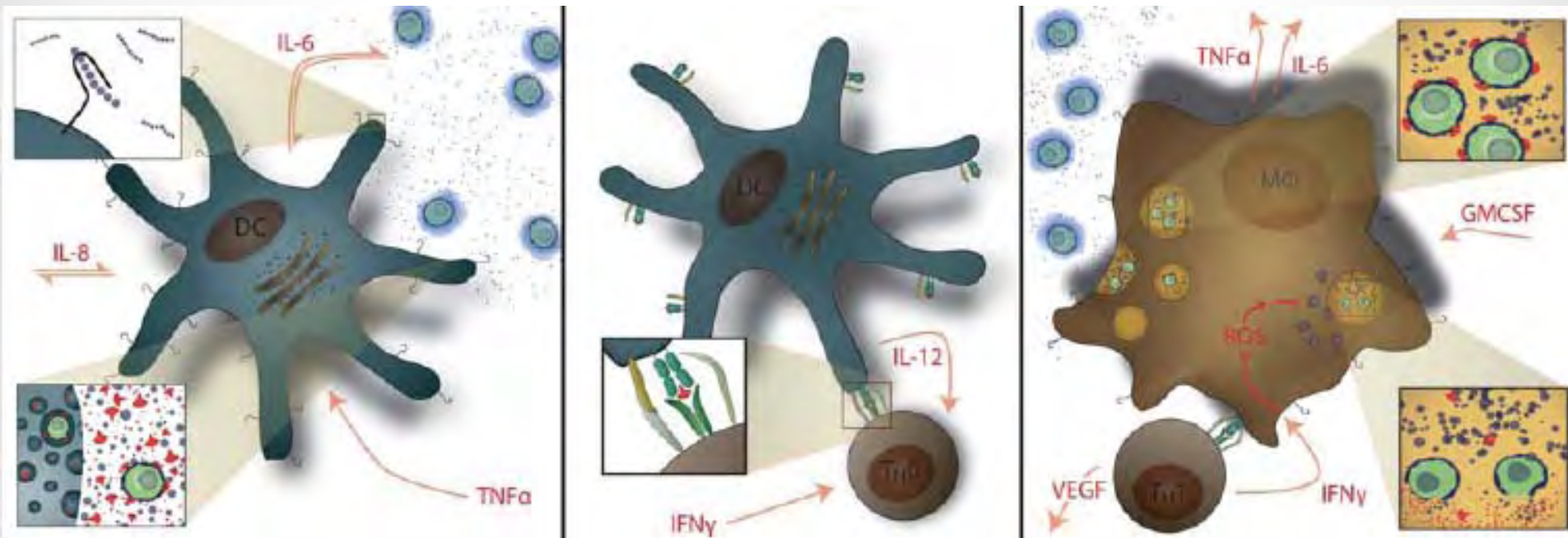
HOMME



Molécules de surface et cellules de l'hôte

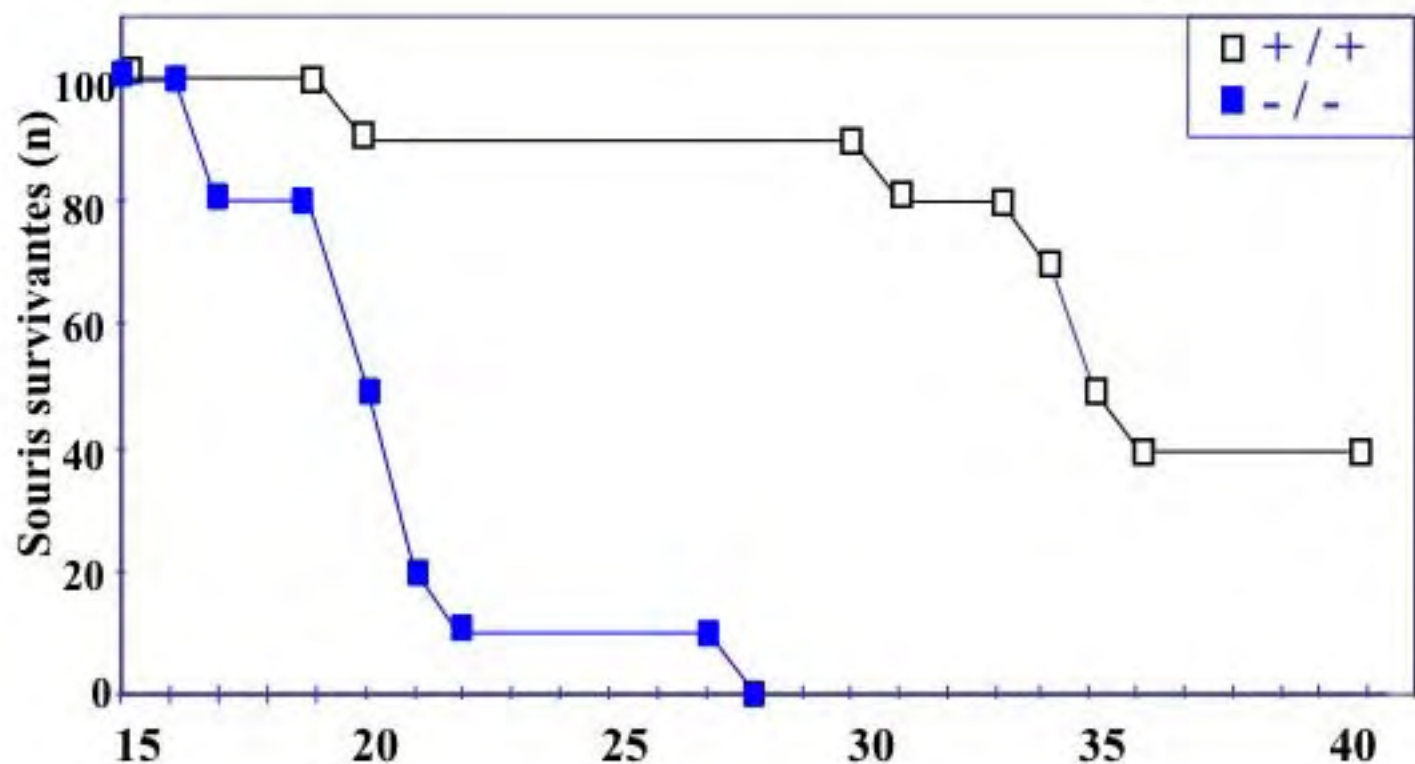


Normal Immunology of Cryptococcosis.



Susceptibilité accrue des souris KO TNF- α /Lt- α

(Rayhane et al. J. Infect. Dis. 1999; 180 (5) : 1637)



Jours après inoculation de *C. neoformans* (2×10^6 i.v.)

Immunité acquise

- **Efficace le plus souvent** (contact permanent avec les champignons)
- **Marquée par réaction granulomateuse :**
 - **Primo-infection fréquente avec Cn... : nodule pulmonaire**
 - **Pas d'infection ultérieure en l'absence de déficit immunitaire**
- **En cas d'invasion tissulaire : activation des Ly T par cytokines et phagocytes**
- **Nécessité d'une réaction Th1 prédominante médiée par IL-12/IFN- γ pour entraîner une résistance à l'infection fongique**

Rôle prépondérant de l'immunité cellulaire dans la réponse immunitaire anti-*C. neoformans*

- ✓ Arguments cliniques : SIDA+++
- ✓ CD4+ et CD8+ (Hill & Harmsen *J. Exp. Med.* 1991;173:755 – Mody et al. *Mycopathologia.* 1994;125:7)
 - indispensable au contrôle de l'infection pulmonaire
 - directement fongistatique sans opsonines
 - CD4+ indispensables à la formation du granulome et à la prévention de la dissémination cérébrale
- ✓ Réponse inflammatoire faible chez les sujets VIH positif
- ✓ Macrophages : rôle clé dans les défenses cellulaires non spécifiques

Cryptococcosis

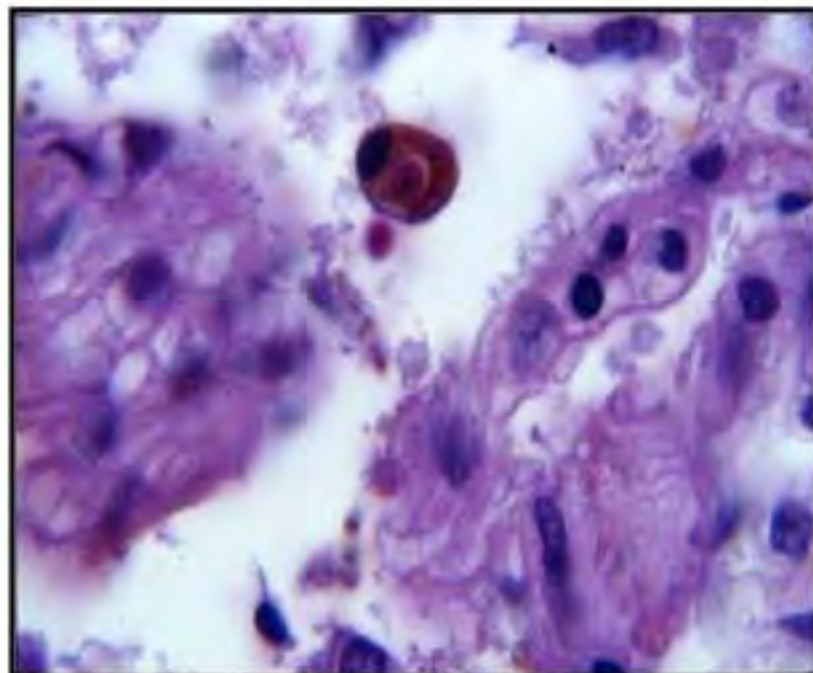
Yeast : *Cryptococcus neoformans/gattii*

Major risk factor (neoformans) = cellular immune deficiency (HIV++)

- AIDS defining illness
- 13-18% of HIV+ subjects in some African or South East Asian countries :
 - ✓ 1st cause of meningitis in the Southern part of Africa
 - ✓ 2nd opportunistic infection after TB
 - ✓ Mortality \geq 50% within the first 15 days
- Major impact of HAART

Who develops cryptococcosis

- **2125 cases in France (1985-2001)**
- **1644 AIDS cases (77.4%)**
- **335 HIV negative :**
 - **17.4% SOT**
 - **36.8% Hem malign/cancers**
 - **20.4% various underlying dis**
 - **25.4% no known immune deficit**

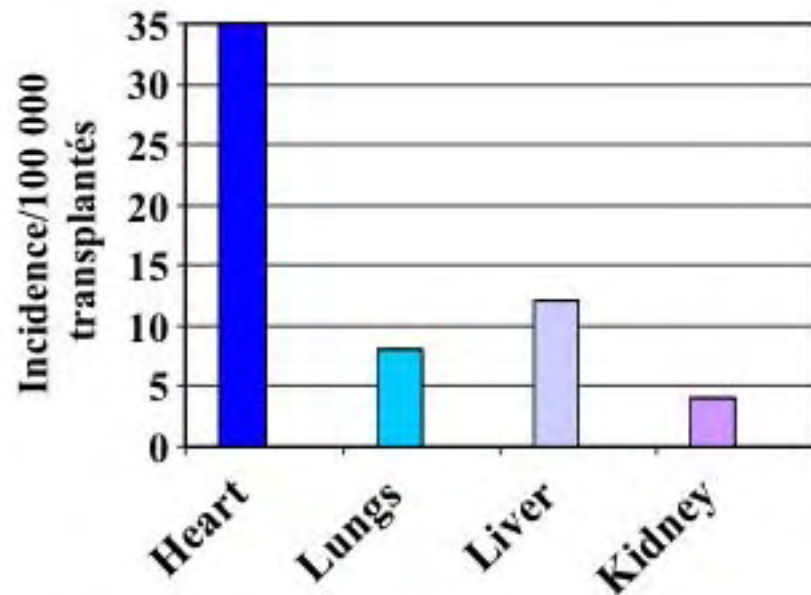


Epidemiology of SOT-associated cryptococcosis (1)

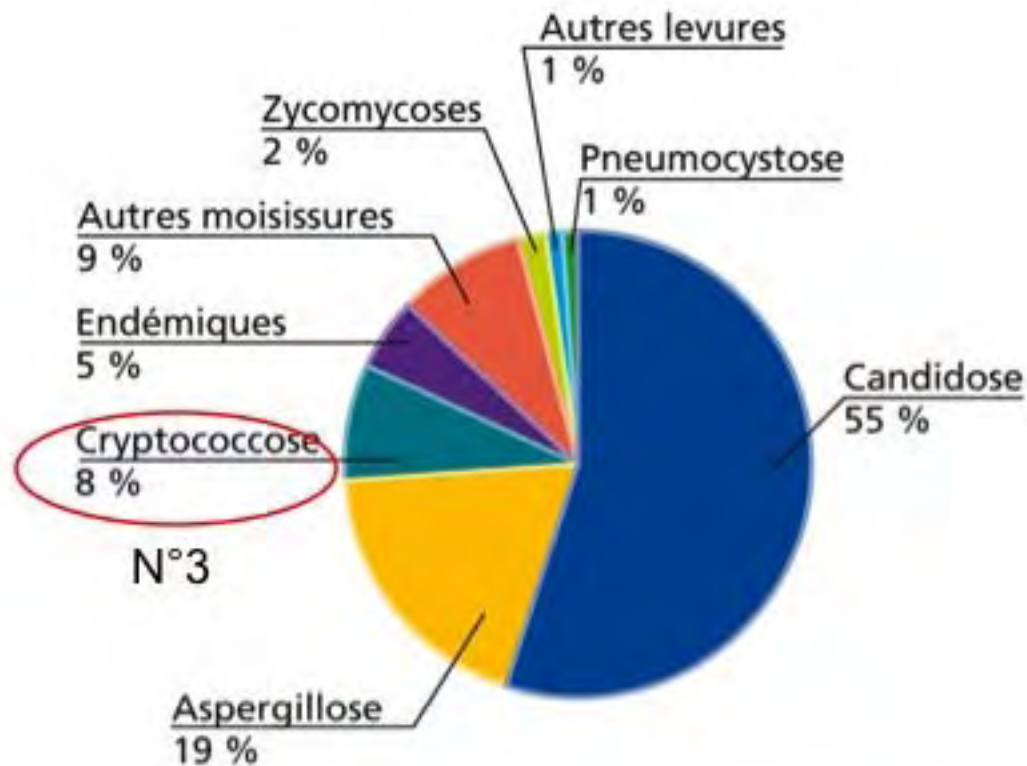
- ✓ **Prevalence : 0.26-5%; 70.1-78% male**
- ✓ **Major role of steroids** [Husain Emerg Infect Dis 2001; Wu Transpl Infect Dis 2002; Vilchez Am J Transplant 2002; Jabbour Transplantation 1996; John Transplantation 1994]
- ✓ **Incidence after anti-thymocyte Ig or alemtuzumab (anti CD-52)** [Silveira, Transpl Infect Dis 2007] :
 - ✓ 0.26% (2/781) if not
 - ✓ 0.3% (2/646) after 1 dose
 - ✓ 2.24% (3/134) after 2 doses ($p = 0,03$)
 - ✓ Median time of occurrence 255 d (7-517 d), 14.2% mortality
- ✓ **Alemtuzumab used for rejection [OR = 3.5; 95%CI, 1.8-6.8]** [Peleg, CID 2007]

Epidemiology of SOT-associated cryptococcosis (2)

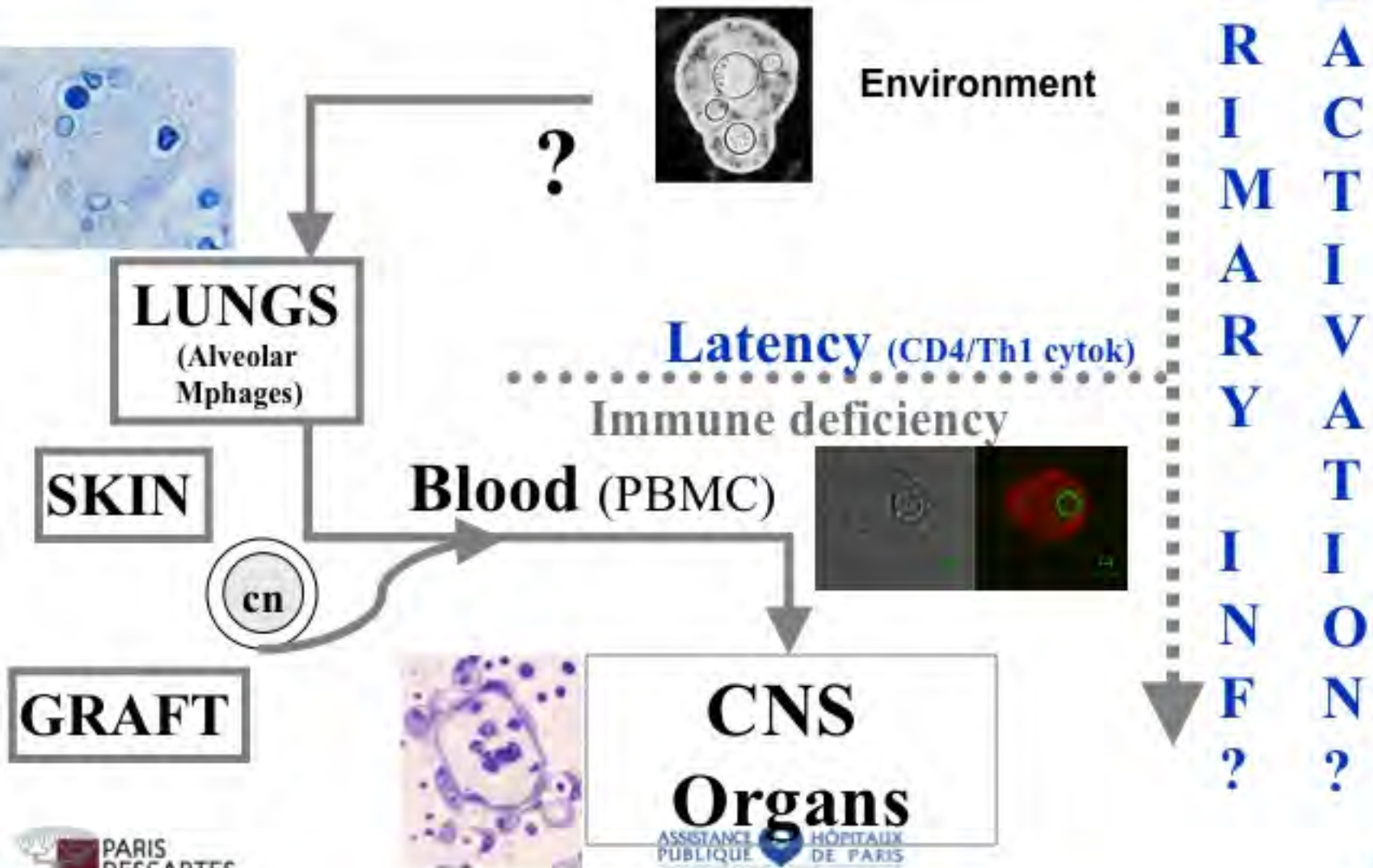
- **Variable incidence according to transplanted organ** [Vilchez et al. Am J Transplant 2002]
- **Liver transplant recipients :** [Singh et al. CID 1997; JID 2007]
 - Older than others
 - Earlier occurrence
 - Skin and bone/joints lesions /
 - Increased risk of dissemination (HR 6.65)
 - 5% of positive blood cultures [Singh Clin Transplant 1997]



Distribution of fungal species in solid organ transplanted patients with IFI in the US



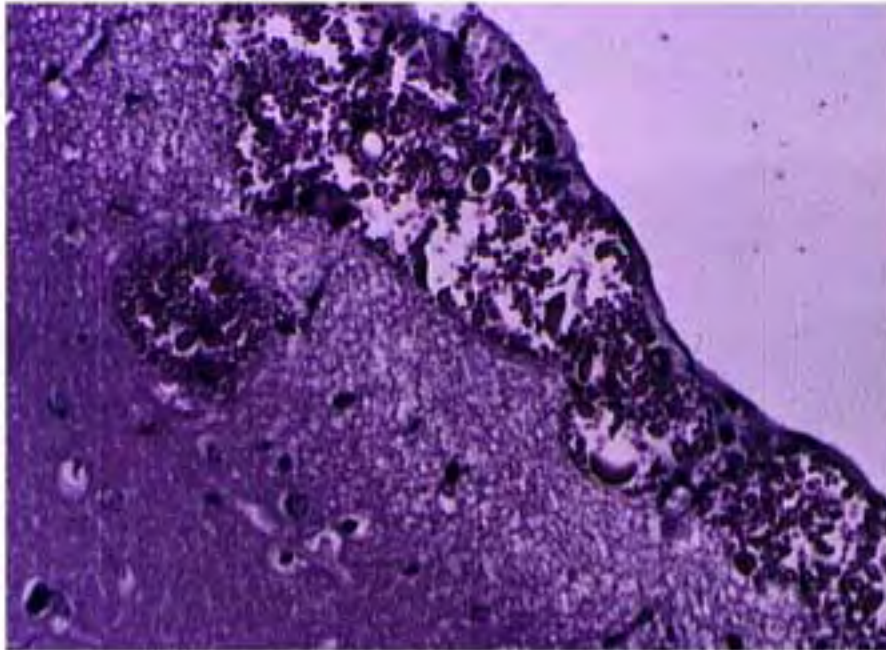
C. neoformans infection pathogenesis during SOT



Lésions cérébrales comparables

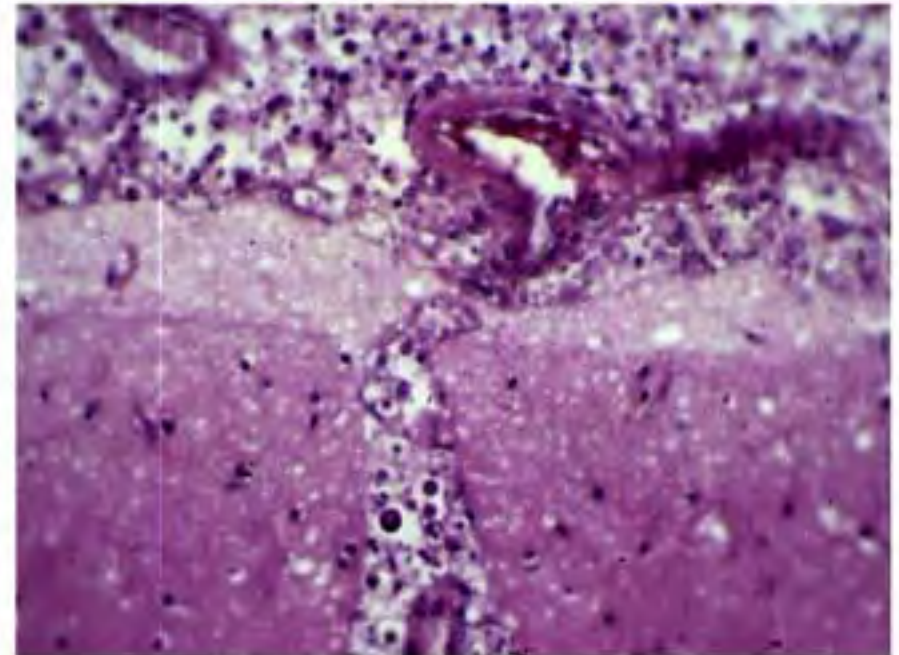
SOURIS

HOMME



J8 après infection i.v.
coloration PAS, F. Gray

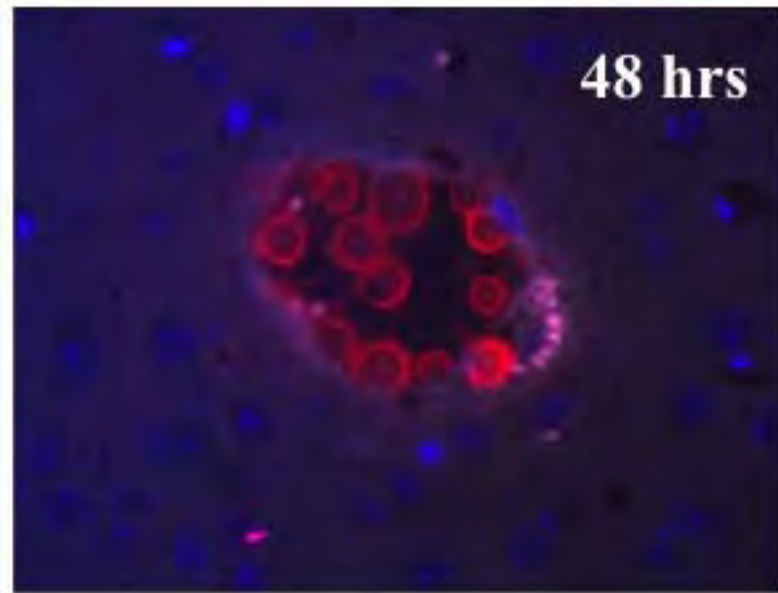
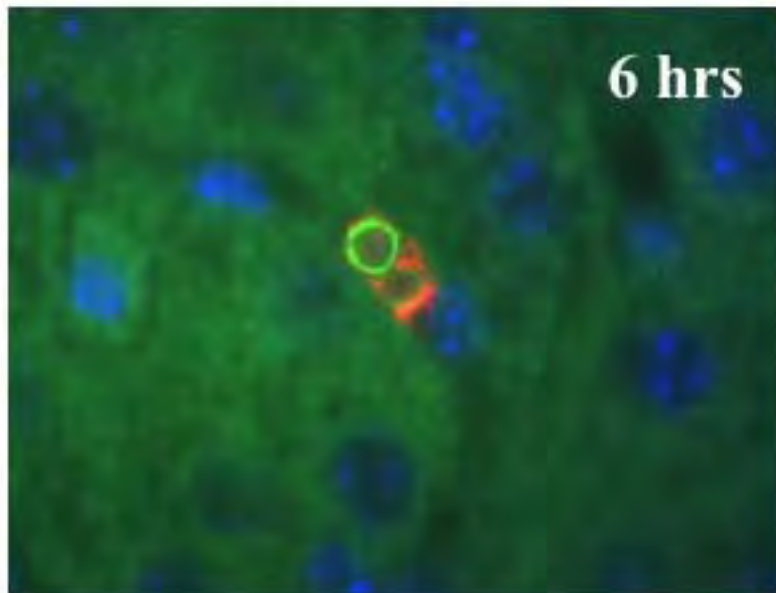
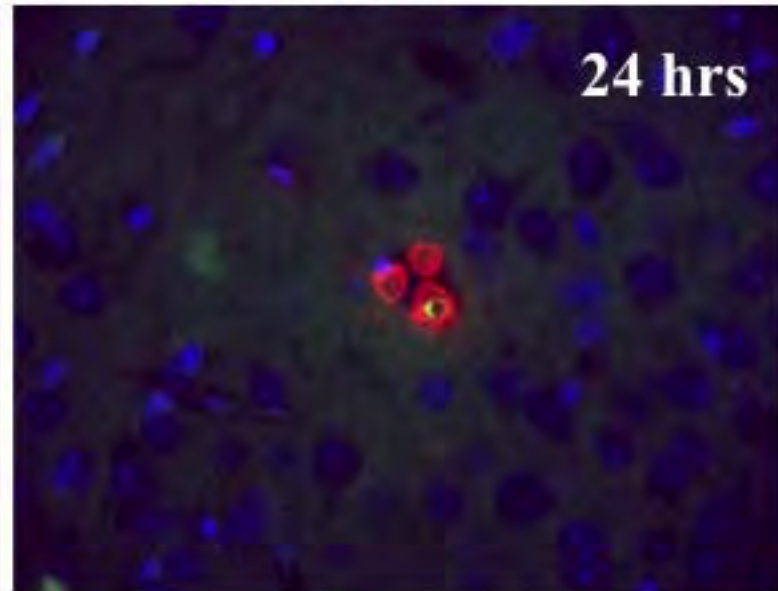
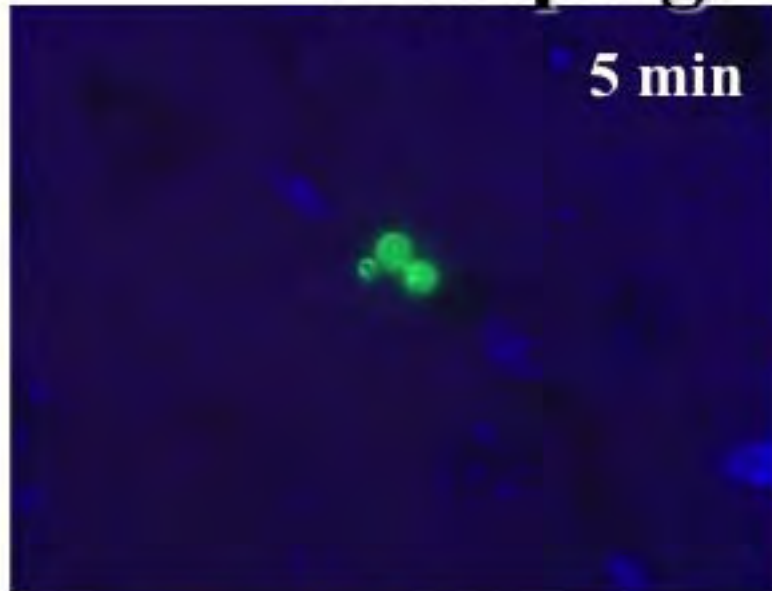
$\log \text{CFU/g} = 6,8 \pm 0,3$



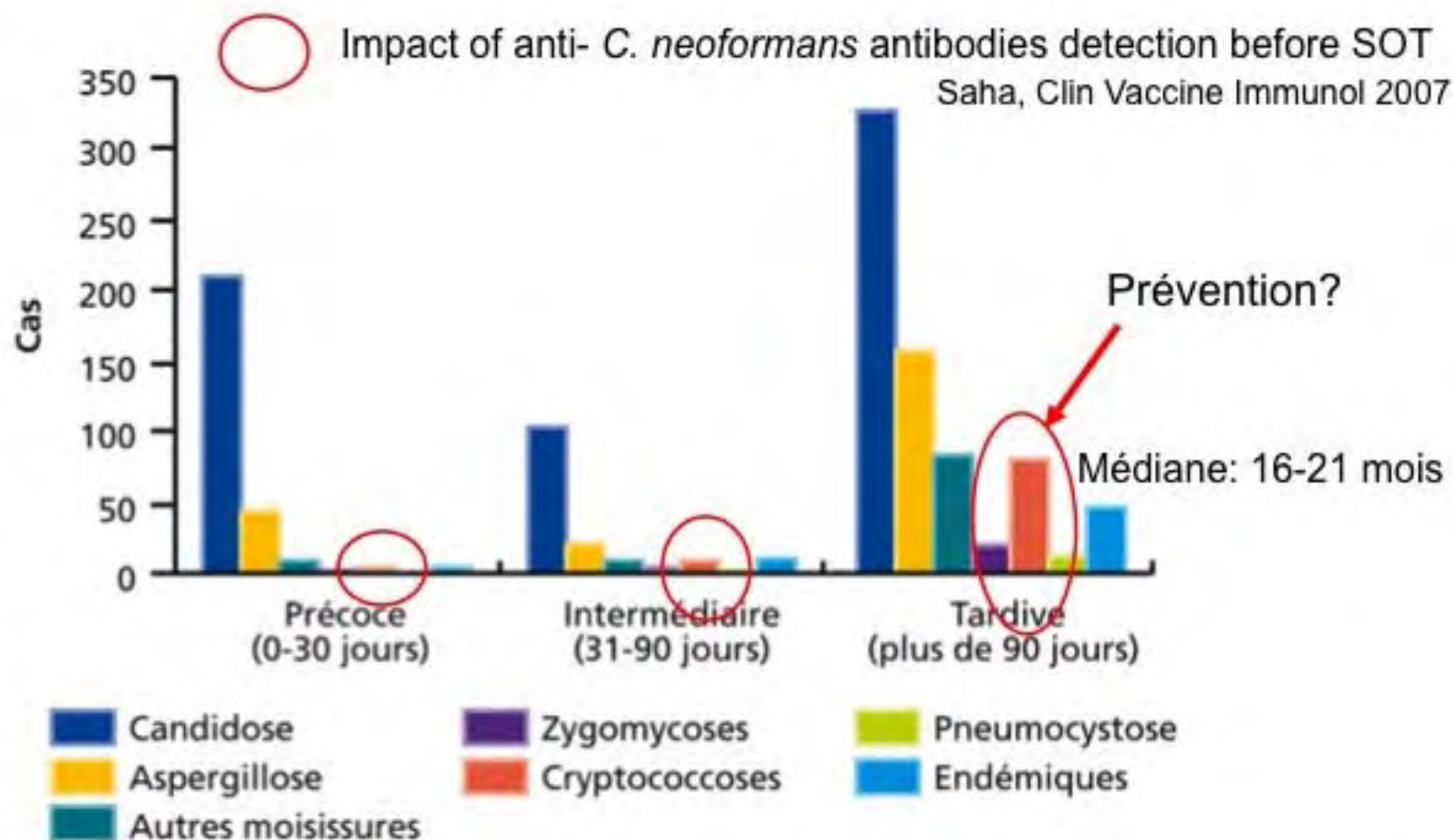
J2 après le diagnostic
coloration HES, M. Huerre

$\log \text{CFU/g} = 6,5$

Marquage E1 / CRND-8



Time interval between transplantation and IFI



Pappas et al. CID 2010

Cryptococcal Collaborative Transplant Study Group

11 original papers published since 2005 in US journals



INVITED ARTICLE

IMMUNOCOMPROMISED HOSTS

David C. Goffman, October 2010

Cryptococcosis in Solid Organ Transplant Recipients: Current State of the Science

USA GUIDELINES

Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

Naveen Singh,¹ Françoise Dromer,² John R. Perfect,³ and Olivier Lortholary^{4*}

¹University of Pittsburgh, Pennsylvania; ²Ghent University, Belgium; ³North Carolina, and ⁴Seattle Pacific, Molecular Mycology Unit, National Reference Center for Mucormycosis and Aspergillosis, and ⁵Chironville Pasteur Diagnostic Center of Infectology, Hôpital Pasteur, Hôpital Pasteur-Edouard Belin, Paris, France

John R. Perfect,¹ William E. Dismukes,² Françoise Dromer,³ David L. Eckman,⁴ John R. Graybill,⁵ Richard J. Haral,⁶ Thomas S. Harrison,⁷ Robert A. Larsen,⁸ Olivier Lortholary,^{9*} Minh-Hong Nguyen,¹⁰ Peter G. Pappas,¹¹ William G. Penderly,¹² Naveen Singh,¹³ Jack H. Sobel,¹⁴ and Tessa C. Svanbäck¹⁵



INSTITUT PASTEUR

Unrecognized pretransplant or donor derived cryptococcosis in SOT

Sun et al. CID, in press

- Multicenter cohort : 175 (SOT) recipients with cryptococcosis
- Very-early and late-onset cryptococcosis were defined as disease occurring ≤ 30 days or >30 days post-transplant, respectively.
- **Very-early onset disease :**
 - 5% ; mean of 5.7 days post-transplant.
 - More frequently liver transplant recipients
 - More frequent unusual locations [transplanted allograft and surgical fossa/site (55.6% vs. 7.2%, $p < .0001$)]
 - May have unrecognized pre-transplant or donor-derived cryptococcosis.

Graft transmitted cryptococcosis in the US

John Baddley et al. Unpublished data

	Alleles						
Locus	CAP59	GPD1	IGS1	LAC1	PLB1	SOD1	URA5
Allele Length	501	489	725	471	533	536	637
Patient 1 blood	8	10	15	8	12	3	11
Patient 2 blood	8	10	15	8	12	3	11
Patient 3 blood	8	10	15	8	12	3	11
Patient 3 CSF	8	10	15	8	12	3	11

MLST similarities of *C. neoformans* isolates from 3 geographically distant SOT recipients from the same donor

Clinical presentation of SOT-associated cryptococcosis

- ✓ **Impact of immunosuppressive therapy :**
 - ✓ **Tacrolimus :**
 - ✓ **< CNS involvement; > skin/subcutaneous/bone/joints lesions** [Husain, EID 2001, Singh, Clin Transplant 1997]
- ✓ **Meningeal symptoms < 1/3 cases** [Vilchez, Am J Transplant 2002] despite involvement in 60% of cases
- ✓ **Pulmonary nodules ± ARDS** [Vilchez, Medicine 2001]
- ✓ **Primary or secondary skin lesions** [Husain, EID 2001]

Cutaneous Cryptococcosis in SOT

Sun et al. Med Mycol 2010

- **26/146 (17.8%) :**
 - nodular/mass (34.8%)
 - maculopapule (30.4%)
 - ulcer/pustule/abscess (30.4%)
 - cellulitis (30.4%)
- 65.2% lower extremities
- **Localized disease in 30.8%**
- Overall mortality at 90 d = 15.4%



146 SOT recipients

Identifying Predictors of Central Nervous System Disease in Solid Organ Transplant Recipients With Cryptococcosis

Ryosuke Otsuwa,^{1,2} Barbara D. Alexander,³ Olivier Lortholary,^{4,5} Françoise Dromer,⁵ Graeme N. Forrest,⁶ G. Marshall Lyon,⁷ Jyoti Somani,⁷ Krishan L. Gupta,⁸ Ramon del Busto,⁹ Timothy L. Pruett,¹⁰ Cassi D. Sifri,¹⁰ Ajit P. Limaye,¹¹ George T. John,¹² Goran B. Klimkait,¹³ Kenneth Purcell,¹⁴ Valenzina Seacor,¹⁵ Michele I. Morris,¹⁶ Lorraine A. Dowdy,¹⁶ Patricia Muñoz,¹⁷ Andre C. Kallil,¹⁸ Julia Garcia-Diaz,¹⁹ Susan Orloff,²⁰ Andrew A. House,²¹ Sally Houston,²² Dannah Wray,²³ Shirish Huprikar,²⁴ Leonard B. Johnson,²⁵ Asad Humar,²⁶ Raymond R. Razonable,²⁷ Robert A. Fisher,²⁸ Shahid Husain,²⁹ Marilyn M. Wagener,² and Nisa Singh^{1,2,20}

(*Transplantation* 2010;89: 69–74)

- 129 (88%)/146 SOT recipients with cryptococcosis with CSF analysis
 - 80 (62%) had CNS disease
- Increased risk of CNS disease :
 - abnormal mental status,
 - > 24 months post-transplantation
 - CPS titer > 1:64
 - fungemia

**Lumbar
puncture
mandatory
for these
patients**

Central Nervous System Cryptococcosis in Solid Organ Transplant Recipients: Clinical Relevance of Abnormal Neuroimaging Findings

Nina Singh,^{1,26} Olivier Lortholary,² Françoise Dromer,³ Barbara D. Alexander,⁴ Krishan L. Gupta,⁵ George T. John,⁶ Ramon del Busto,⁷ Goran B. Klönschalm,⁸ Jyoti Somani,⁹ G. Marshall Lyon,⁹ Kenneth Pursell,¹⁰ Valentina Seosor,¹¹ Patricia Muñoz,¹² Ajla P. Limaye,¹³ Andre C. Kall,¹⁴ Timothy E. Pruett,¹⁵ Julia García-Díaz,¹⁶ Azul Humar,¹⁷ Sally Houston,¹⁸ Andrew A. House,¹⁹ Dannah Wray,²⁰ Susan Orloff,²¹ Lorraine A. Dowdy,²² Robert A. Fisher,²³ Joseph Heitman,²⁴ Marilyn M. Wagener,¹ Shahid Husain,^{1,25} and the Cryptococcal Collaborative Transplant Study Group

(Transplantation 2008;86: 647-651)

- 122 SOT with cryptococcosis (50% with CNS involvement)
- **CNS lesions were identified in 16/61 patients (26.3%)**
 - leptomeningeal lesions in eight,
 - parenchymal lesions in six
 - hydrocephalus in two
 - 13/16 CNS lesions at diagnosis
 - 3 CNS Immune reconstitution inflammatory syndrome
- CPS titers significantly higher :
 - meningeal versus parenchymal lesions
 - hydrocephalus
- Mortality higher if parenchymal lesions

Cryptococcosis diagnosis: extensive work up

(Dromer et al. PLoS Medicine 2007)

Parameter	Percentage of patients (n) according to HIV status		P		
	Positive (n = 177) ^a	Negative (n = 53)			
Mycological results					
Positive blood culture	46	(168)	12	(51)	<10 ⁻³
Positive CSF culture	89	(176)	69	(42)	0.003
Positive urine culture	30.5	(154)	25	(52)	NS
Disseminated infection	61	(170)	39	(52)	0.007
Serotype A isolate	76	(171)	61	(51)	0.048
Positive serum antigen detection in tested patients w/	95	166	74.5	51	<10 ⁻³
Disseminated cryptococcosis	100	(96)	89	(19)	0.028
Meningoencephalitis	97	(146)	86	(29)	0.027
Mean serum antigen titer in log ₂ [95%CI]	9.2 [8.5 – 9.9]	(158)	6.1 [4.9 – 7.3]	(38)	<10 ⁻³
CSF characteristics in patients with meningoencephalitis^c					
Positive India ink	88	(156)	52	(31)	<10 ⁻³
Median CSF cell count/mm ³ [IQR] ^d	9 [2 – 65]	(153)	31 [1 – 130]	(29)	NS
Median CSF protein conc (g/l) [IQR]	0.7 [0.4 – 1.2]	(152)	0.85 [0.5 – 1.1]	(31)	NS
Mean CSF:serum glucose conc. [95%CI]	0.46 [0.42 – 0.50]	(141)	0.35 [0.27 – 0.44]	(26)	0.040
Positive CSF antigen	97	(141)	100	(27)	NS
Mean CSF antigen titer (log ₂)[95% CI]	8.3 [7.6 – 9.0]	(137)	6.2 [4.3 – 8.1]	(29)	0.019

Pulmonary Cryptococcosis in Solid Organ Transplant Recipients: Clinical Relevance of Serum Cryptococcal Antigen

Nina Singh,¹ Barbara D. Alexander,² Olivier Lortholary,^{19,20} Françoise Dromer,¹⁹ Krishan L. Gupta,²² George T. John,²³ Ramon del Busto,³ Goran B. Klintnalm,⁴ Jyoti Somani,⁵ G. Marshall Lyon,⁵ Kenneth Pursell,⁶ Valentina Stosor,⁷ Patricia Muñoz,²¹ Ajit P. Limaye,⁹ Andre C. Kalil,⁷ Timothy L. Pruett,²⁰ Julia Garcia-Diaz,²² Atul Humar,^{17,*} Sally Houston,¹³ Andrew A. House,¹⁸ Dannah Wray,¹⁵ Susan Orloff,¹⁶ Lorraine A. Dowdy,¹⁴ Robert A. Fisher,¹¹ Joseph Heitman,² Marilyn M. Wagener,¹ and Shahid Husain¹

CID 2008

Prospective, multicenter study.

- Serum CPS + : 83% (40/48) of patients
- Extrapulmonary lesions: Ag most often + (p=0.018)
- Higher titers if extrapulmonary lesions (p=0.003) or fungemia (p=0.045)
- Isolated nodule : Ag less often + (p=0.053)
- Lung transplants: less often Ag + (p=0.003)

Antifungal Management Practices and Evolution of Infection in Organ Transplant Recipients with *Cryptococcus Neoformans* Infection

Nina Singh,¹⁻²² Olivier Lortholary,² Barbara D. Alexander,³ Krishan L. Gupta,⁴ George T. John,⁵ Kenneth J. Pursell,⁶ Patricia Muñoz,⁷ Goran B. Klintmalm,⁸ Valentina Stosor,⁹ Ramon del Busto,¹⁰ Ajit P. Limaye,¹¹ Jyoti Somani,¹² Marshall Lyon,¹² Sally Houston,¹³ Andrew A. House,¹⁴ Timothy L. Pruett,¹⁵ Susan Orloff,¹⁶ Atul Humar,¹⁷ Lorraine A. Dowdy,¹⁸ Julia Garcia-Diaz,¹⁹ Andre C. Kalil,²⁰ Robert A. Fisher,²¹ Joseph Heitman,³ and Shahid Husain¹

(*Transplantation* 2005;80: 1033–1039)

- **International cohort study of 83 patients**
- Duration of follow-up of 2.1-5.2 yrs.
- **Amphotericin B vs. Fluconazole:**
 - CNS infection (69% vs. 16%, $p = 0.00001$),
 - Disseminated infection (82.7% vs. 20%, $p = 0.00001$)
 - Fungemia (29% vs. 8%, $p = 0.046$)
- M6 survival < if CSF Wk2 culture + (50% vs. 91%, $p = 0.06$)
- Median duration of maintenance therapy = 183 days
- Relapse = 1.3% (1/79)

Are lipid formulations of AmB better for CNS cryptococcosis in SOT ?

Sun et al. CID 2009

75 patients with SOT-cryptococcosis treated with polyenes

- 55 (73.3%) received lipid formulations
- 20 (26.7%) received AmBd
- **Overall mortality at 90 d**
 - 10.9% w AmB lipid formulations
 - 40.0% w AmBd
- **AmB lipid formulations independently associated with a lower mortality (OR, 0.11; 95% CI,0.02-0.57; P = .008)**
- Mortality did not differ with or without flucytosine

Optimal therapeutic strategy during cryptococcosis: impact of the Crypto A/D study

- 208 patients with cryptococcosis: analysis of failure (death or mycological failure) at W2 or M3
- **AmB + 5FC = best strategy in case of**
 - Meningoencephalitis
 - High fungal burden
 - Neurological abnormalities (26% failure vs. 56% if other strategies, $p < 0.001$)
- **Flucytosine for less than 14 d** (OR = 3.30 [1.12-9.70], $p = 0.030$)
independently associated with failure at M3

Dromer et al. PLoS ONE 2008

Management of cryptococcal meningitis in SOT Patients

IDSA Guidelines CID 2010

Regimen	Duration	Evidence
Induction therapy: ^a liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day) ^b	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

^a Immunosuppressive management may require sequential or step-wise reductions.

^b Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

Flucytosine monitoring : 30-80 µg/ml 2h after administration

Factors associated with mycological failure at W2 : Crypto A/D study

- ✓ **Dissemination** : OR 2.4 [95%CI, 1.2-4.9] p = 0.015
- ✓ **Serum Ag > 1/512** : OR 2.6 [95%CI, 1.3-5.4] p = 0.008
- ✓ **Lack of flucytosine** : OR 3.8 [95%CI, 1.9-7.8] p < 0.001
[+++ ≥ 14d]

Dromer et al. PLoS Medicine 2007/PLoS One 2008

Independent factors associated with Week 2 mortality : Prospective Crypto A/D Study

- ✓ **Neurological abnormality : 12 vs 3%**
- ✓ **Abnormal cerebral imaging : 12 vs. 2%**
- ✓ **Abnormal thoracic imaging : 11 vs. 3%**
- ✓ **Hyponatremia : 10 vs. 2%**

Dromer et al. PLoS Medicine 2007

Risk factors for death during SOT-associated cryptococcosis

A study of 111 patients

Singh, Alexander, Lortholary et al. JID 2007

- ✓ **Use of calcineurin inhibitors** : HR = 0.21, p = 0.008
- ✓ **Renal failure** : HR = 3.14, p = 0.037 [only factor found in literature review Husain EID 2001]
- ✓ **14% mortality rate at day 90** (42% in literature review; Husain EID 2001)
- ✓ **During meningitis** : vigilance disturbances, lack of headache and liver failure [Wu, Transpl Infect Dis 2002]

Calcineurin Inhibitor Agents Interact Synergistically with Antifungal Agents In Vitro against *Cryptococcus neoformans* Isolates: Correlation with Outcome in Solid Organ Transplant Recipients with Cryptococcosis^V

Dimitrios P. Kontoyiannis,^{1*} Russell E. Lewis,¹ Barbara D. Alexander,² Olivier Lortholary,³ Françoise Dromer,² Krishan L. Gupta,⁵ George T. John,⁶ Ramon del Busto,⁷ Goran B. Klintmalm,⁸ Jyoti Somani,⁹ G. Marshall Lyon,⁹ Kenneth Pursell,¹⁰ Valentina Stosor,¹¹ Patricia Muñoz,¹² Ajit P. Limaye,¹³ Andre C. Kalil,¹⁴ Timothy L. Pruett,¹⁵ Julia Garcia-Diaz,¹⁶ Atul Humar,¹⁷ Sally Houston,¹⁸ Andrew A. House,¹⁹ Dannah Wray,²⁰ Susan Orloff,²¹ Lorraine A. Dowdy,²² Robert A. Fisher,²³ Joseph Heitman,³ Nathaniel D. Albert,¹ Marilyn M. Wagener,²⁴ and Nina Singh^{24*}

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2008, p. 735–738



An Immune Reconstitution Syndrome–Like Illness Associated with *Cryptococcus neoformans* Infection in Organ Transplant Recipients

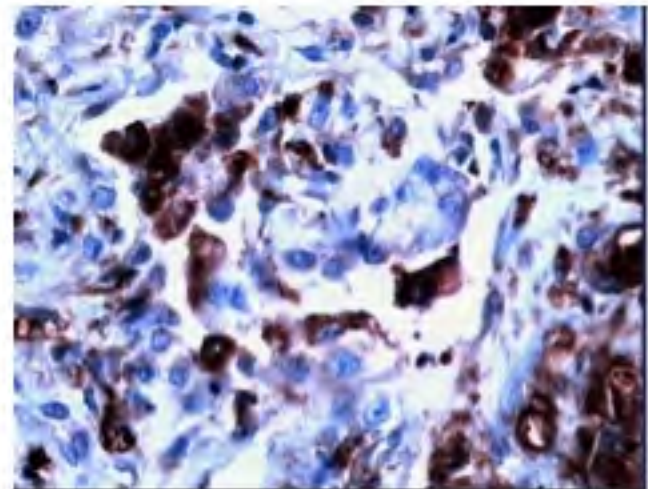
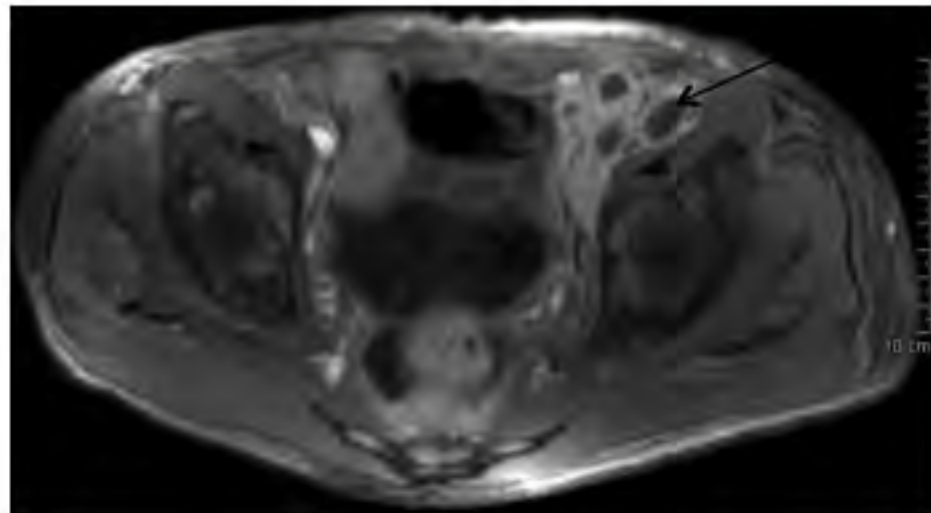
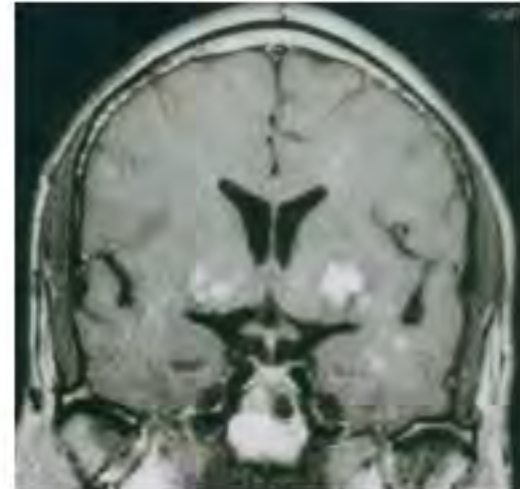
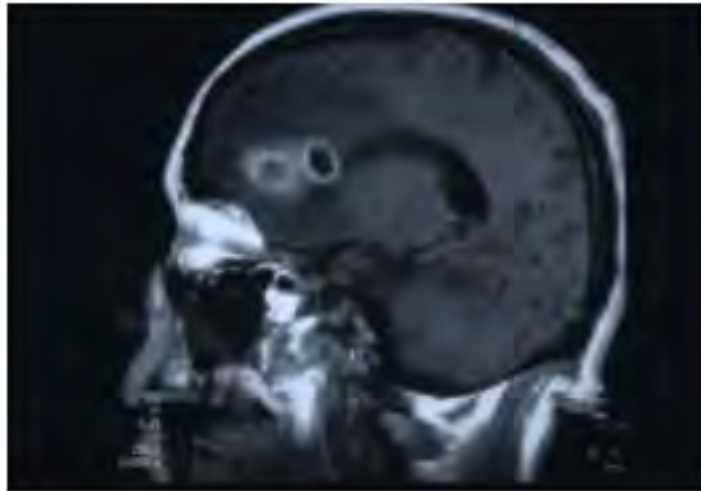
Prospective multicenter cohort: 4.8% pts

Nina Singh,¹ Olivier Lortholary,^{1b} Barbara D. Alexander,² Krishan L. Gupta,^{3a} George T. John,^{3b} Kenneth Pursell,³ Patricia Munoz,¹⁷ Goran B. Klintmalm,³ Valentina Stosor,⁴ Ramon del Busto,⁶ Ajit P. Limaye,⁷ Jyoti Somani,⁸ Marshall Lyon,⁸ Sally Houston,⁹ Andrew A. House,¹⁰ Timothy L. Pruett,¹¹ Susan Orloff,¹⁸ Atul Kumar,²¹ Lorraine Dowdy,¹⁹ Julia Garcia-Diaz,¹¹ Andre C. Kalil,¹⁹ Robert A. Fisher,¹² Shahid Husain,¹ and the Cryptococcal Collaborative Transplant Study Group*

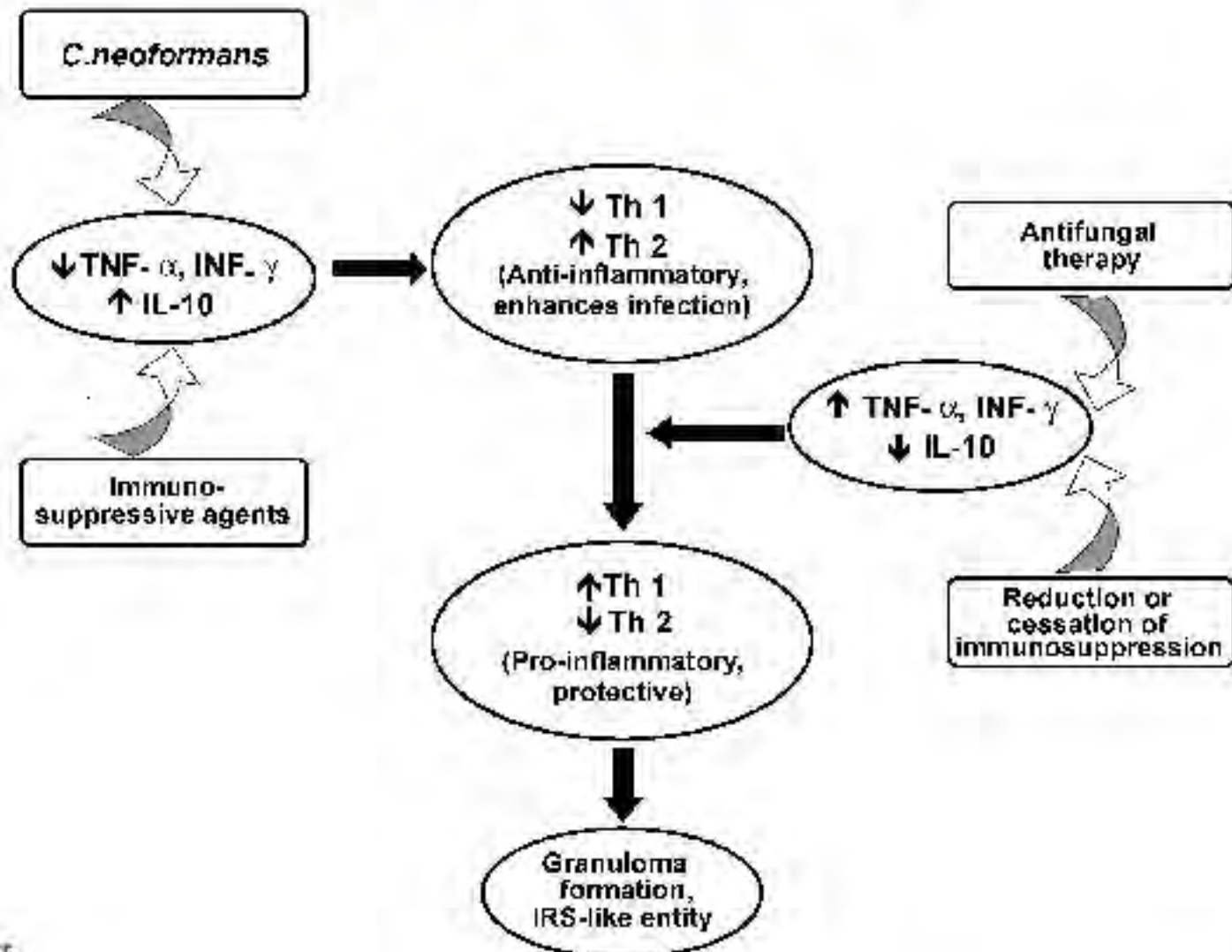
CID 2005

Type of transplant	
Kidney	2/4
Kidney-pancreas	1/4
Liver	1/4
Time to onset of <i>C. neoformans</i> infection post-transplant, median (range)	10.5 months (3-29 months)
Immunosuppressive regimen	
Tacrolimus, mycophenolate mofetil, prednisone	4/4
Initial sites of involvement	
Pulmonary (any)	2/4
Skin, soft tissue (any)	2/4
Central nervous system (any)	2/4
Disseminated infection ^a	4/4
Time to onset of IRS-like syndrome after antifungal therapy, median (range)	3.5 weeks (4-12 weeks)

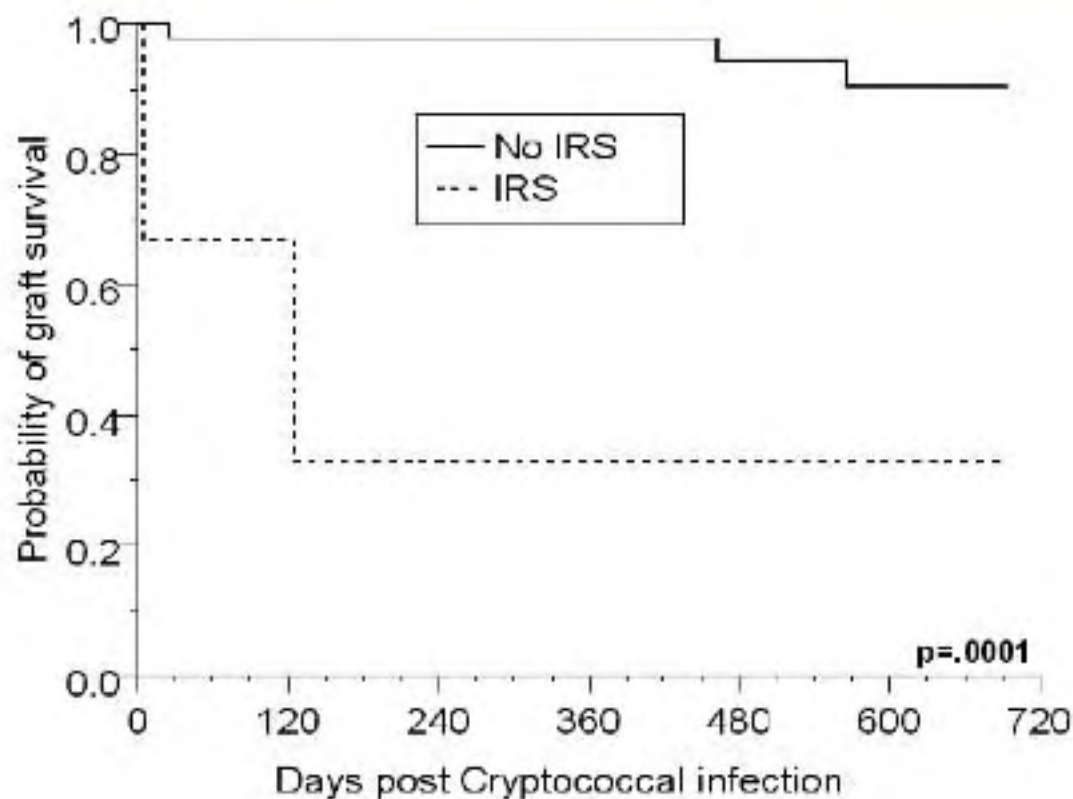
Clinical cases of cryptococcal IRIS during AIDS



Reversal Th2/Th1 and proinflammatory responses and occurrence of cryptococcal IRIS during SOT ?



Probability of graft survival in renal transplant recipients with cryptococcosis according to IRIS



Therapeutic recommendations for cryptococcosis-associated IRIS

(IDSA Guidelines, CID 2010)

- No need to alter direct antifungal therapy (B-III)
- No specific recommendation for minor IRIS (B-III)
- **Major complications (CNS inflammation) :**
 - Management of raised intracranial pressure
 - Role of steroids (≥ 0.5 mg/kg/d; 2-6 weeks) + antifungal (B-III)
 - NSAIDs/thalidomide? (C-III)

Conclusion

- **Cryptococcosis represents 8% of IFI in SOT**
- **Primary infection/reactivation or graft transmission**
- **Serum CPS may be negative**
- **Clinical manifestations and outcome influenced by the immunosuppressive protocol**
- **IRIS may occur in up to 5% of patients**
- **AmB lipid formulation as first line therapy if CNS involvement**

Thanks

Françoise Dromer

Support

Institut Pasteur
SPILF, SNFMI
SFMM, SIDACTION

Geneviève Chêne (INSERM U 593, Bordeaux)

Nina Singh (University of Pittsburgh)

Arnaud Fontanet (Unité d'Epidémiologie, IP)

Simone Mathoulin (Fondation Bergonié, Bordeaux)

Caroline Charlier

Fabrice Chrétien

Eric Dannaoui

Bertrand Dupont

Dea Garcia-Hermoso

Damien Hoinard

Amaury de Gouvello

Odile Launay

Romain Micol

Dorothee Raoux

Karine Sitbon

Patrick Schwarz

**All clinicians and microbiologists from the French
Mycosis Study Group**