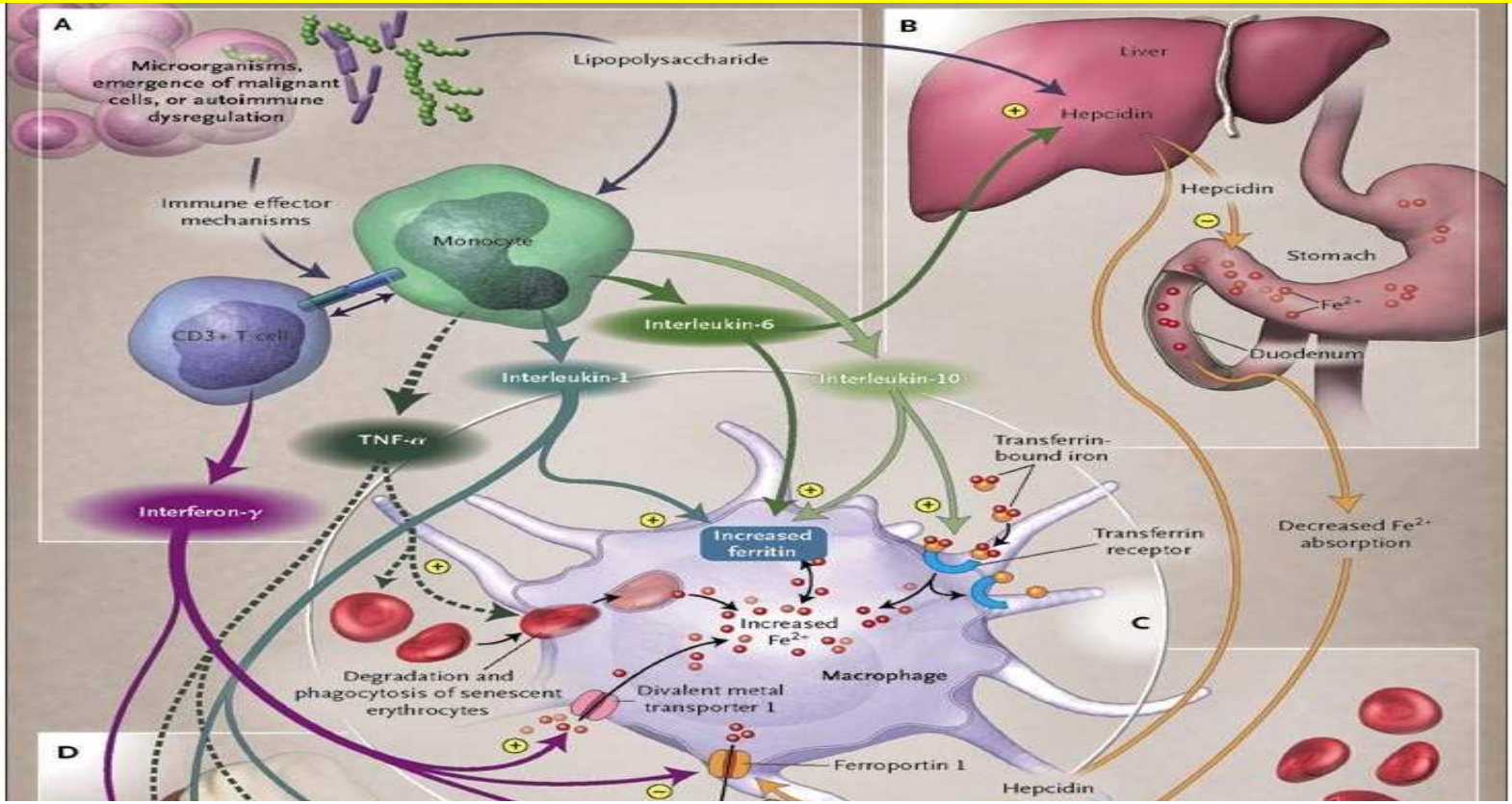
Role of iron in invasive fungal infections



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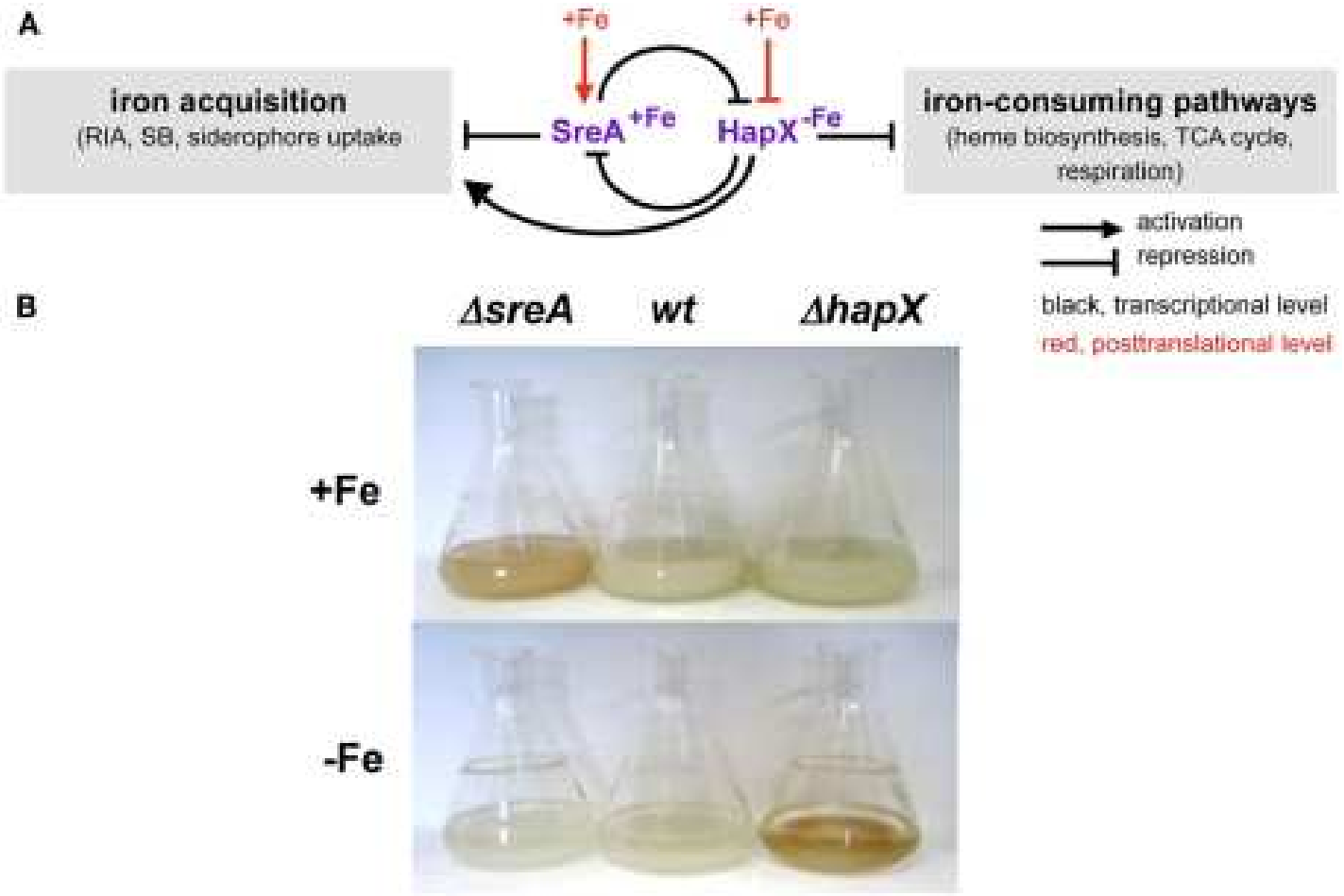
Iron at the host-pathogen-interface

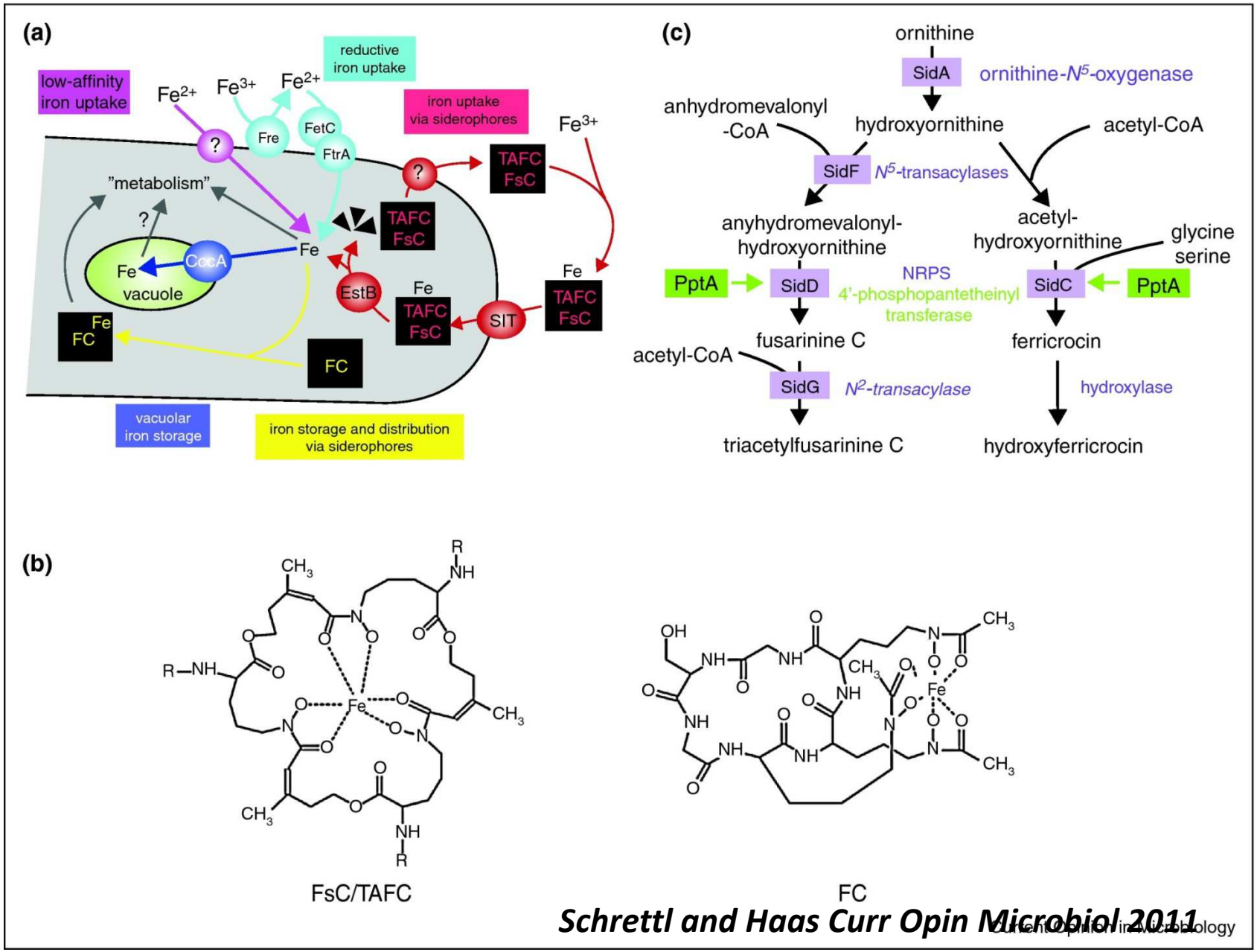
essential for growth and proliferation of several microbes

Expression of iron acquisition/ siderophore systems is linked to microbial pathogenicity



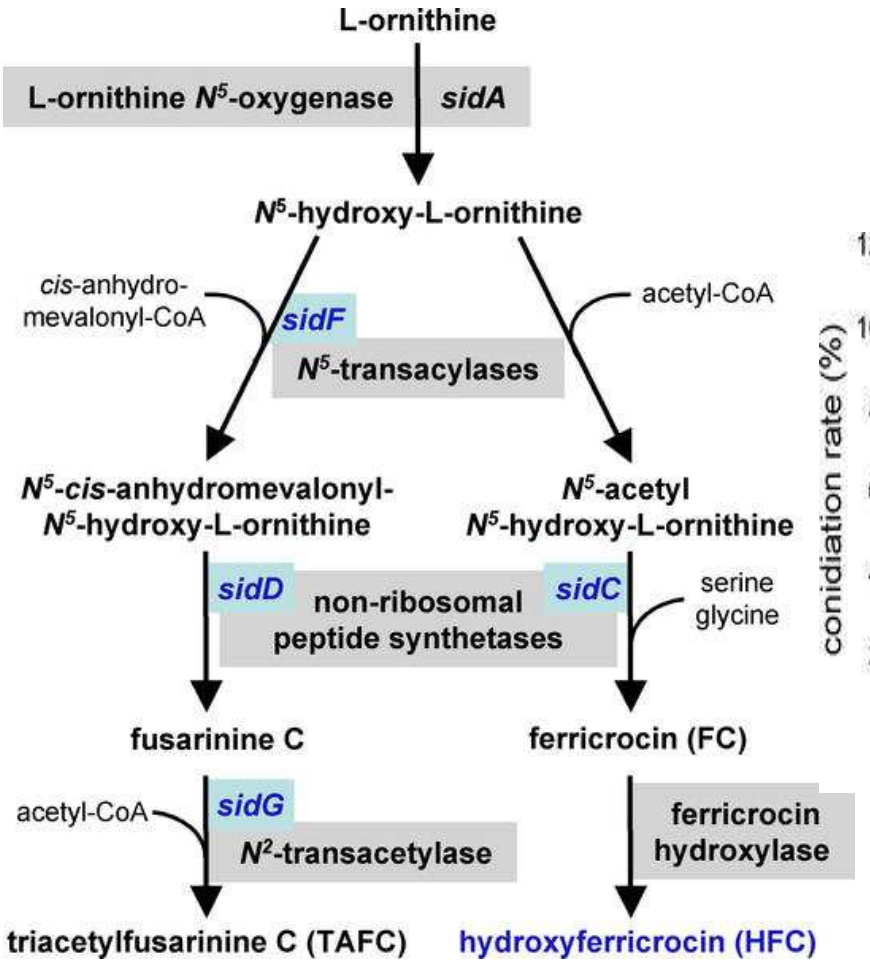
Haas H.. Front Biosci 2012

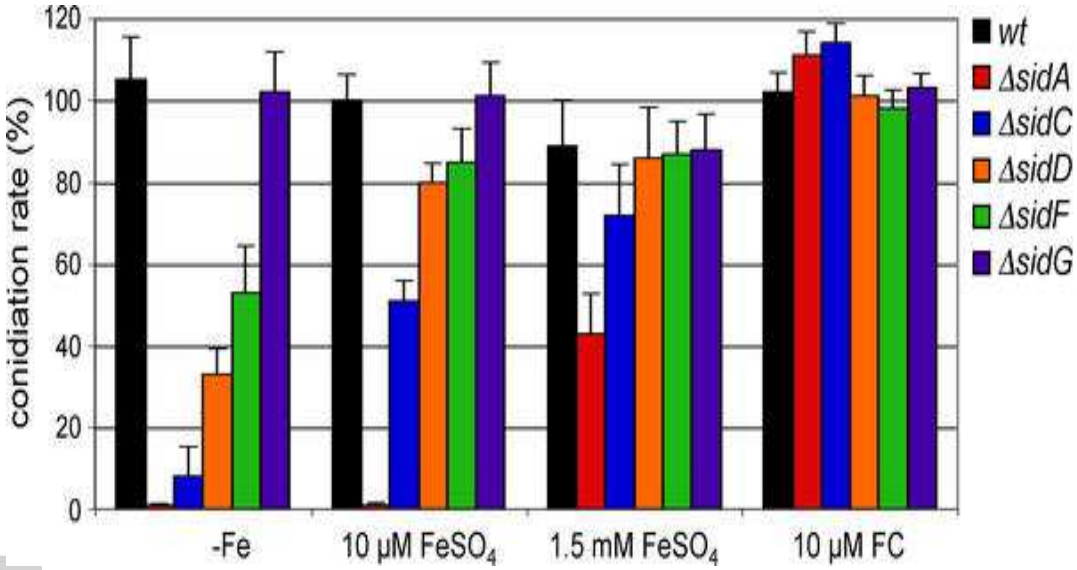
Iron acquisition pathways of Aspergillus spp.



Schrettl and Haas Curr Opin Microbiol 2011

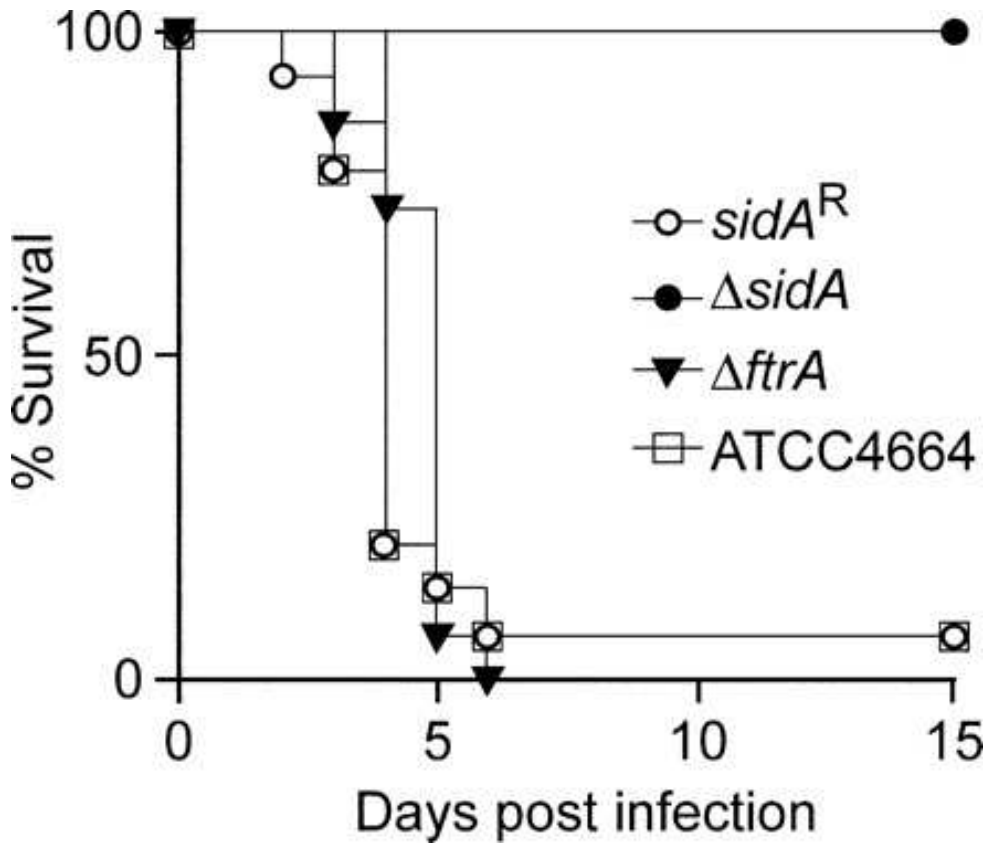
Molds (Aspergillus spp.) need iron for proliferation and pathogenicity
Acquisition of iron is managed via intra- and extracellular fungal siderophores





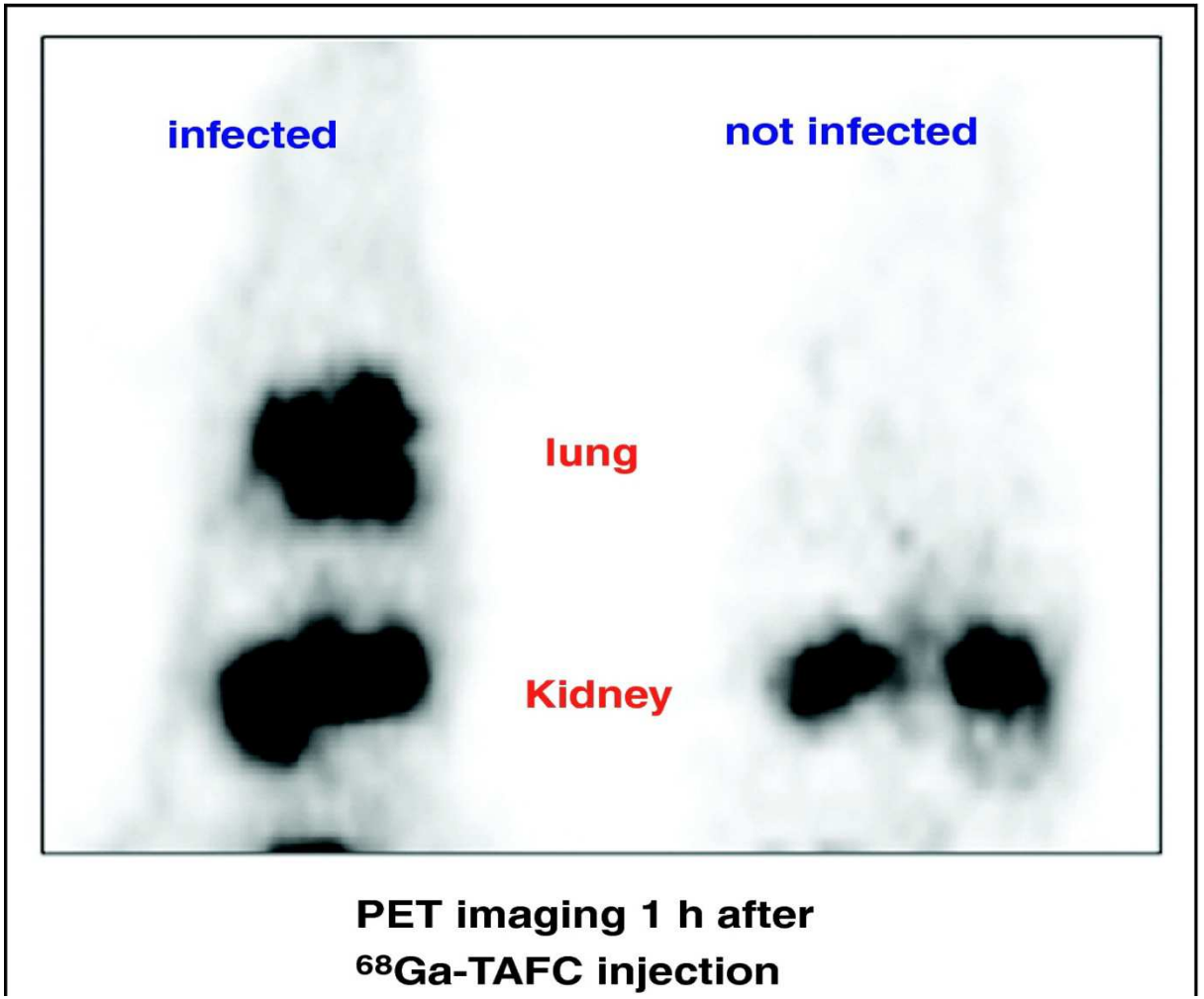
Schrettl et al. PLoS Pathog. 2007 Sep 28;3(9):1195-207

Siderophore-Synthesis is essential for virulence of Aspergillus spp.



Schrettl et al. J Exp Med. 2004

Fungal Iron acquisition as a diagnostic tool



PET imaging of invasive pulmonary aspergillosis in a rat model using ^{68}Ga-TAFC. Images demonstrating accumulation of ^{68}Ga in infected lungs were taken one hour after injection of ^{68}Ga-TAFC into the femoral vein. Kidneys are labeled in infected and non-infected animals owing to renal excretion of ^{68}Ga-TAFC ***Petrik et al. J Nucl Med 2010***

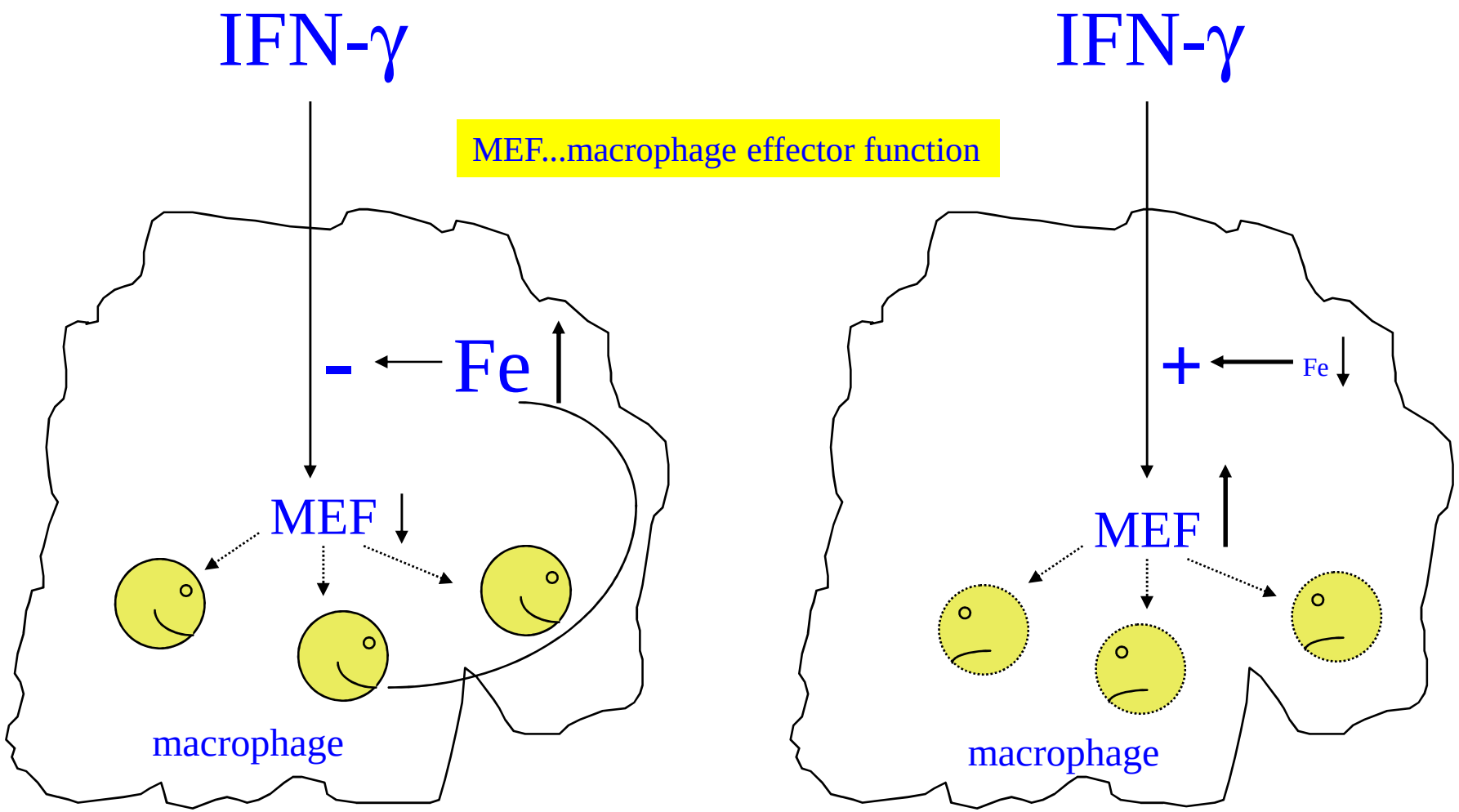
Iron at the host-pathogen-interface

essential for growth and proliferation of several microbes

Expression of iron acquisition/ siderophore systems is linked to microbial pathogenicity

exerts subtle effects on cell mediated immunity *in vitro* (macrophage effector pathways, IFN-γ activity, iNOS expression)

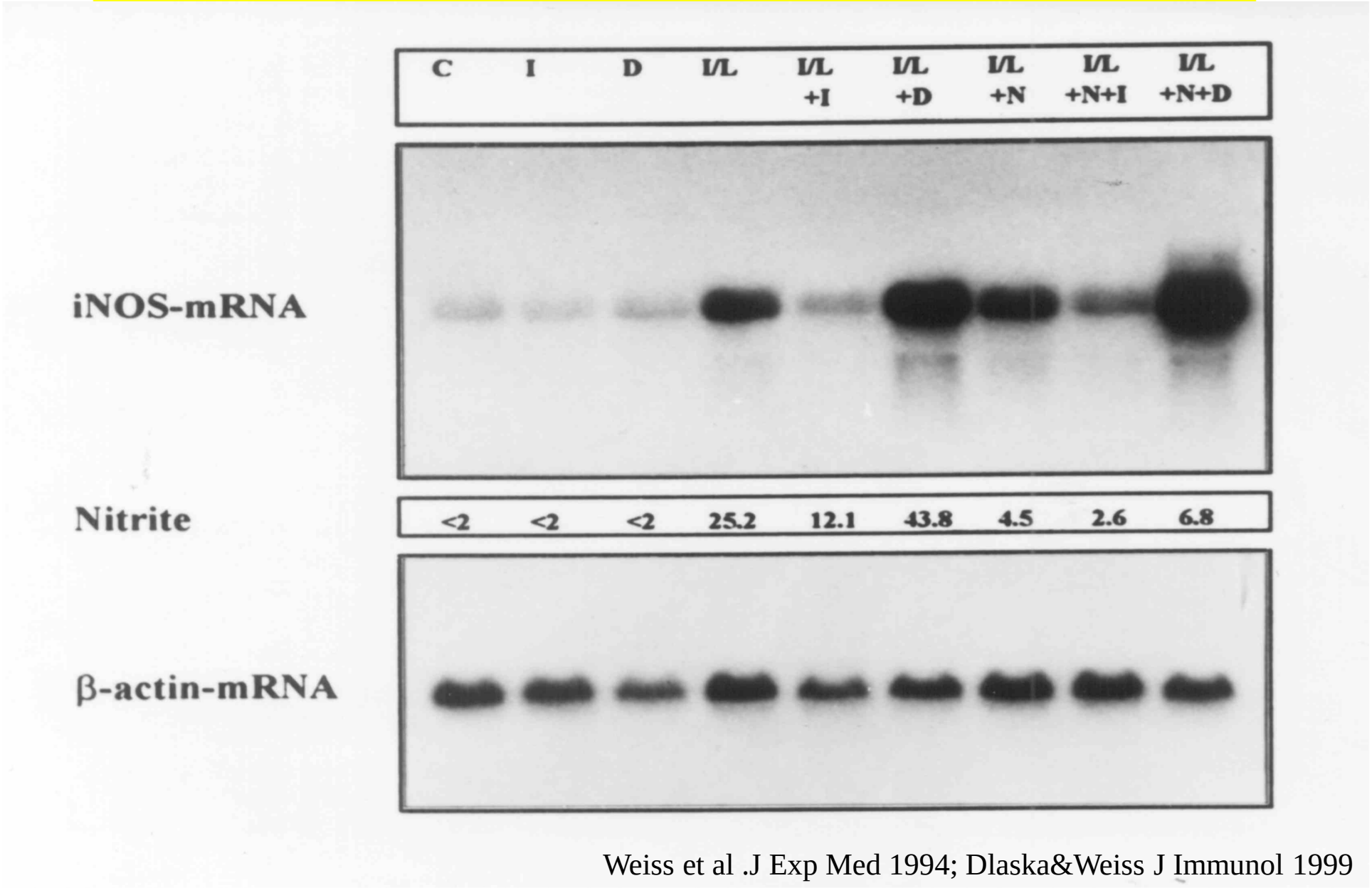
Iron loading of macrophages impairs their ability to kill intracellular pathogens by IFN-γ mediated pathways



But iron overload also negatively affects neutrophil function and phagocytosis

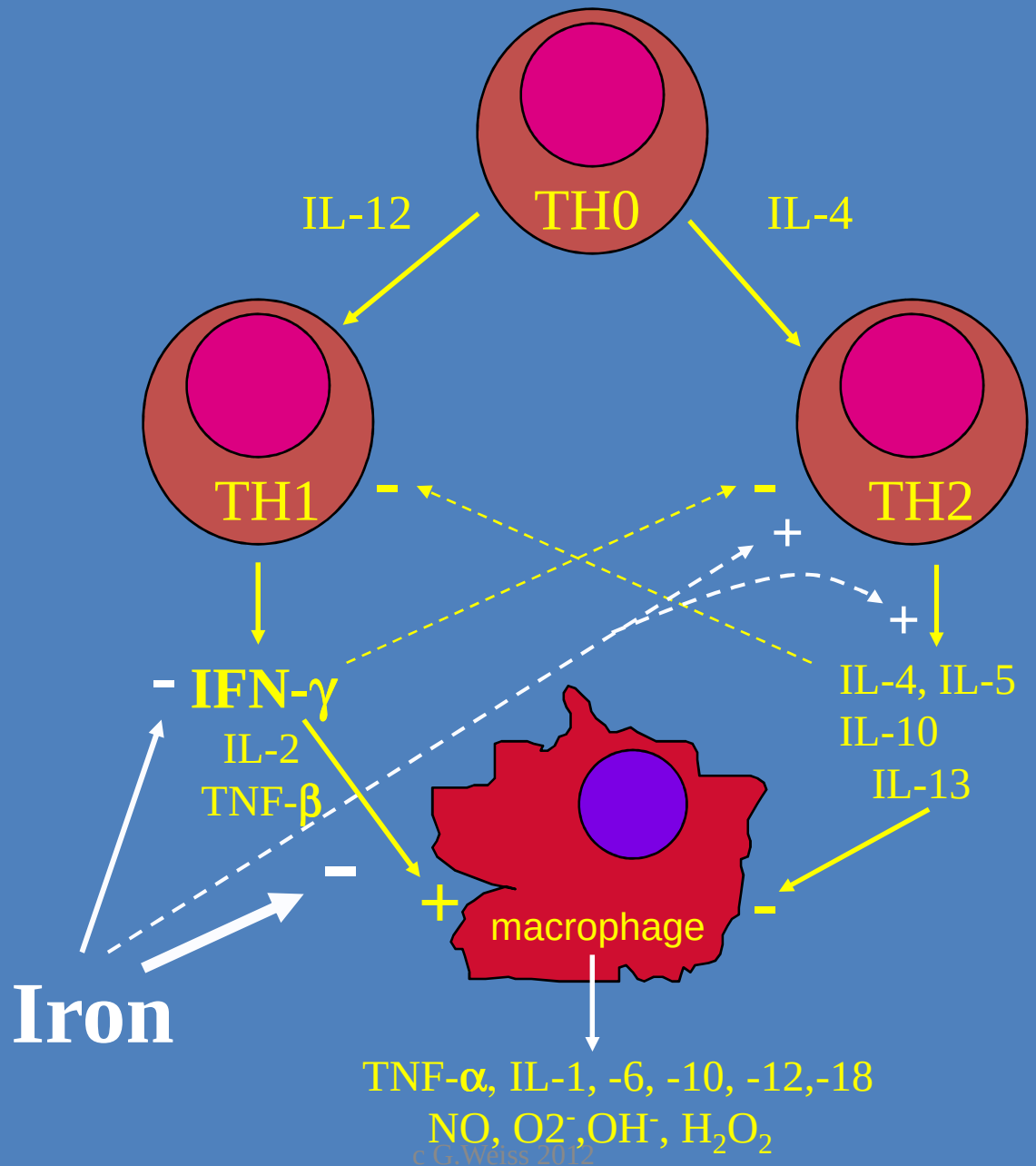
Weiss et al. Exp Hematol 1992; EMBO J 1993;Immunol Today 1995; J Infect Dis 1999; Oexle et al. J Leukoc Biol 2003

Regulation of NO formation and iNOS mRNA in activated murine macrophages (J774) by iron

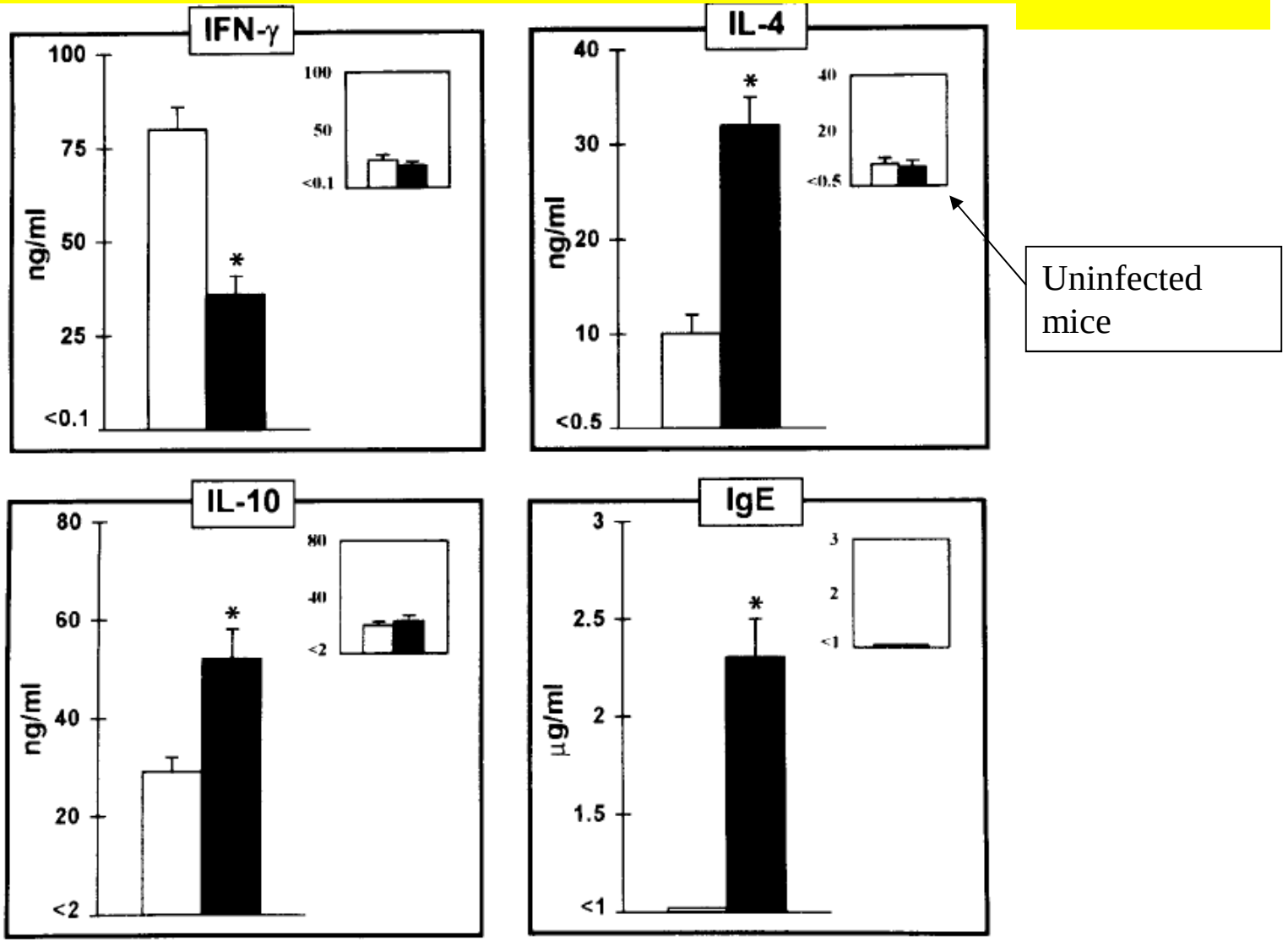


Weiss et al .J Exp Med 1994; Dlaska&Weiss J Immunol 1999

Iron alters the TH-1/TH-2 balance

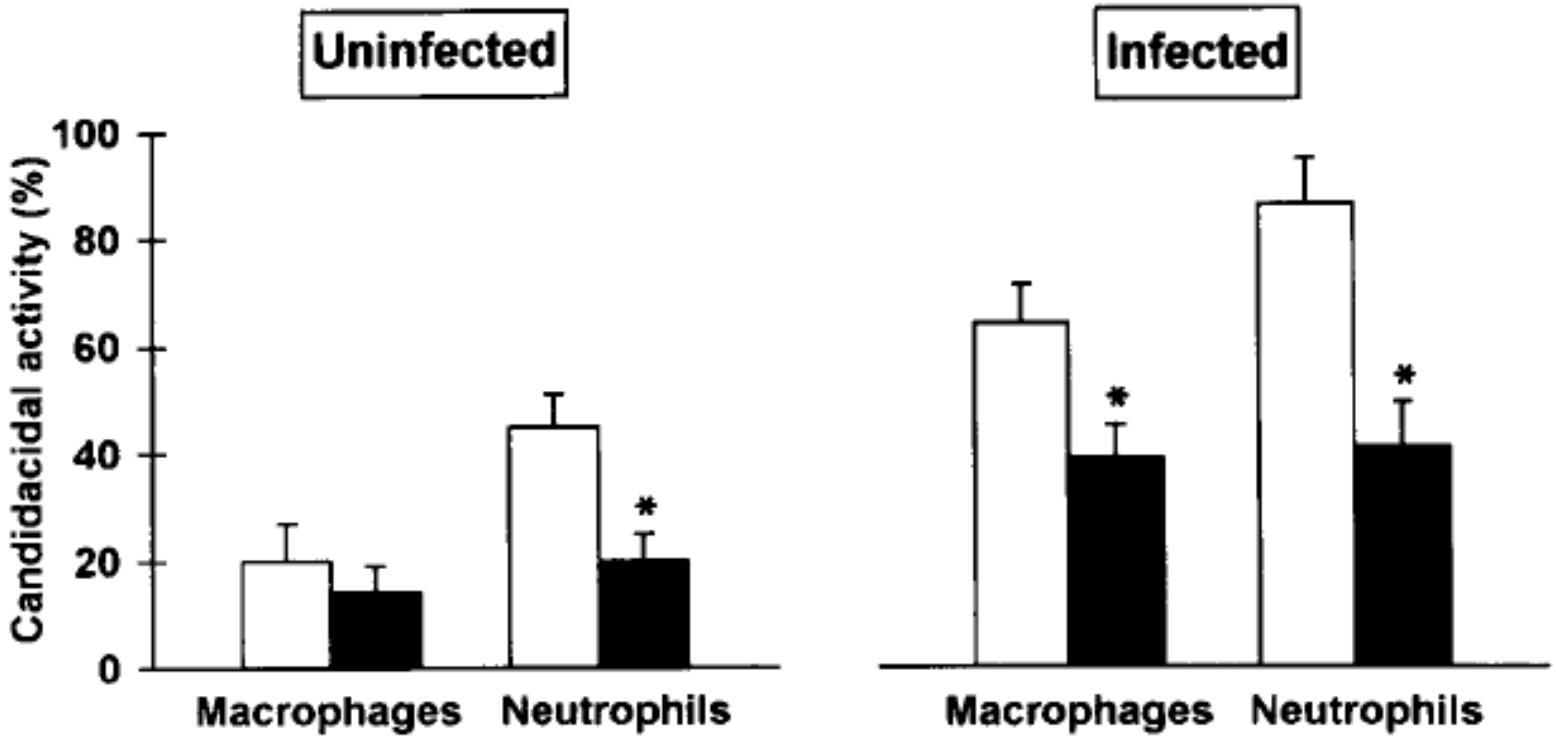


Effect of iron treatment (black bars) on TH-1/TH-2 immune response in Candida albicans infected mice



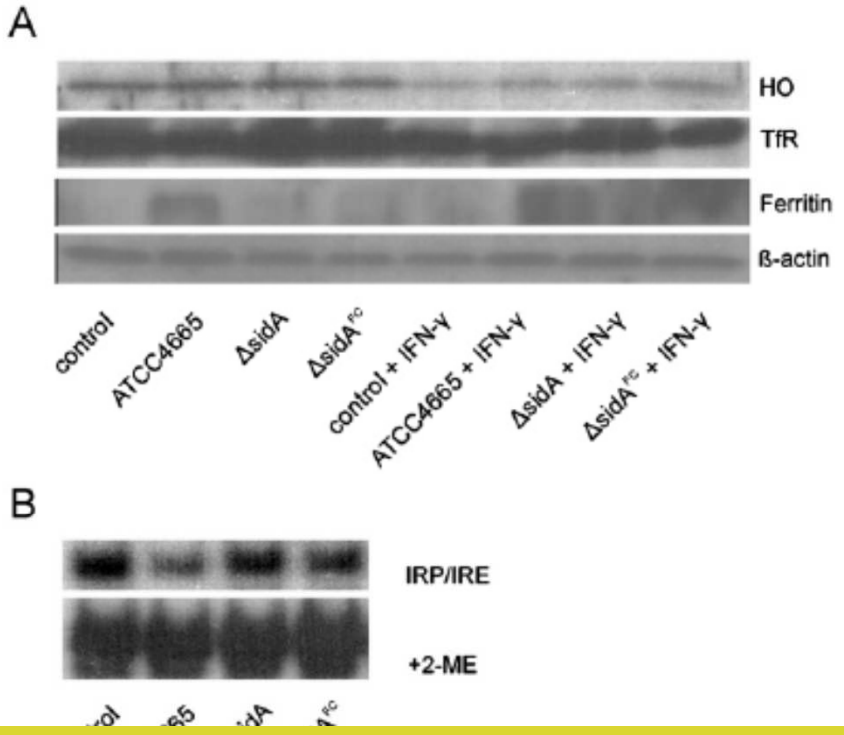
Mencacci et al. JID 1997

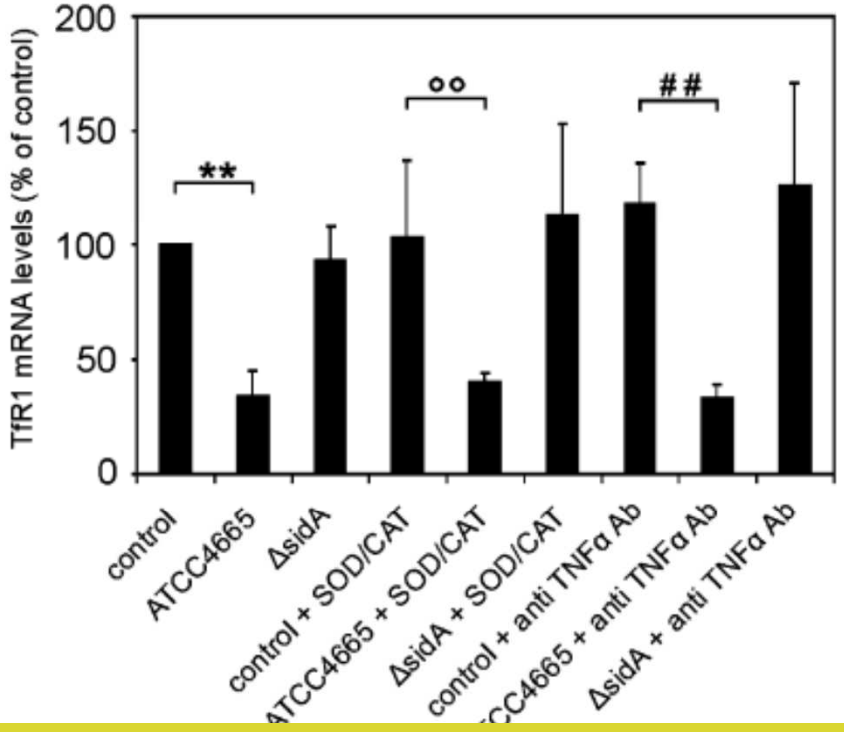
Anti-candida activity of normal and iron treated cells



Mencacci et al JID 1997

Aspergillus fumigatus manipulates host iron homeostasis via its siderophore system





Aspergillus fumigatus mediated modulation of macrophage iron homeostasis increases the supply of this essential nutrient for the mold and weakens anti-microbial immune effector pathways

Seifert et al. Immunobiology 2008

Iron at the host-pathogen-interface

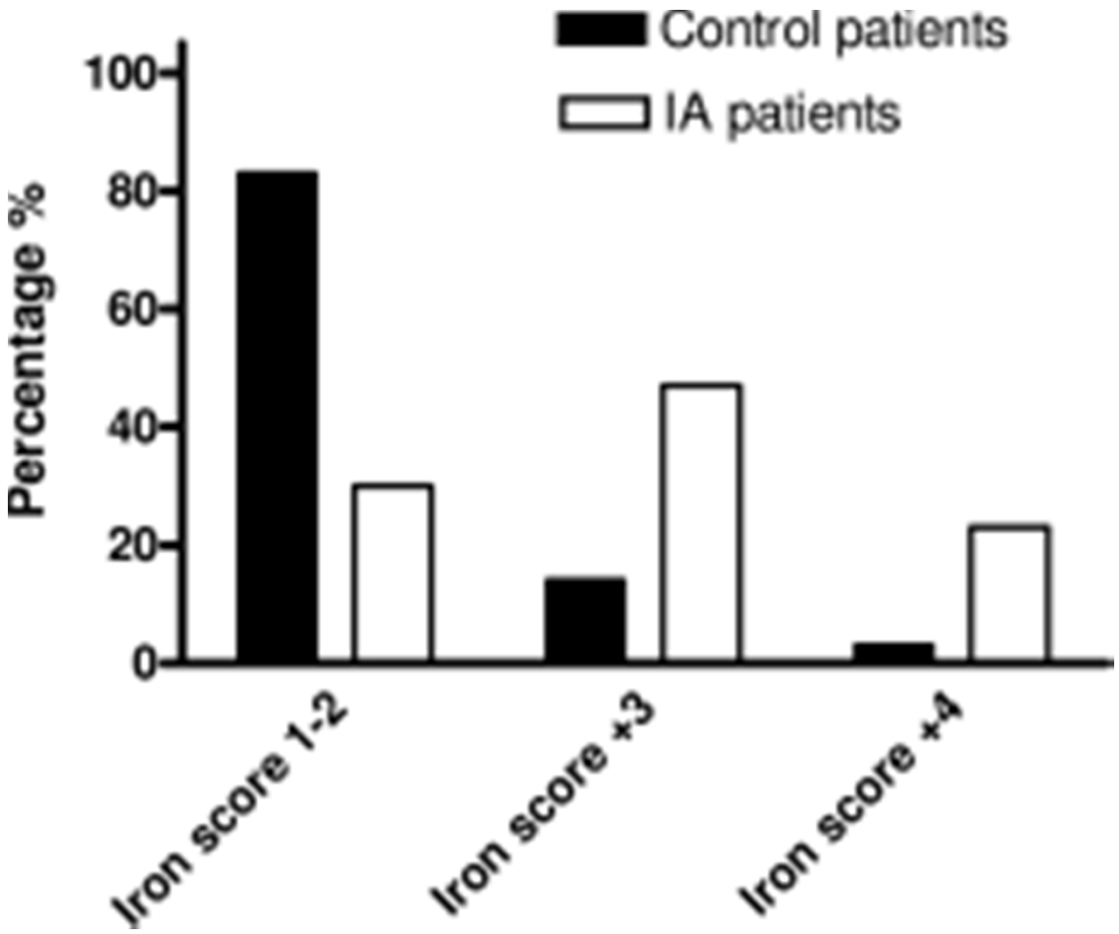
essential for growth and proliferation of several microbes

Expression of iron acquisition/ siderophore systems is linked to microbial pathogenicity

exerts subtle effects on cell mediated immunity *in vitro* (macrophage effector pathways, IFN-γ activity, iNOS expression)

The control over iron homeostasis is of importance for the course of an infection

Bone marrow iron stores is an independent risk factor for invasive aspergillosis in patients undergoing allogenic HSCT



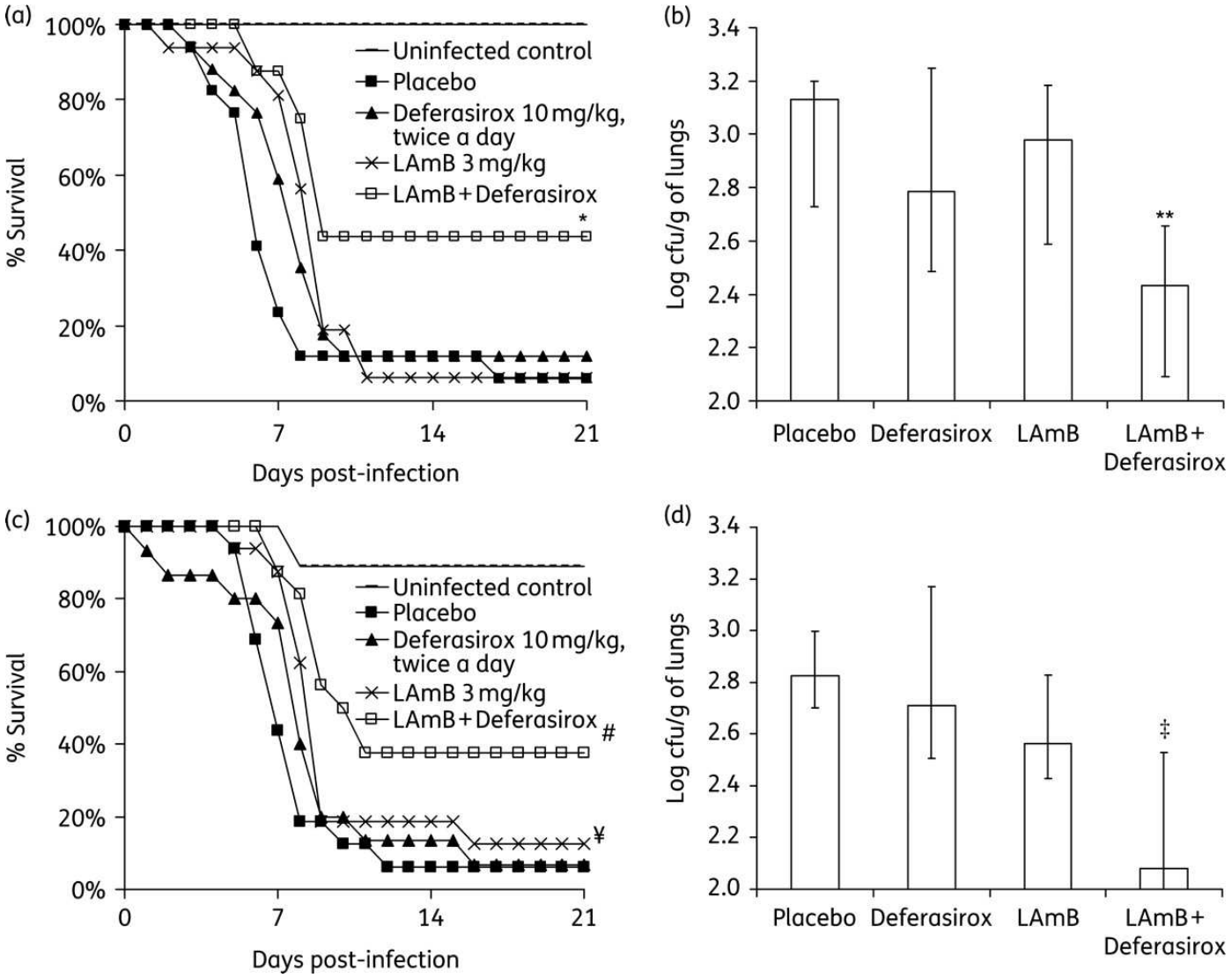
Kontoyiannis et al. CANCER 2007

Characteristics of Patients in the Control and Study Groups and Results of Univariate and Multivariate Analyses

Characteristic	Control patients	Patients with IA	OR (95% CI)	*P*	OR (95% CI)	*P*
APACHE II score > 11	17/33 (52%)	26/33 (79%)	3.5 (1.2-10.3)	.0300	5.16 (1.3-20.5)	.0100
Malnutrition (albumin level < 3 mg/dL)	17/33 (52%)	22/33 (67%)	-	.3100	-	-
Increased BMIS score (>3)	6/33 (18%)	23/33 (70%)	10.4 (3.2-32.8)	<.0001	12.3 (3.4-44.9)	< .0001

Kontoyiannis et al. CANCER 2007

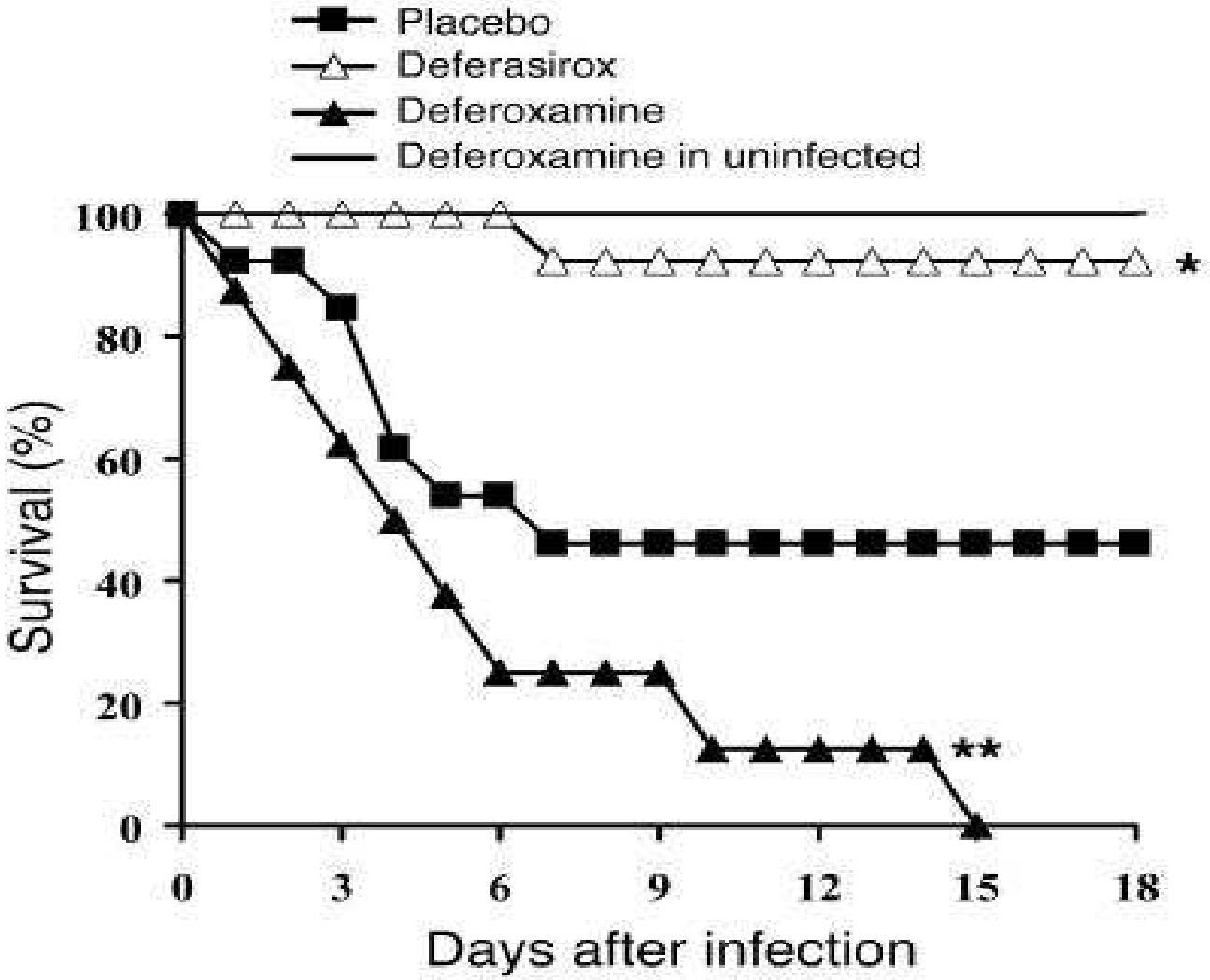
Efficacy of delayed (a and b) or prophylactic (c and d) combination deferasirox+LAmB versus monotherapy in a murine model of IPA.



Ibrahim A S et al. J. Antimicrob. Chemother. 2010;65:289-292

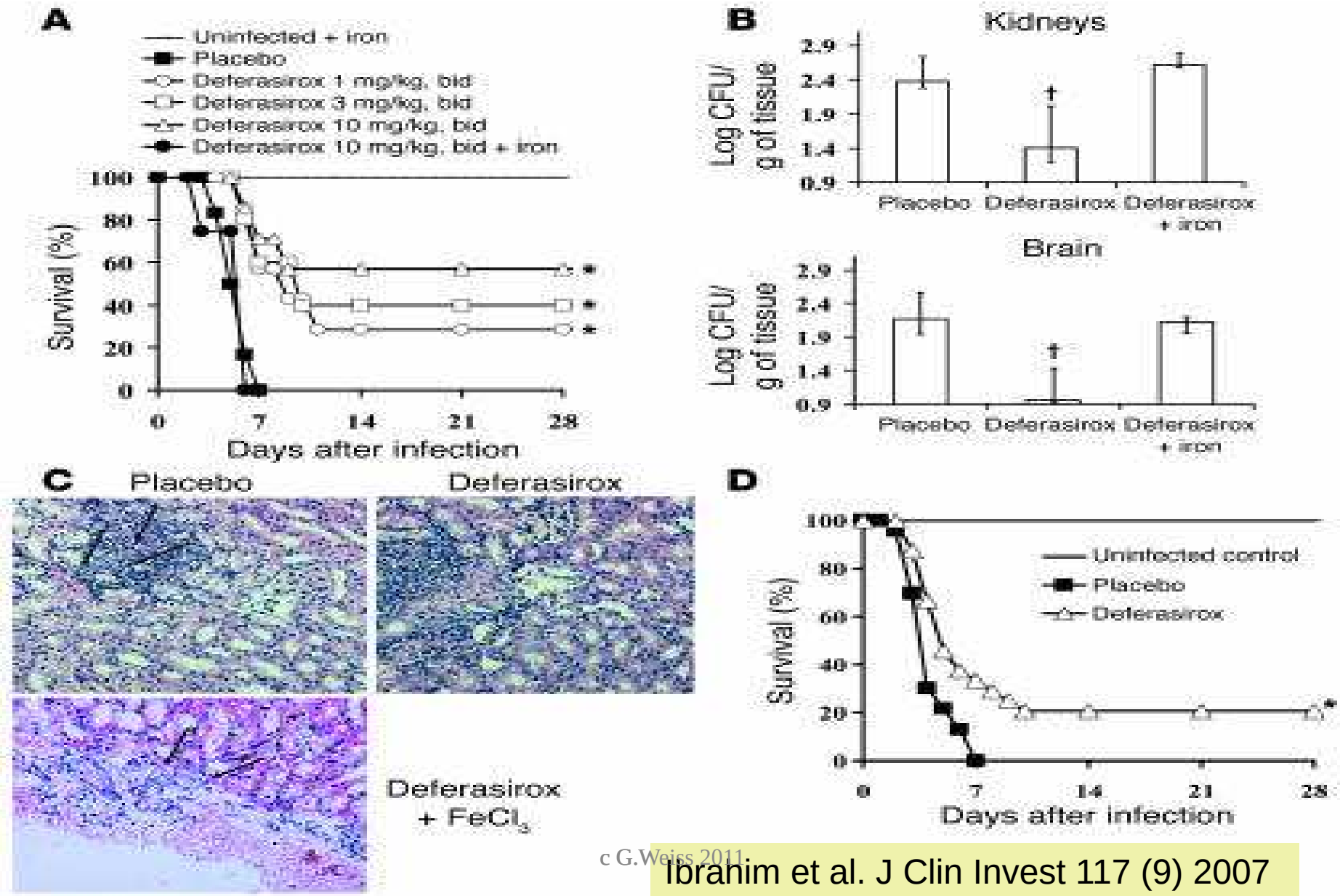
Not all iron chelators are equal– at least in respect to treatment of IFI

Diabetic ketoacidotic mice infected intranasally with *R. oryzae*



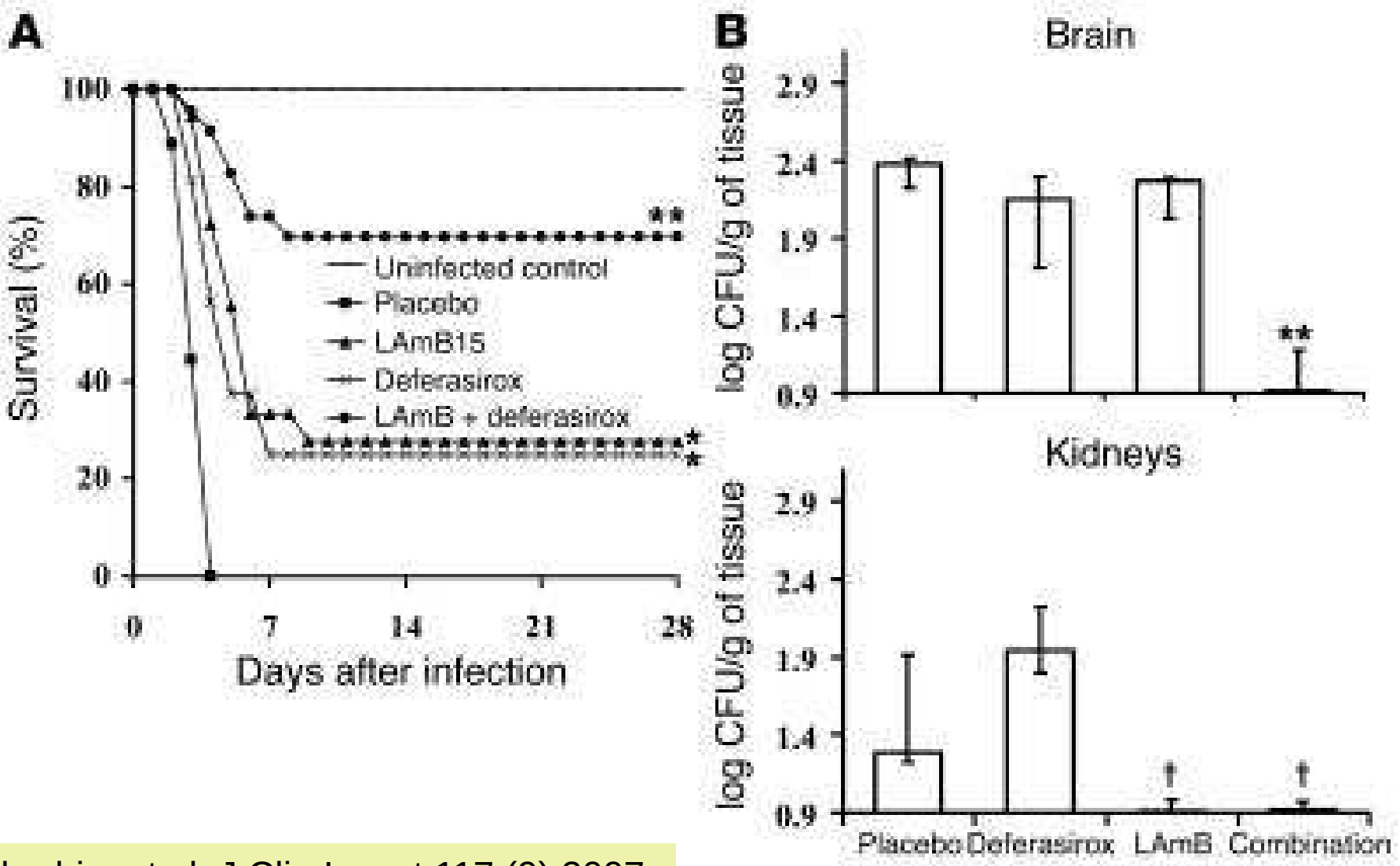
Boelaert et al. J Clin Invest 1993; Waldorf et al. J Clin Invest 1984

Iron chelators modify the course of Mucor infection



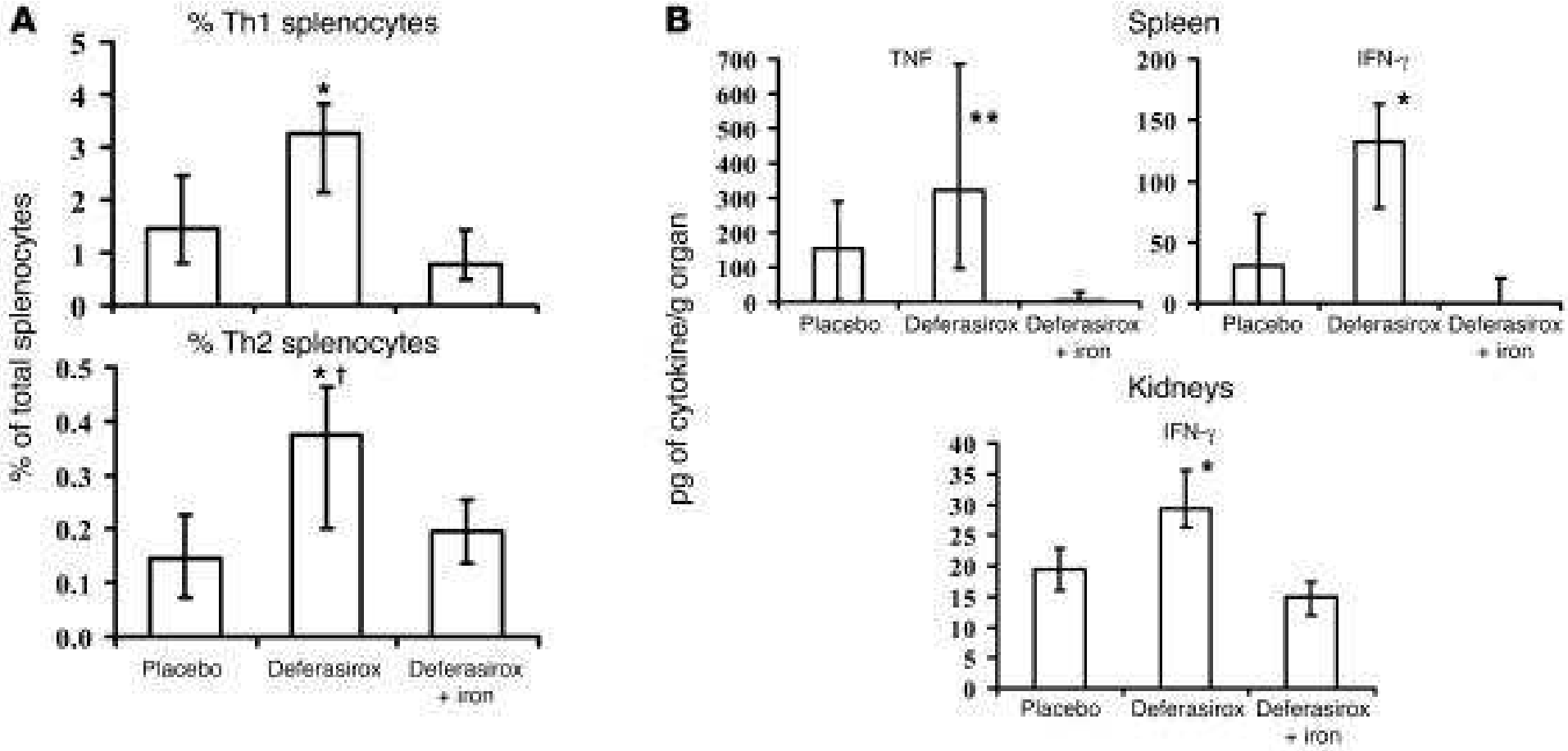
Ibrahim et al. J Clin Invest 117 (9) 2007

Syergistic effects of iron chelators in murine mucormycosis



Ibrahim et al. J Clin Invest 117 (9) 2007

Immune-modulatory effects of iron chelation



Ibrahim et al. J Clin Invest 117 (9) 2007

Iron, Infection and Immunity

•Central battlefield deciding about the fate of infections

•Iron affects cell mediated immune function and thus host responses towards pathogens and tumor cells (iron inhibts pro-inflammatory/IFN-γ mediated immune effector pathways)

Microbes including fungi need iron for their growth and pathogencity

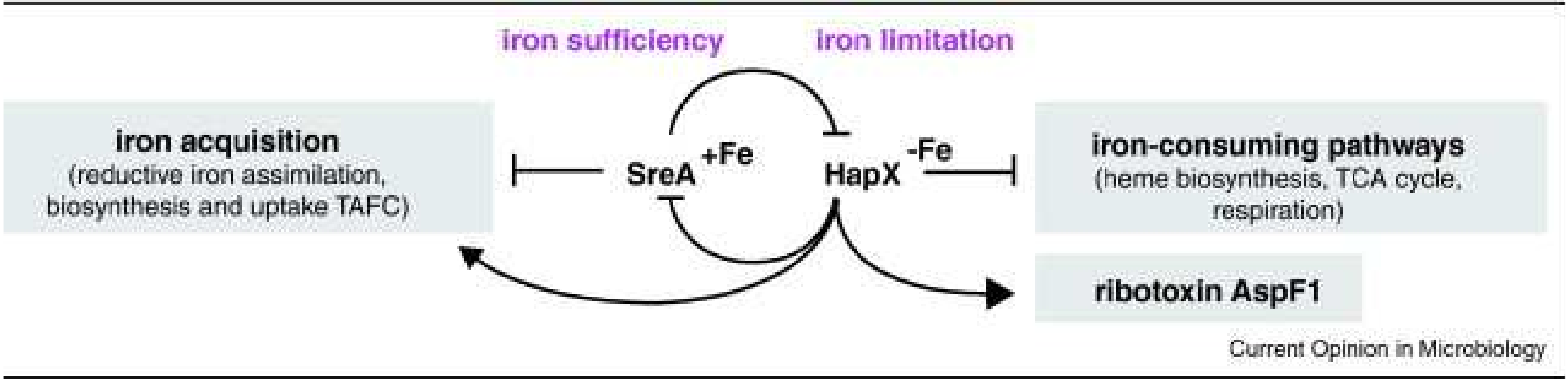
Modulation of iron homeostasis may be of therapeutic benefit in invasive fungal infections by

• limiting the availabiltiy of the essential nutrient for the pathogen

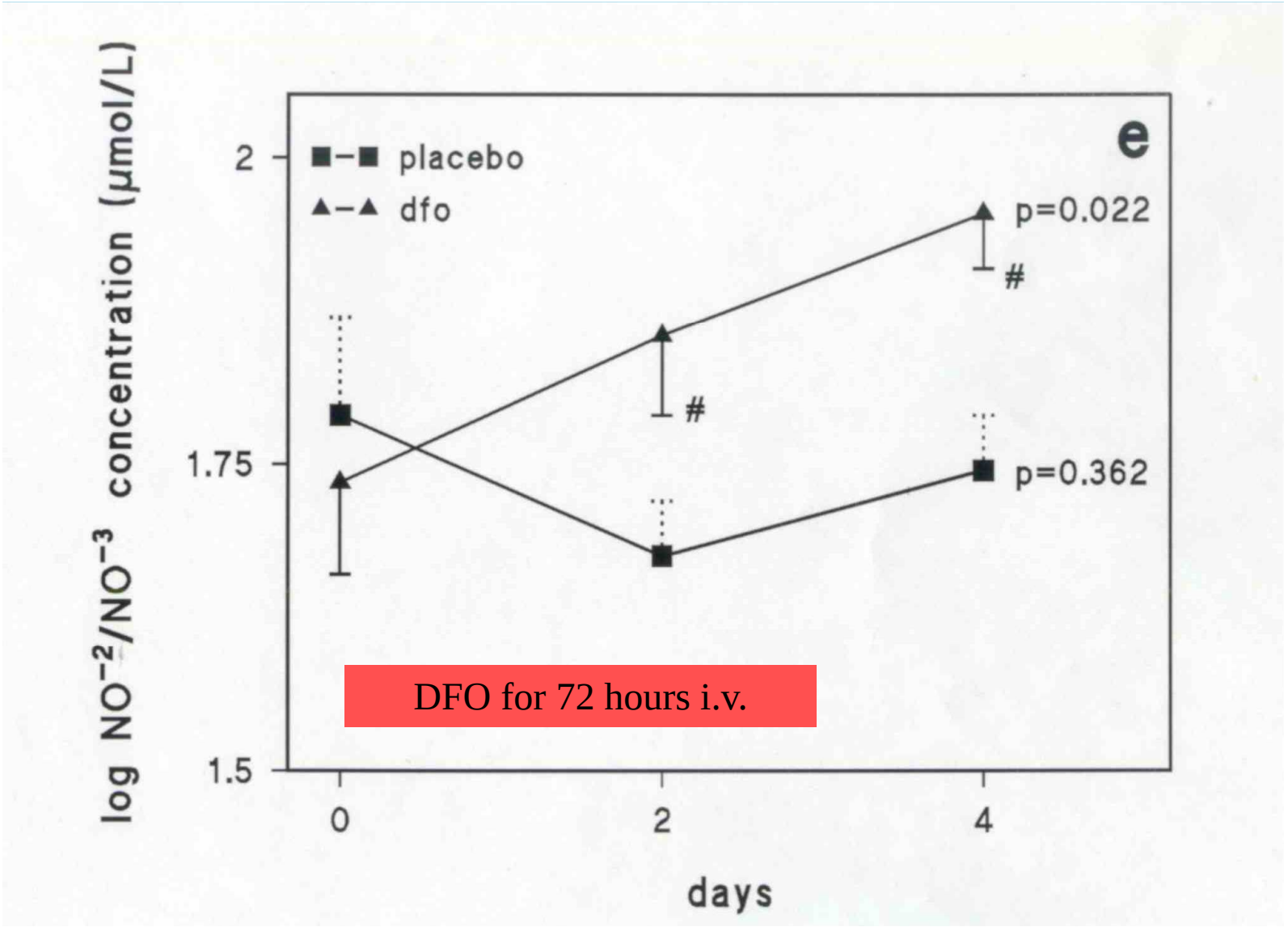
•by strengthening anti-fungal immune effector pathways


DANKE

Iron regulation in *A. fumigatus*



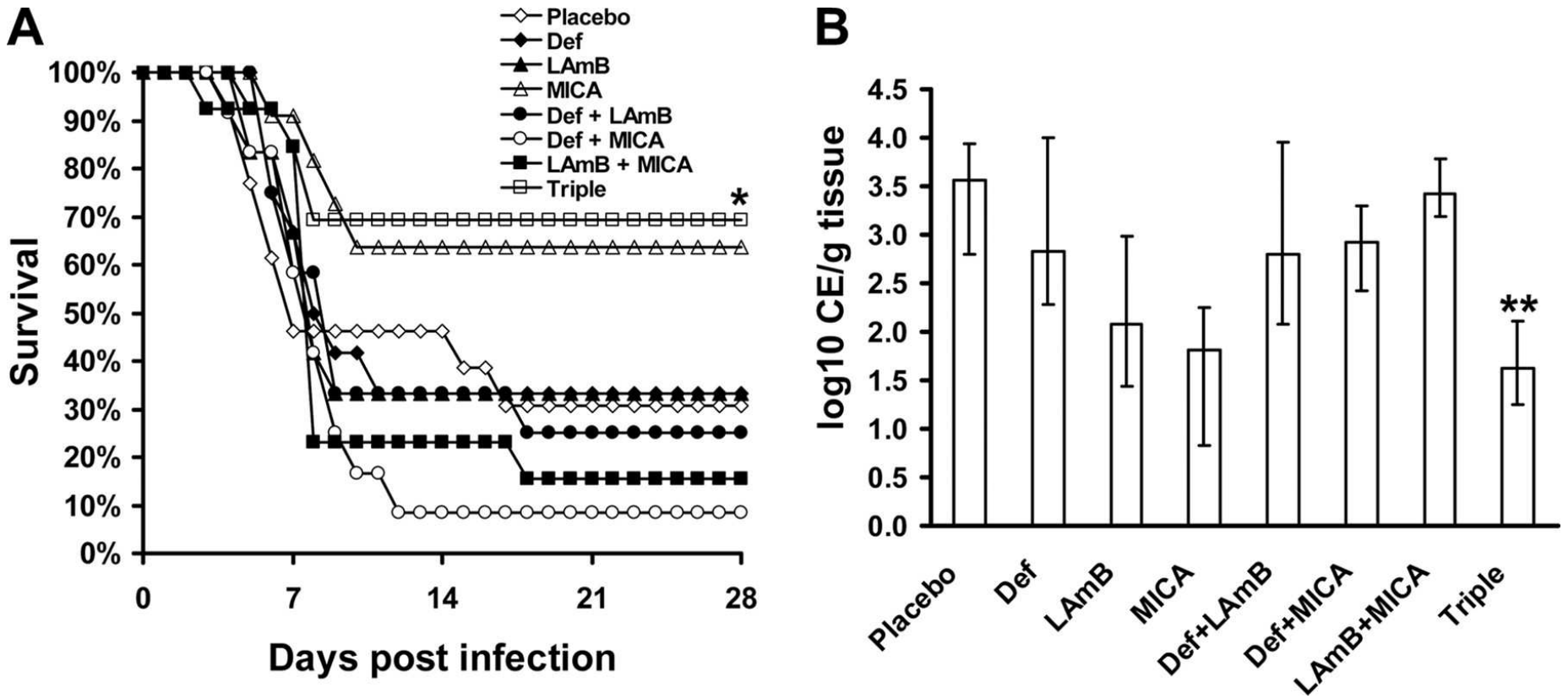
Schrettl and Haas Curr Opin Microbiol 2011



Effect of iron chelation therapy with desferrioxamine (DFO) on nitric oxide formation in vivo in human cerebral *Pl. falciparum* malaria

Gordeuk et al. N Engl JMed 1992; Weiss et al J Infect Dis 1997

Efficacy of triple therapy in murine model of IPA



Ibrahim, A. S. et al. 2011. Antimicrob. Agents Chemother. 55(4):1768-1770