

ISHAM

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What Can We Learn From Immunodeficiency Syndromes About Treating IFI

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Lots of Fungi (>1.5M!) Not Too Many Are Important To Us

Filamentous molds

Aspergillus, Mucor, Trichophyton

Dimorphic fungi

*Histoplasma, Coccidioides, Paracoccidioides,
Blastomyces, Sporothrix, Penicillium*

Yeasts

Candida, Cryptococcus, Trichosporon

We Will Not Talk About Mucosal Fungal Disease and PIDs Today

IL-17 signaling and CMC

(IL-17RA, IL-17RC, IL-17F, ACT1; direct)

(STAT3, STAT1, AIRE, DOCK8, IRF8, STK4; indirect)

What is New?

GATA2 deficiency: *Aspergillus*, *Histoplasma*, *Cryptococcus*

Anti-IFN γ autoantibodies: *P. marneffe*

Anti-GM-CSF autoantibodies: cryptococcal meningitis

STAT1 GOF mutations: coccidioidomycosis, histoplasmosis, penicilliosis, fusariosis, *Apophysomyces trapeziformis*

IL-12R β 2 mutation: refractory coccidioidomycosis

CARD9 deficiency: Mucosal & CNS *Candida*, phaeohyphomycosis, deep dermatophytosis

PIDs and IFIs

- ◆ **Filamentous Fungi (Molds)**
- ◆ Endemic Dimorphic Fungi
- ◆ Yeasts

What Leads to Inherited Susceptibility to Mold Infections?

- ◆ Chronic Granulomatous Disease
- ◆ GATA2 Deficiency
- ◆ *STAT1* GOF mutations
- ◆ Unknown Immunodeficiency
- ◆ Job's syndrome (*STAT3* mutations)

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CGD and Molds

- ◆ *Aspergillus* in about 40% of patients
- ◆ Mucormycosis only with steroid use
- ◆ Fusariosis rare

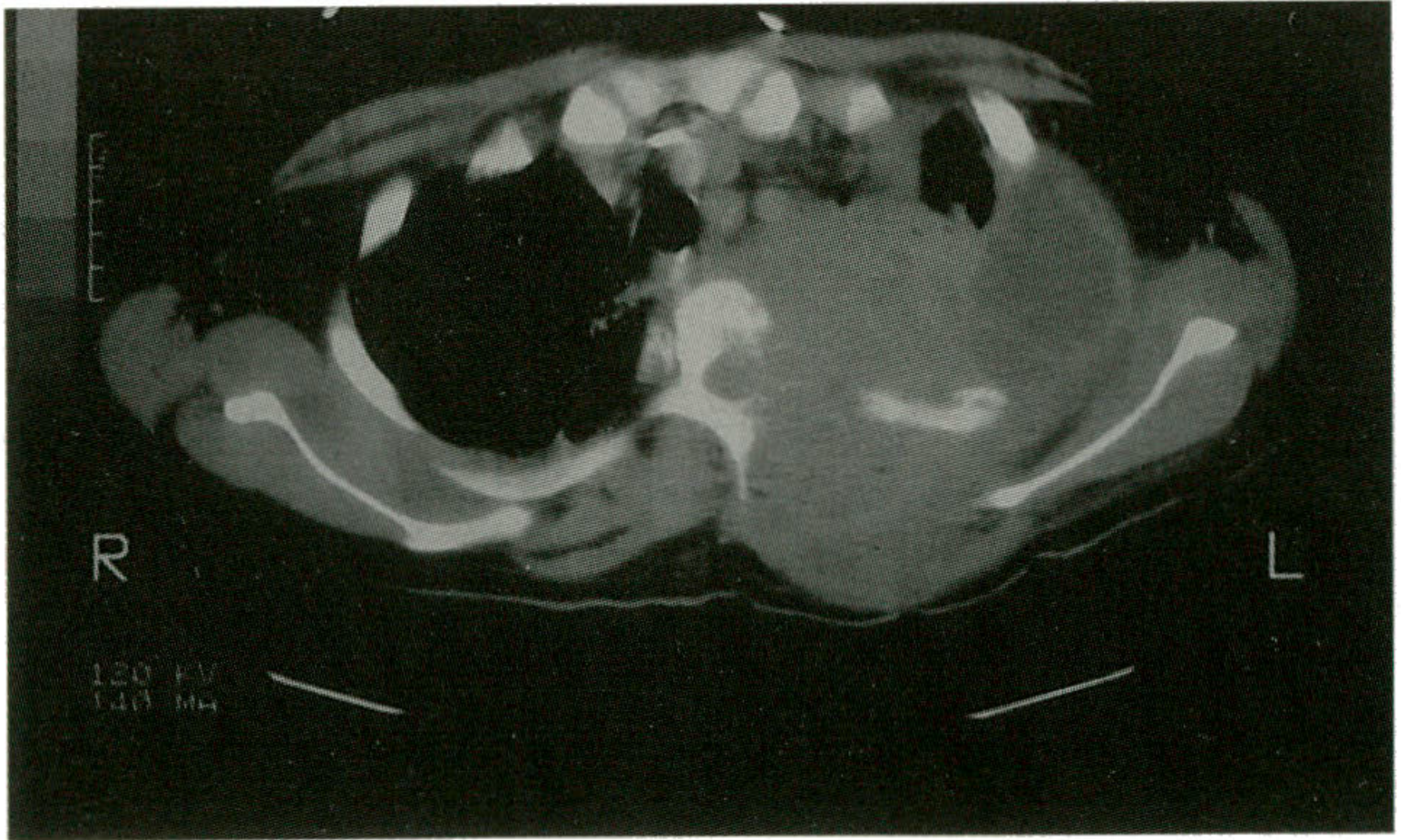
Mucormycosis in chronic granulomatous disease: Association with iatrogenic immunosuppression

Vihn D *et al.*, *JACI*. 2009

A. nidulans in CGD

- Second most common *Aspergillus* species after *A. fumigatus* in CGD
- Not a cause of infection in other patients who develop aspergillosis (transplant, neutropenia)
- Difficult to treat due to propensity to invade contiguous tissue planes and inherent resistance to antifungal drugs

A. nidulans in CGD



Courtesy of Steve Holland, NIH

The New England Journal of Medicine

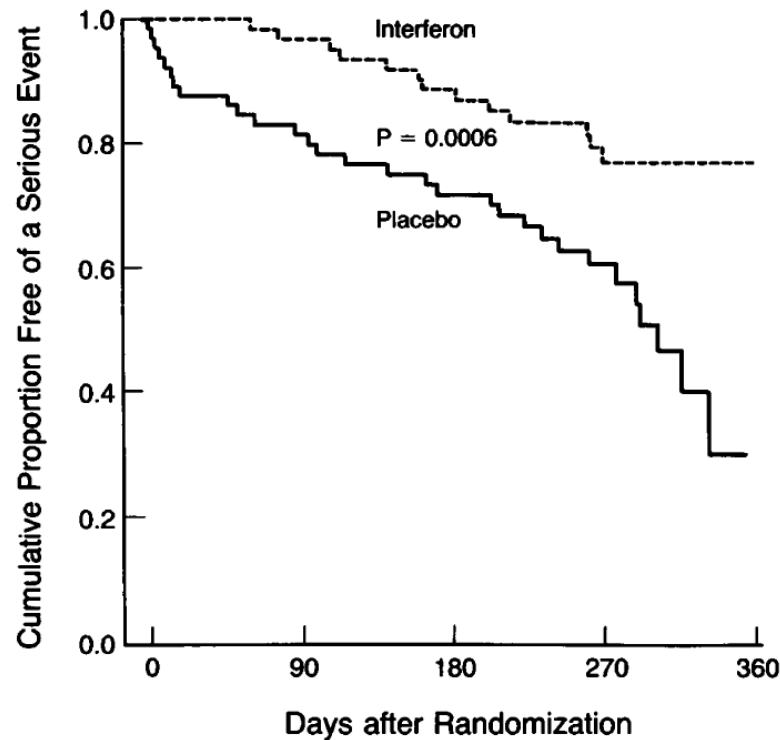
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A CONTROLLED TRIAL OF INTERFERON GAMMA TO PREVENT INFECTION IN CHRONIC GRANULOMATOUS DISEASE

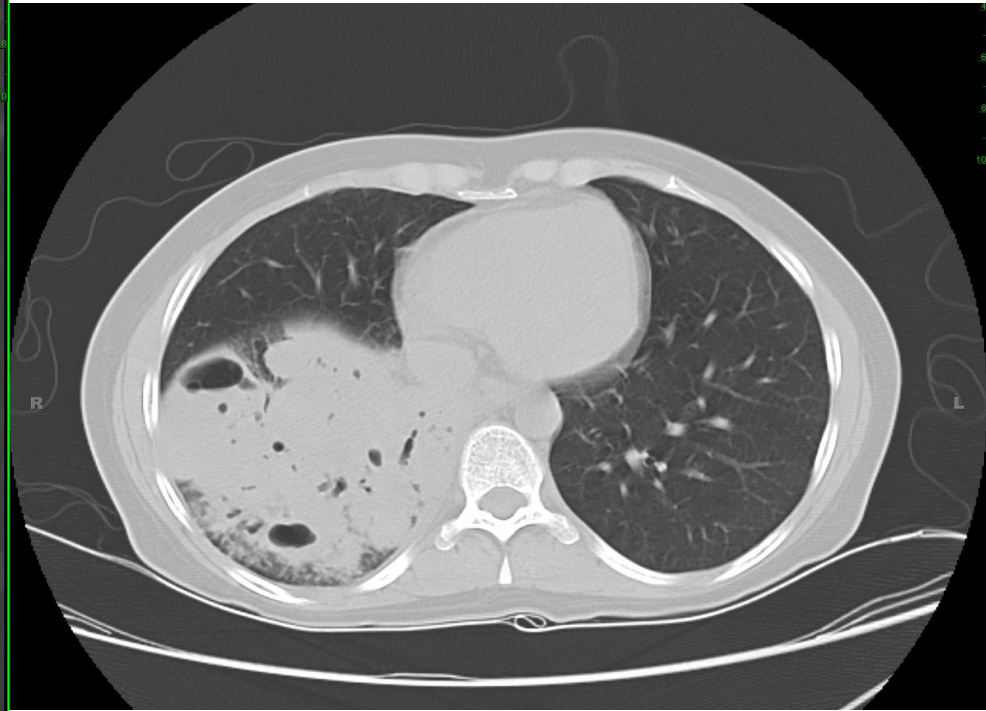


**Transplantation of CGD
Patients with Uncontrolled
Refractory Mold Disease is
Successful in Controlling
Infection**

What Leads to Inherited Susceptibility to Mold Infections?

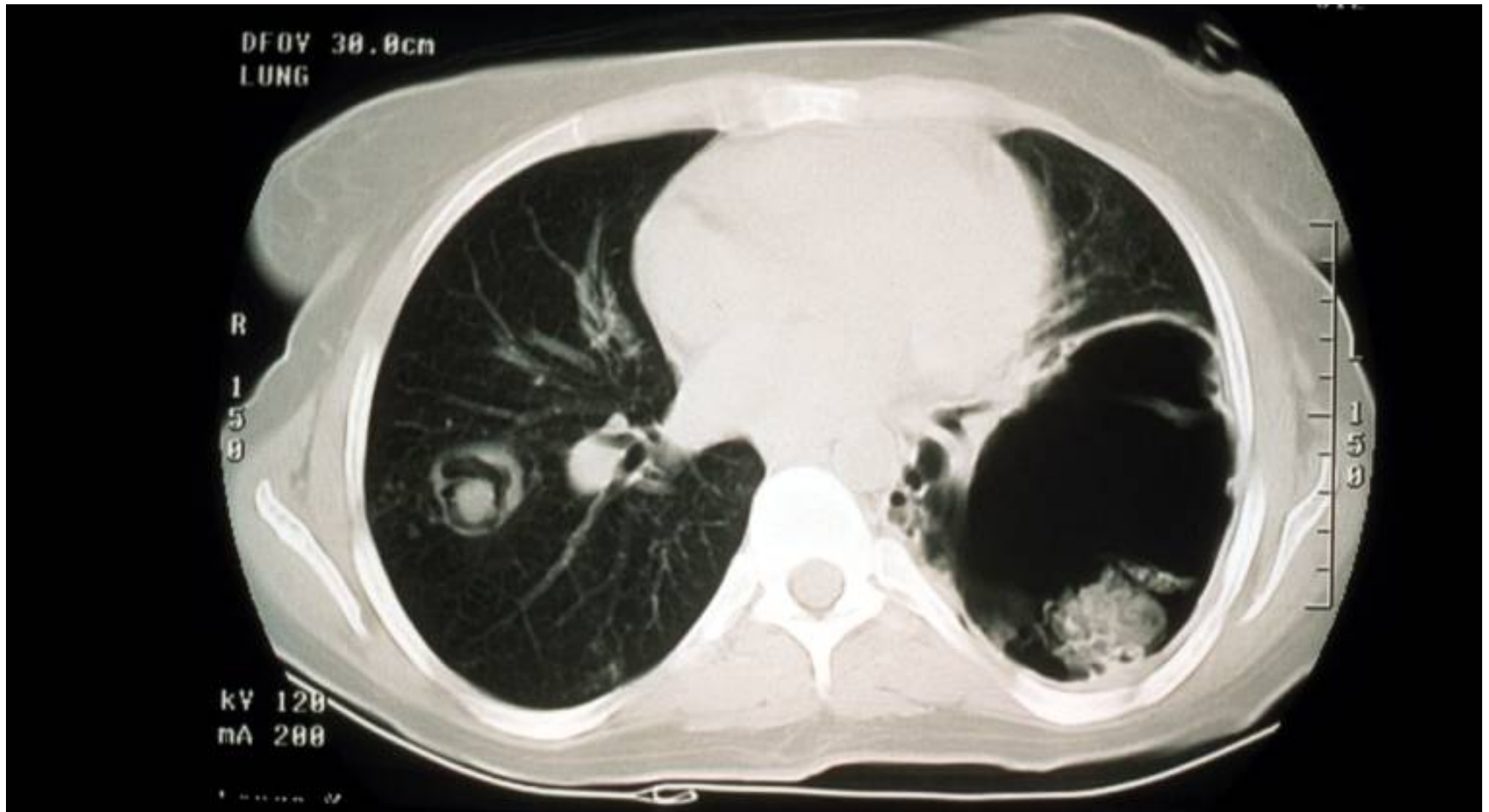
- ◆ Chronic Granulomatous Disease
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Staphylococcus aureus Pneumonia in Job's Syndrome



Courtesy of Steve Holland, NIH

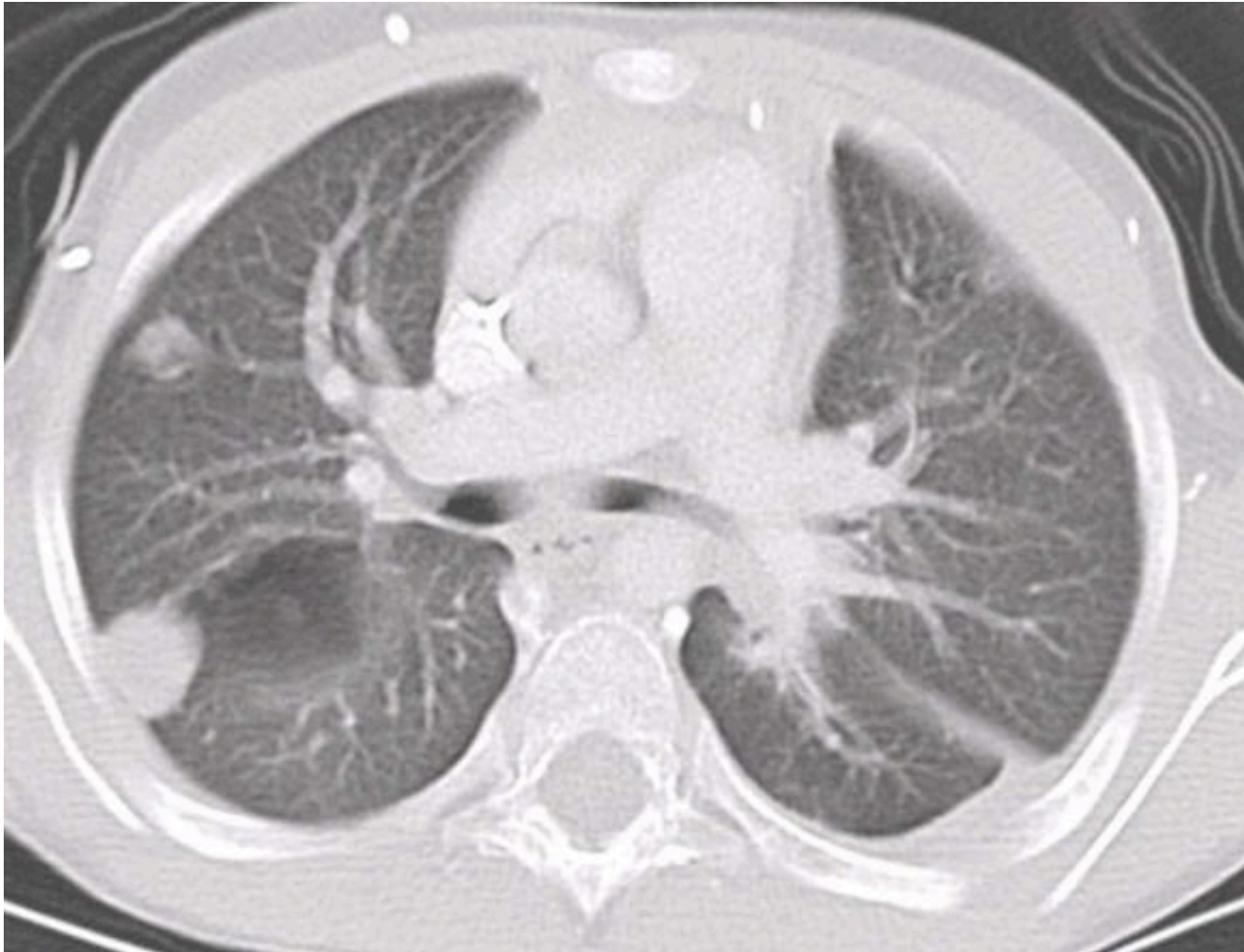
Impaired Tissue Remodeling After Pyogenic Pneumonias in Job's Syndrome



Structural Lung Disease from Recurrent Bacterial Infections Results in Secondary Colonization and Infection by Molds

- Incidence: 25-30%
- *Aspergillus* more common followed by *Scedosporium* spp
- Mortality: 15-20%
- No defects in phagocyte effector function (as opposed to CGD)

Aspergillosis in a Job's Patient



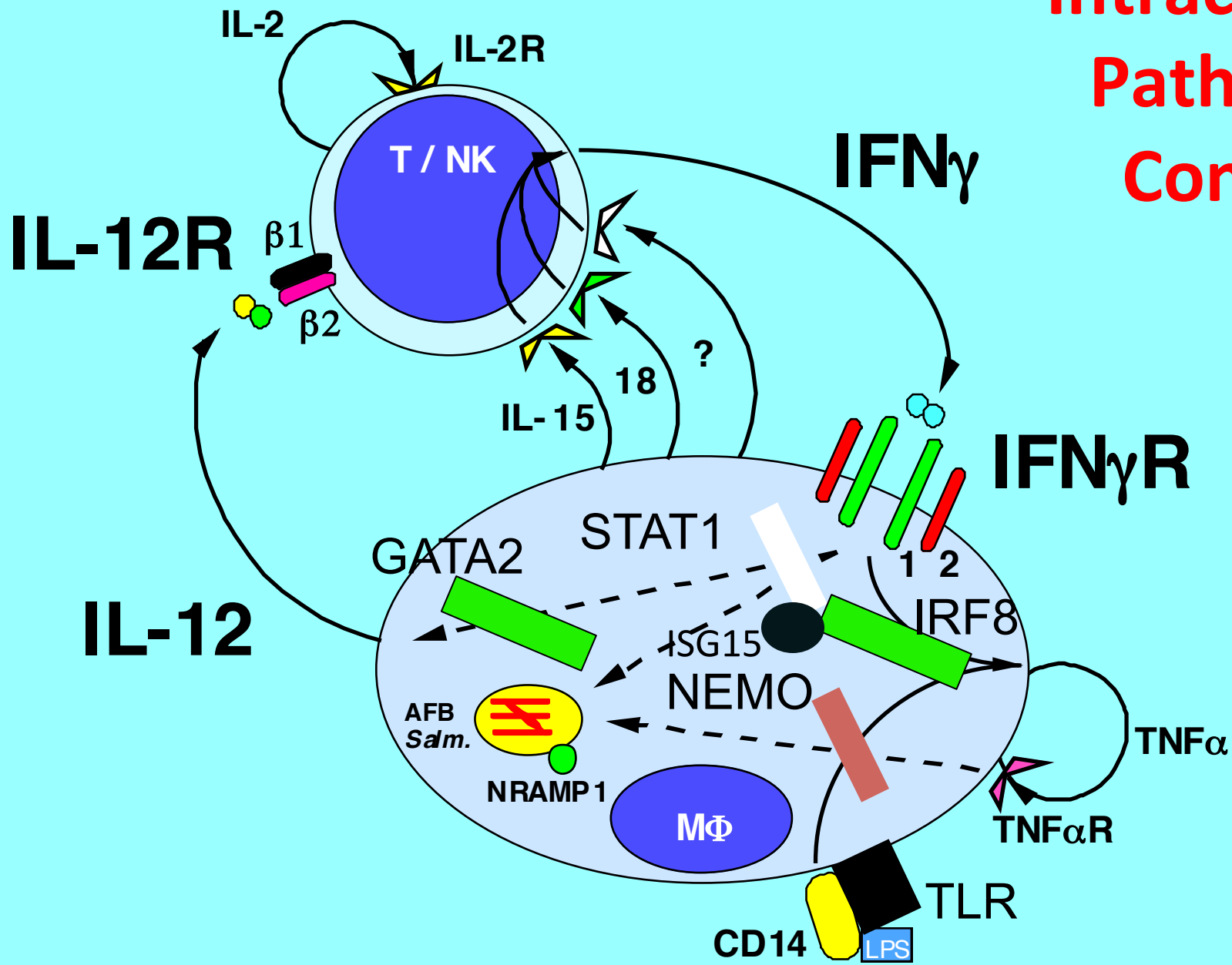
PIDs and IFIs

- ◆ Filamentous Fungi (Molds)
- ◆ **Endemic Dimorphic Fungi**
- ◆ Yeasts

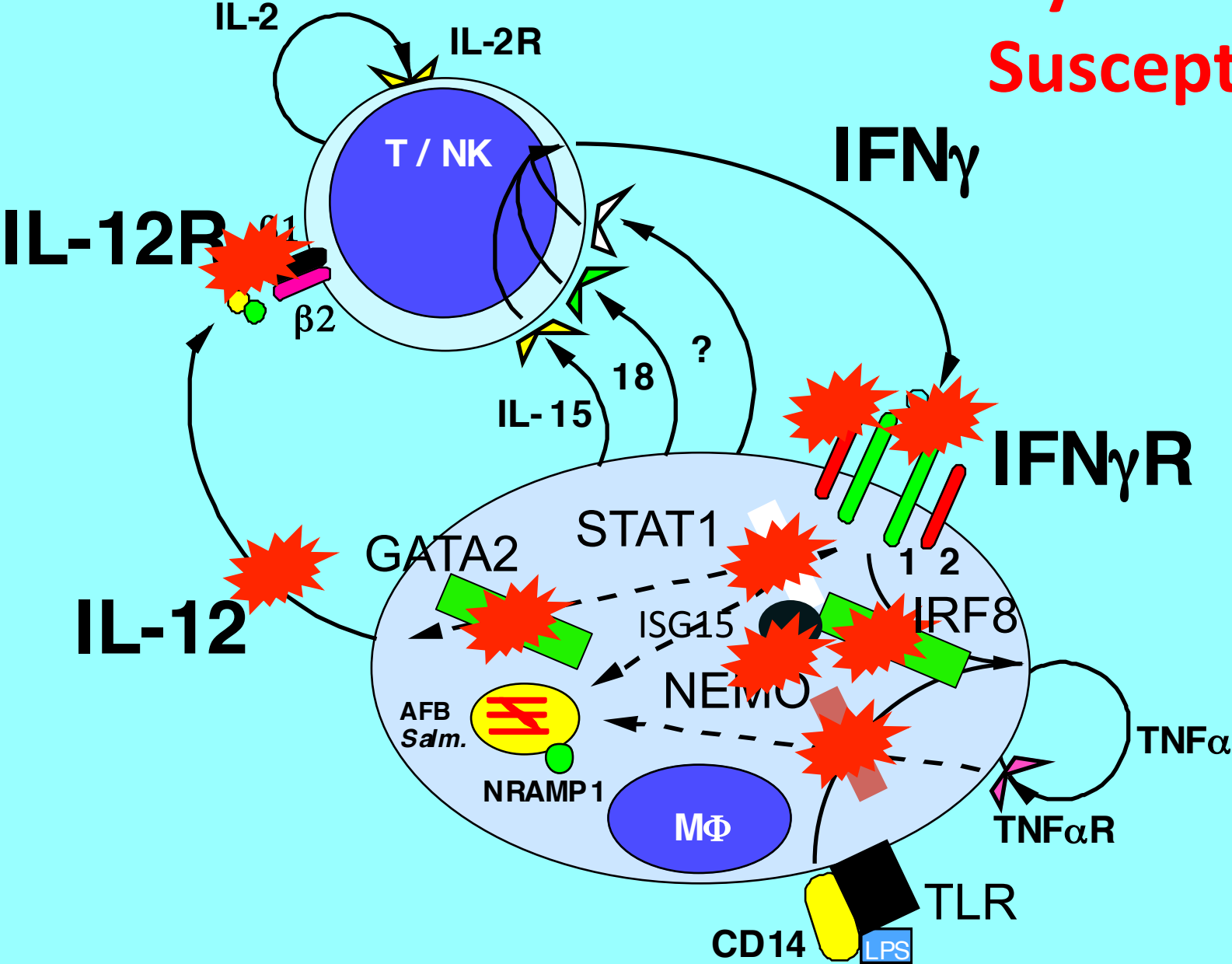
Endemic Dimorphic Fungi Seen in Patients with Inborn Errors of Immunity

- ◆ *Histoplasma*
- ◆ *Coccidioides*
- ◆ *Paracoccidioides*
- ◆ *Penicillium*
- ◆ *Sporothrix*
- ◆ *Blastomyces*

Intracellular Pathogen Control



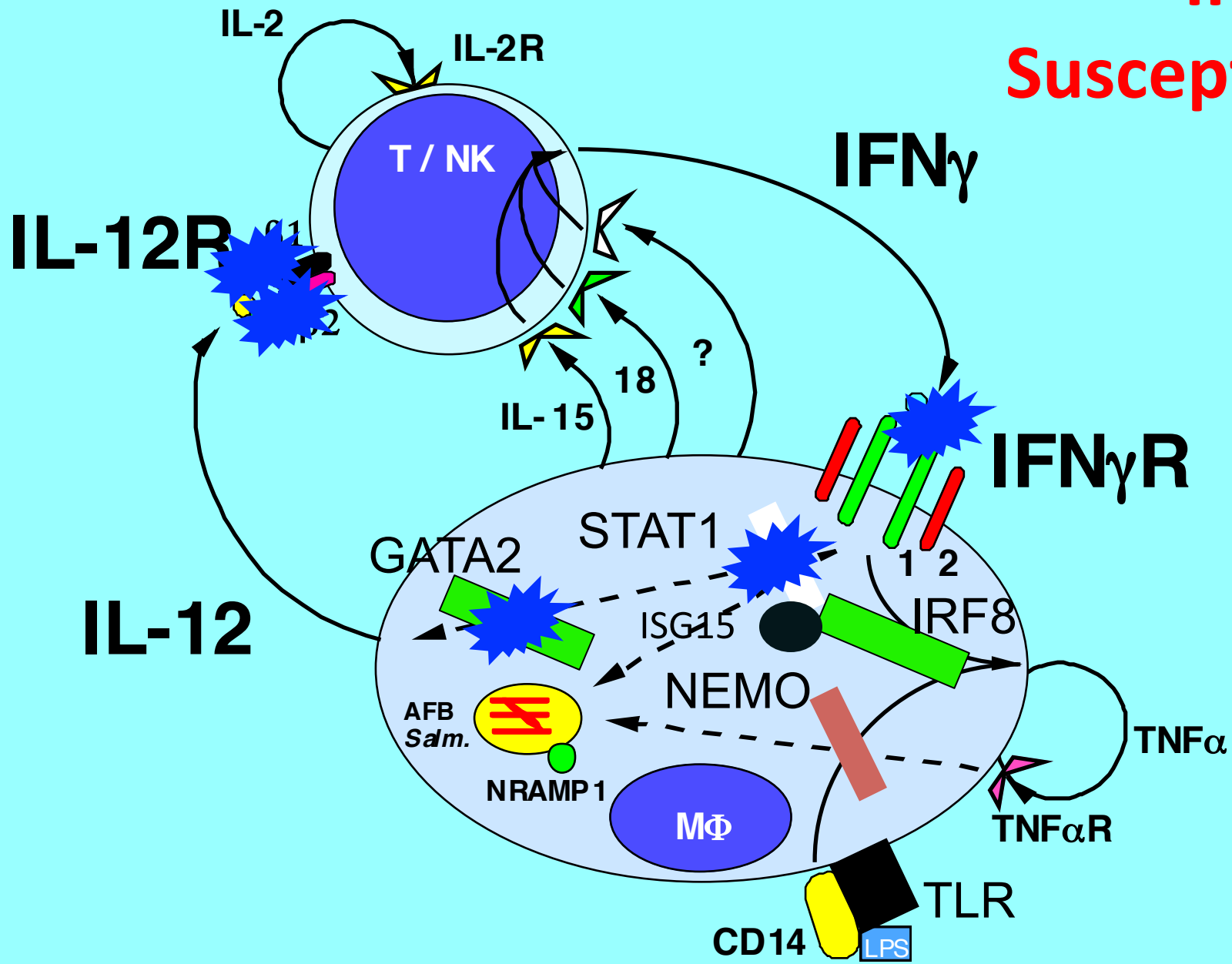
Mycobacterial Susceptibility



Courtesy of Steve Holland, NIH

IFI

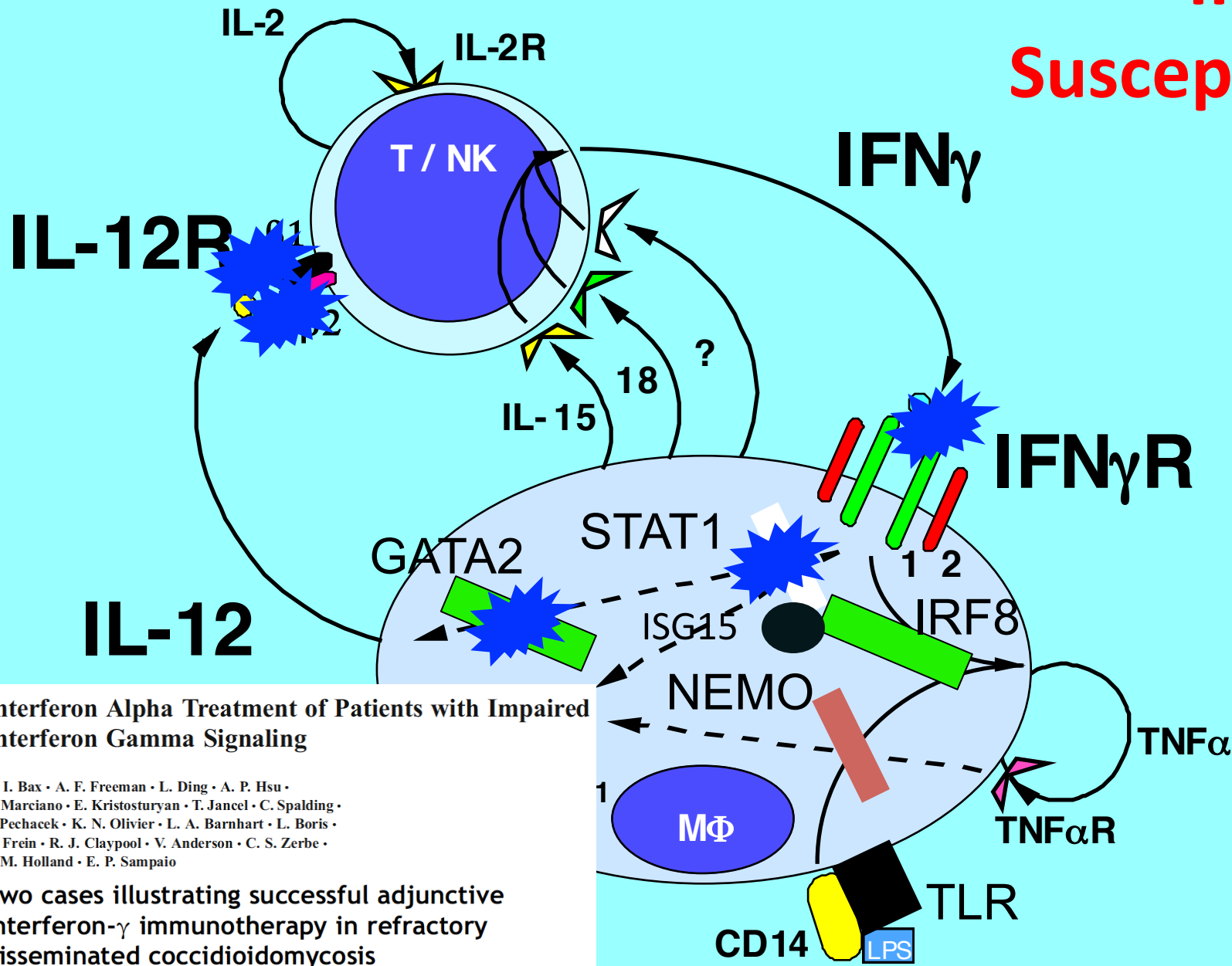
Susceptibility



Courtesy of Steve Holland, NIH

IFI

Susceptibility



Interferon Alpha Treatment of Patients with Impaired Interferon Gamma Signaling

H. I. Bax · A. F. Freeman · L. Ding · A. P. Hsu ·
B. Marciano · E. Kristosturyan · T. Jancel · C. Spalding ·
J. Pechacek · K. N. Olivier · L. A. Barnhart · L. Boris ·
C. Frein · R. J. Claypool · V. Anderson · C. S. Zerbe ·
S. M. Holland · E. P. Sampaio

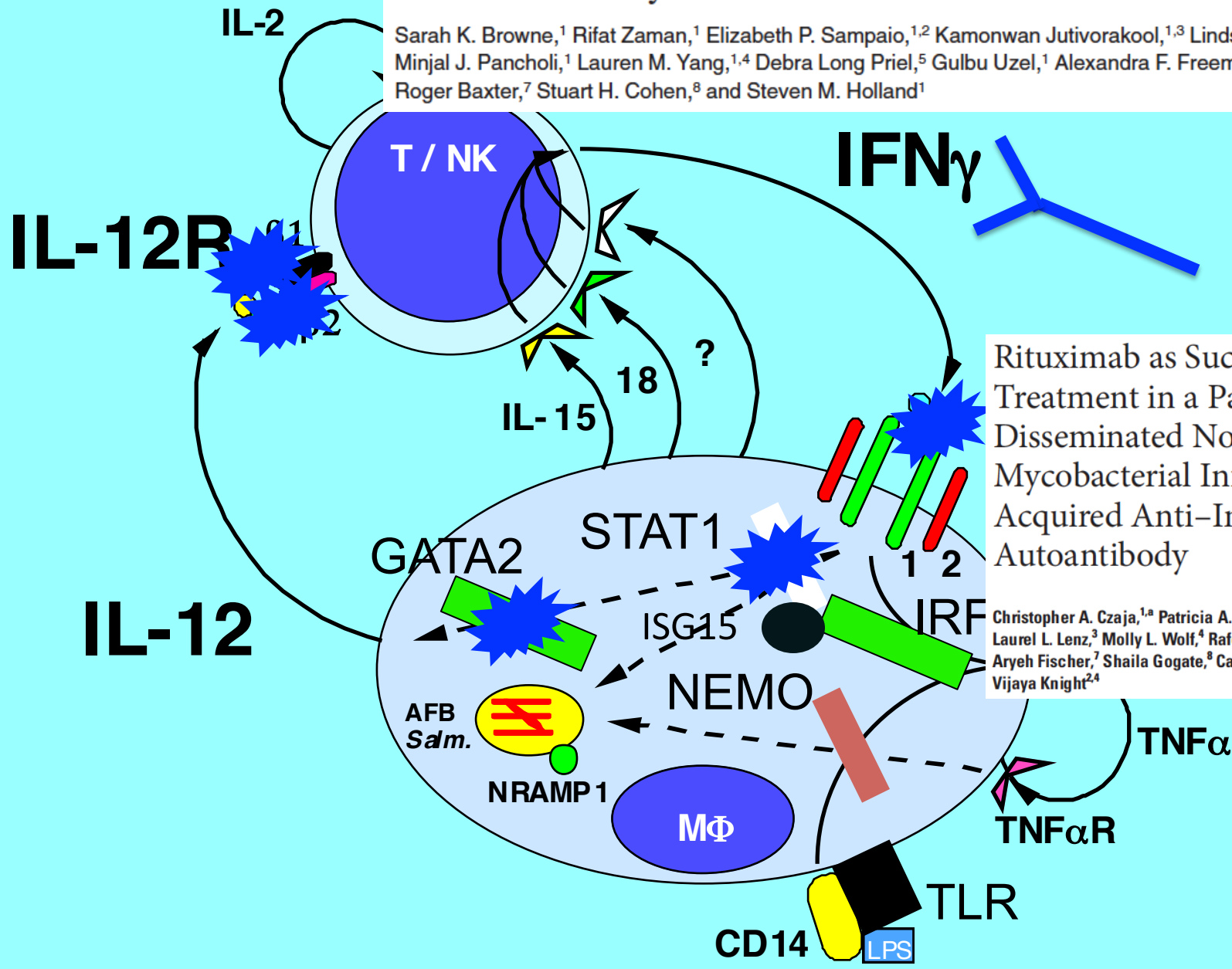
Two cases illustrating successful adjunctive interferon-γ immunotherapy in refractory disseminated coccidioidomycosis

Christopher A. Duplessis^{a,*}, Drake Tilley^a, Mary Bavaro^a, Braden Hale^a,
Steven M. Holland^b

Courtesy of Steve Holland, NIH

Anti-CD20 (rituximab) therapy for anti-IFN- γ autoantibody-associated nontuberculous mycobacterial infection

Sarah K. Browne,¹ Rifat Zaman,¹ Elizabeth P. Sampaio,^{1,2} Kamonwan Jutivorakool,^{1,3} Lindsey B. Rosen,¹ Li Ding,¹ Minjal J. Pancholi,¹ Lauren M. Yang,^{1,4} Debra Long Priel,⁵ Gulbu Uzel,¹ Alexandra F. Freeman,¹ Carlton E. Hayes,⁶ Roger Baxter,⁷ Stuart H. Cohen,⁸ and Steven M. Holland¹



Rituximab as Successful Adjunct Treatment in a Patient With Disseminated Nontuberculous Mycobacterial Infection Due to Acquired Anti-Interferon- γ Autoantibody

Christopher A. Czaja,^{1,a} Patricia A. Merkel,^{2,a} Edward D. Chan,¹ Laurel L. Lenz,³ Molly L. Wolf,⁴ Rafeul Alam,⁵ Stephen K. Frankel,⁶ Aryeh Fischer,⁷ Shaila Gogate,⁸ Carlos M. Perez-Velez,⁹ and Vijaya Knight^{2,4}

What Leads to Inherited Susceptibility to Endemic Dimorphic Fungal Infections?

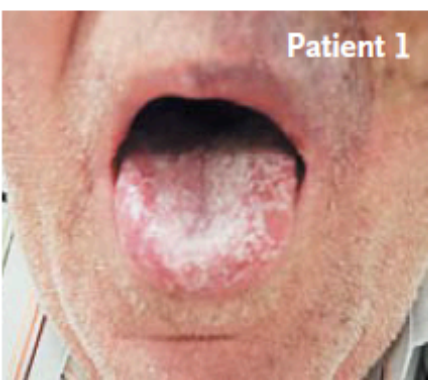
- ◆ IL-12R β 1 & IL-12R β 2 Mutations
- ◆ IFN γ R1 Mutations or IFN γ AAbs
- ◆ *STAT1* GOF Mutations
- ◆ GATA2 Deficiency
- ◆ Hyper-IgE syndrome (*STAT3*, *DOCK8*)

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STAT1 Mutations in Autosomal Dominant Chronic Mucocutaneous Candidiasis

Frank L. van de Veerdonk, M.D., Ph.D., Theo S. Plantinga, Ph.D., Alexander Hoischen, Ph.D., Sanne P. Smeekeens, M.Sc., Leo A.B. Joosten, Ph.D., Christian Gilissen, Ph.D., Peer Arts, Ph.D., Diana C. Rosentul, M.Sc., Andrew J. Carmichael, M.D., Chantal A.A. Smits-van der Graaf, M.D., Ph.D., Bart Jan Kullberg, M.D., Ph.D., Jos W.M. van der Meer, M.D., Ph.D., Desa Lilic, M.D., Ph.D., Joris A. Veltman, Ph.D., and Mihai G. Netea, M.D., Ph.D.

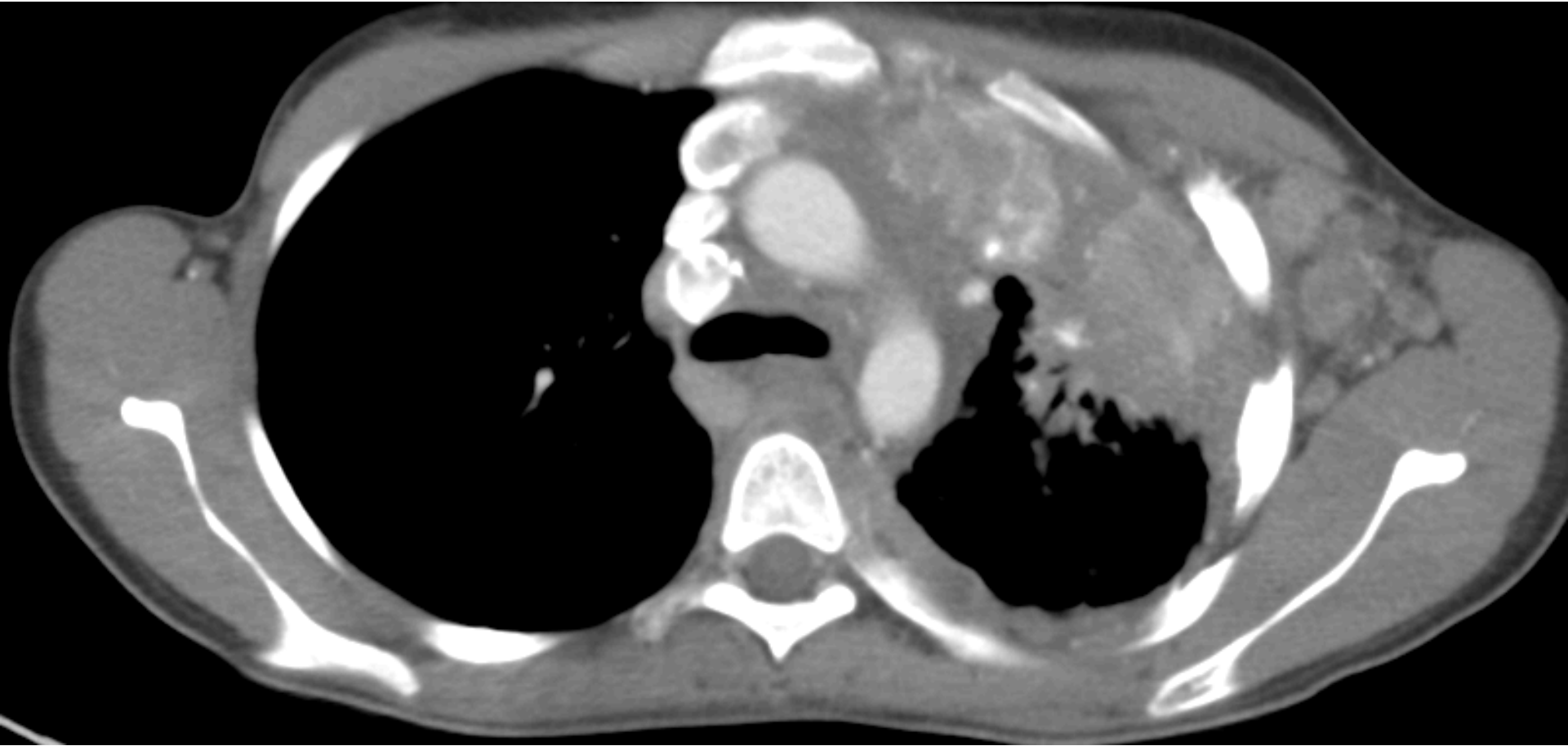


JEM 2011 Article

Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis

Luyan Liu,¹ Satoshi Okada,² Xiao-Fei Kong,² Alexandra Y. Kreins,² Sophie Cypowij,² Avinash Abhyankar,² Julie Toubiana,³ Yuval Itan,² Magali Audry,² Patrick Nitschke,⁴ Cécile Masson,⁴ Beata Toth,⁹ Jérôme Flatot,¹¹ Mélanie Migaud,¹ Maya Chrabieh,¹ Tatiana Kochetkov,² Alexandre Bolze,^{1,2} Alessandro Borghesi,¹ Antoine Toulon,⁵ Julia Hiller,¹⁰ Stefanie Eyerich,¹⁰ Kilian Eyerich,^{10,11} Vera Gulácsy,⁹ Ludmyla Chernyshova,¹² Viktor Chernyshov,¹³ Anastasia Bondarenko,¹² Rosa María Cortés Grimaldo,¹⁴ Lizbeth Blancas-Galicia,¹⁵ Ileana Maria Madrigal Beas,¹⁴ Joachim Roesler,¹⁶ Klaus Magdorf,¹⁷ Dan Engelhard,¹⁸ Caroline Thumerelle,¹⁹ Pierre-Régis Burgel,²⁰ Miriam Hoernes,²¹ Barbara Drexel,²¹ Reinhard Seger,²¹ Theresia Kusuma,²² Annette F. Jansson,²² Julie Sawalle-Belohradsky,²² Bernd Belohradsky,²² Emmanuelle Jouanguy,^{1,2} Jacinta Bustamante,¹ Mélanie Bué,²³ Nathan Karin,²⁴ Gizi Wildbaum,²⁴ Christine Bodemer,⁵ Olivier Lortholary,⁶ Alain Fischer,⁷ Stéphane Blanche,⁷ Saleh Al-Muhsen,²⁴ Janine Reichenbach,²¹ Masao Kobayashi,²⁶ Francisco Espinosa Rosales,¹⁵ Carlos Torres Lozano,¹⁴ Sara Sebnem Kilic,²⁷ Matias Oleastro,²⁸ Amos Etzioni,²⁴ Claudia Traidl-Hoffmann,^{10,11} Ellen D. Renner,²² Laurent Abel,^{1,2} Capucine Picard,^{1,6,8} László Maródi,⁹ Stéphanie Boisson-Dupuis,^{1,2} Anne Puel,¹ and Jean-Laurent Casanova^{1,2,7,25}

**16 year old Caucasian girl, 8 years refractory *Coccidioides*
Arizona native. Brain and eye involvement. No CMC**



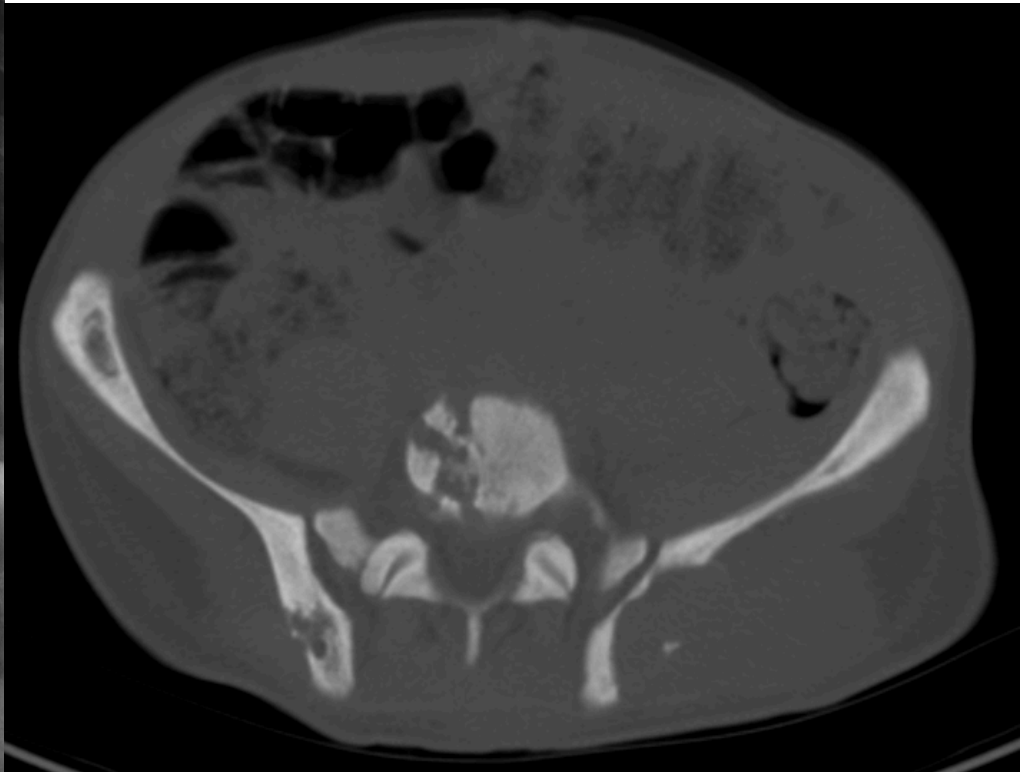
Courtesy of Steve Holland, NIH



18 year old healthy African American

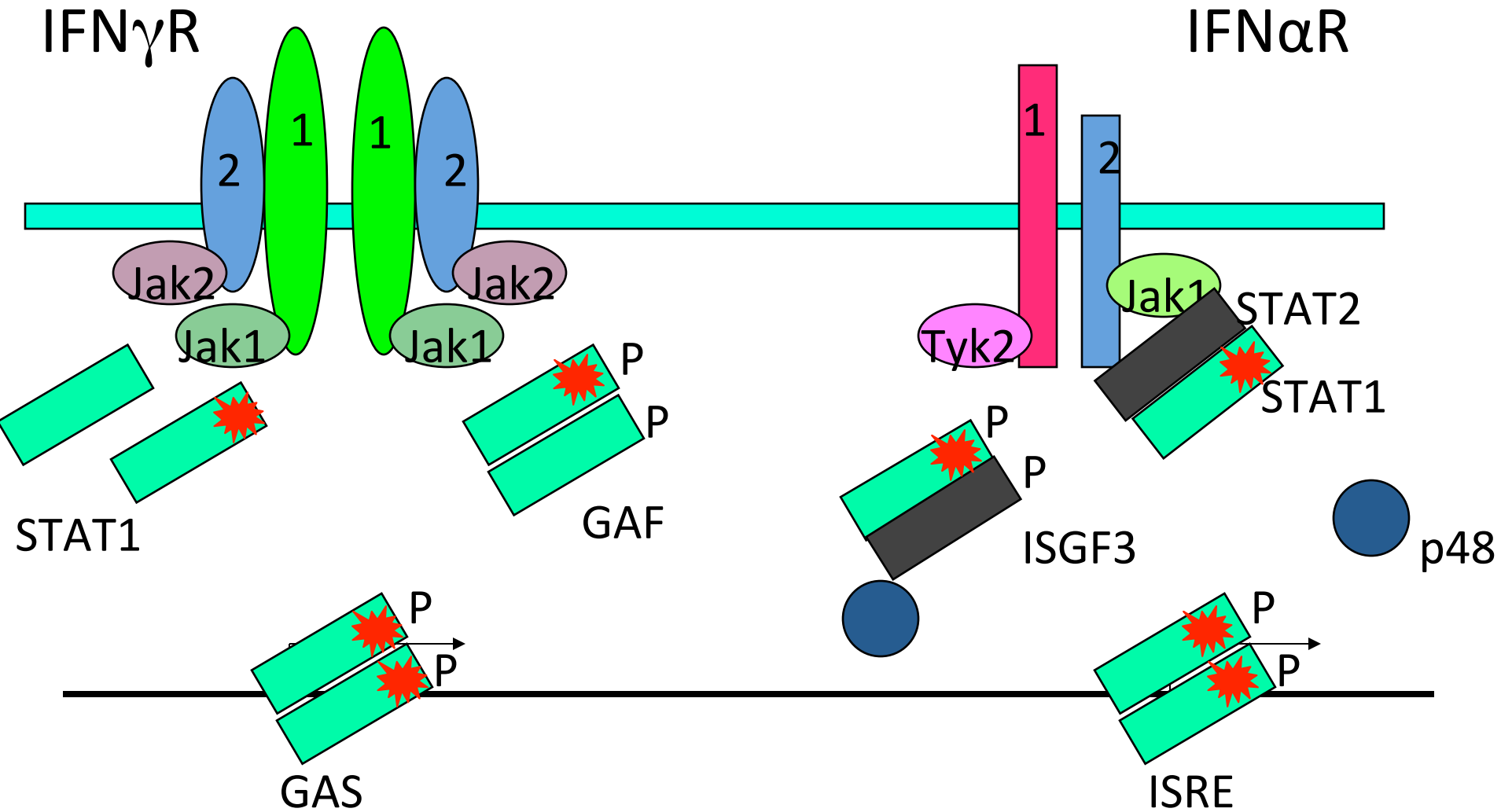
Chicago to Tucson, Arizona

**Extensive bony coccidioidomycosis,
multiple relapses, breakthroughs**



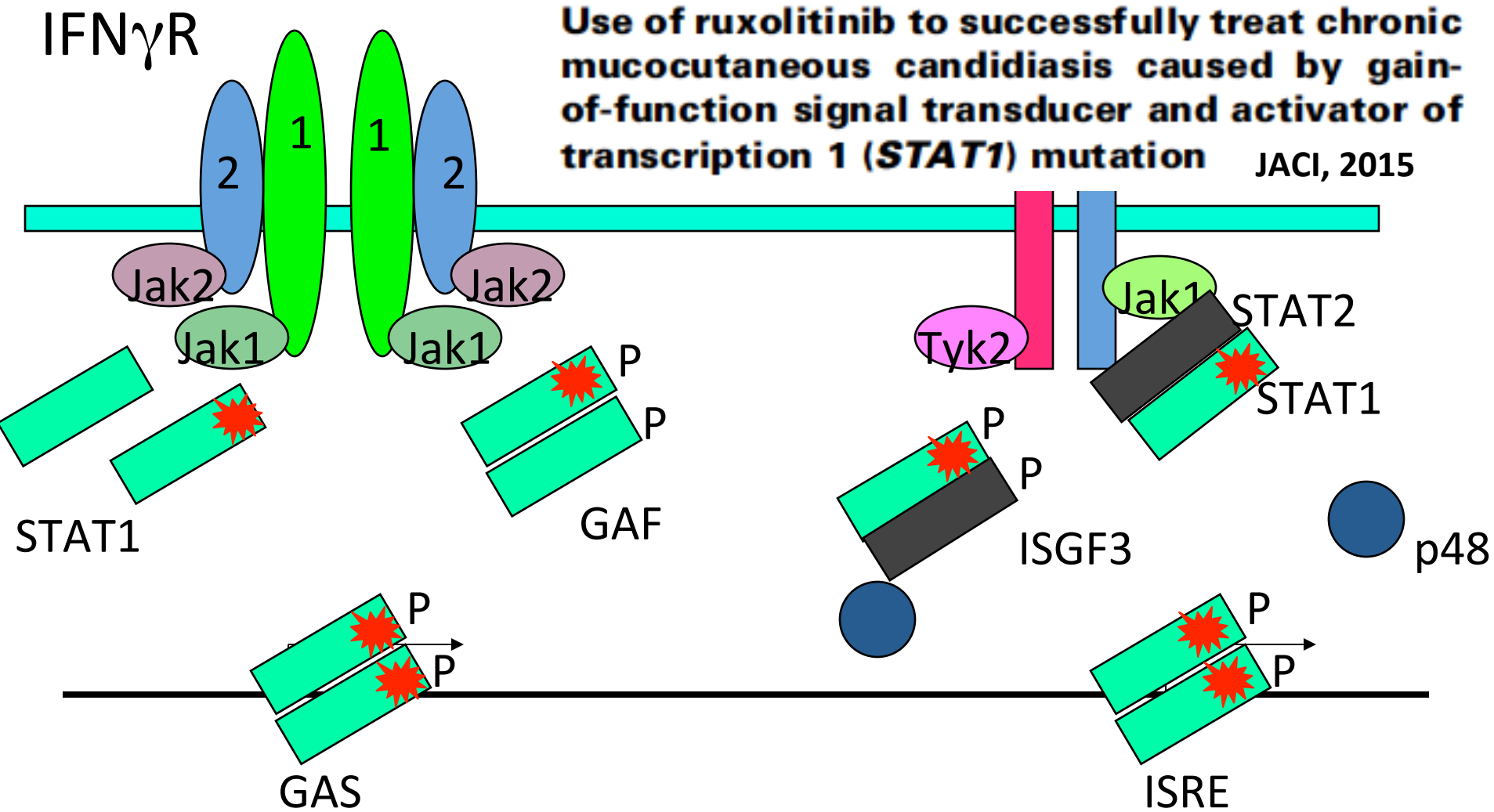
Courtesy of Steve Holland, NIH

STAT1 Activation by IFNs: Hypermorphic



Courtesy of Steve Holland, NIH

STAT1 Activation by IFNs: Hypermorphic



PIDs and IFIs

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- ◆ Endemic Dimorphic Fungi
- ◆ **Yeasts**

What Leads to Inherited Susceptibility to Cryptococcosis?

- ◆ Idiopathic CD4 Lymphocytopenia
- ◆ GATA2 Deficiency
- ◆ IL-12R, STAT3, DOCK8 Mutations
- ◆ GM-CSF autoAbs (acquired; *C. gattii*?)
- ◆ Unknown Immunodeficiency

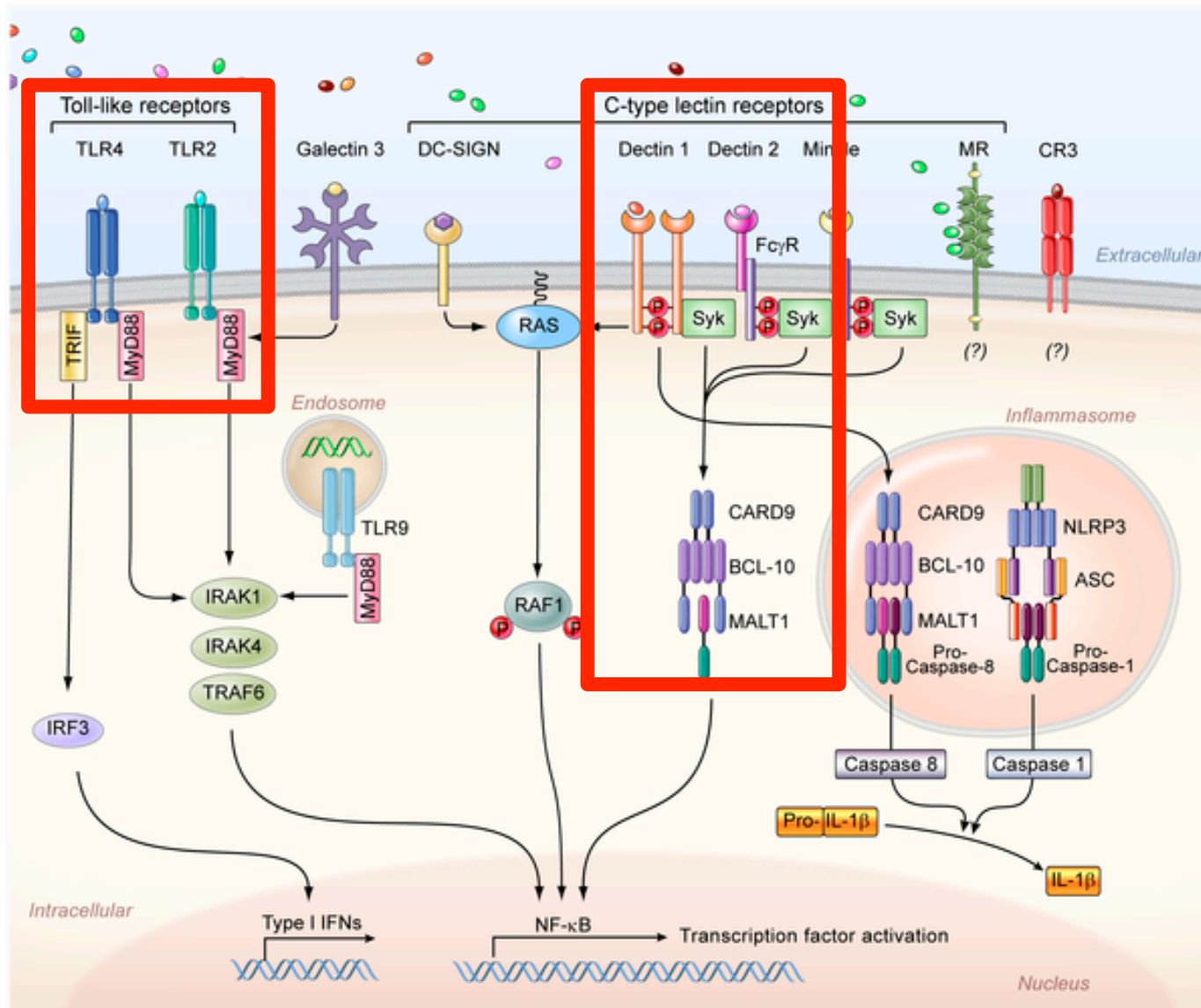
What Leads to Inherited Susceptibility to Invasive Candidiasis?

- ◆ Chronic Granulomatous Disease (rare)
- ◆ Complete MPO Deficiency (uncommon)
- ◆ CARD9 Deficiency

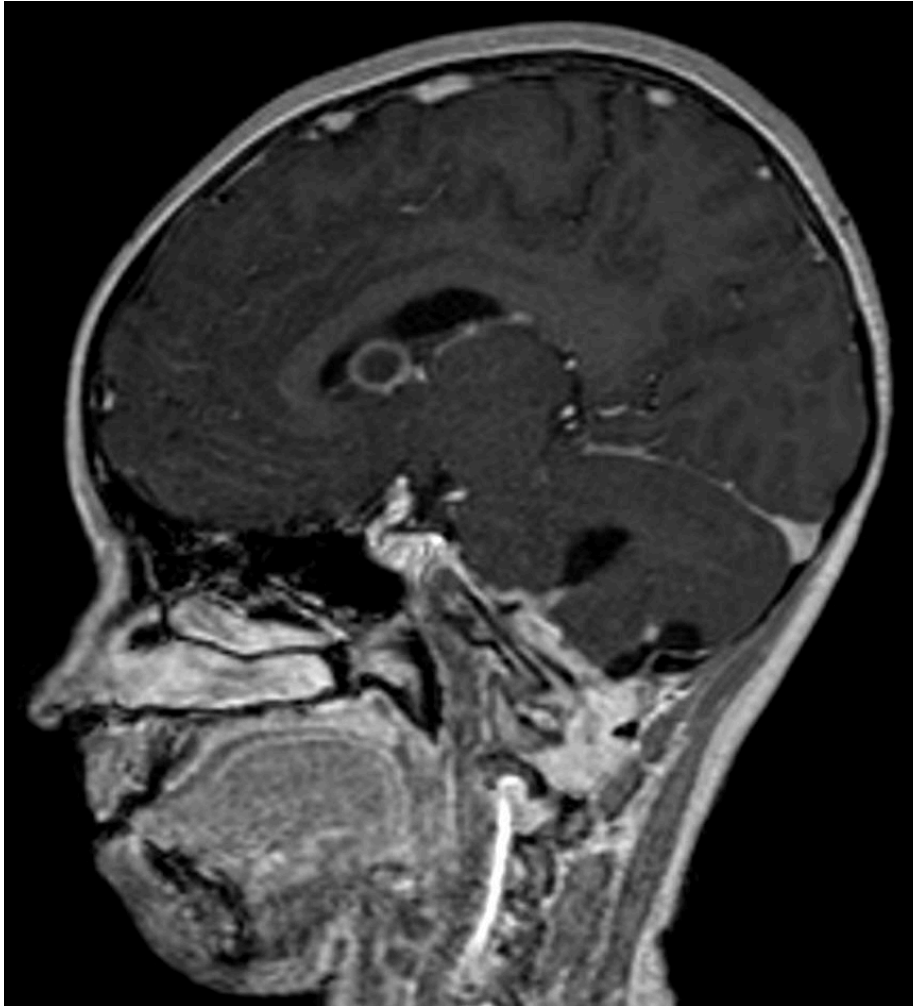
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- ◆ **CARD9 Deficiency**

The Role of Pattern-Recognition Receptors in *Candida* Sensing



Candida Meningoencephalitis



CARD9 Deficiency and Spontaneous Central Nervous System Candidiasis: Complete Clinical Remission With GM-CSF Therapy

Christina Gavino,¹ Anthony Cotter,¹ Daniel Lichtenstein,¹ Duncan Lejtenyi,² Claude Fortin,³ Catherine Legault,⁴ Najmeh Alirezaie,⁵ Jacek Majewski,⁵ Donald C. Sheppard,⁶ Marcel A. Behr,⁷ William D. Foulkes,⁸ and Donald C. Vinh¹

CID, 2014

CARD9 is a Central Hub for Mucosal & Systemic Antifungal Immunity

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Deep Dermatophytosis and Inherited CARD9 Deficiency

Fanny Lanternier, M.D., Saad Pathan, Ph.D., Quentin B. Vincent, M.D., Luyan Liu, M.Sc.,
Sophie Cypowj, Ph.D., Carolina Prando, M.D., Ph.D., Mélanie Migaud, B.S.,
Lynda Taibi, M.D., Aomar Ammar-Khodja, M.D., Omar Boudghene Stambouli, M.D.,
Boumediene Guellil, M.D., Frederique Jacobs, M.D., Ph.D.,
Jean-Christophe Goffard, M.D., Ph.D., Kinda Schepers, M.D., Ph.D.,
Véronique del Marmol, M.D., Ph.D., Lobna Boussofara, M.D., Mohamed Denguezli, M.D.,
Molka Larif, M.D., Hervé Bachelez, M.D., Ph.D., Laurence Michel, Ph.D.,
Gérard Lefranc, Ph.D., Rod Hay, M.D., Ph.D., Gregory Jouvion, Ph.D.,
Fabrice Chretien, M.D., Ph.D., Sylvie Fraitag, M.D., Marie-Elisabeth Bougnoux, M.D., Ph.D.,
Merad Boudia, M.D., Laurent Abel, M.D., Ph.D., Olivier Lortholary, M.D., Ph.D.,
Jean-Laurent Casanova, M.D., Ph.D., Capucine Picard, M.D., Ph.D.,
Bodo Grimbacher, M.D., Ph.D., and Anne Puel, Ph.D.

CARD9 is a Central Hub for Mucosal & Systemic Antifungal Immunity

Inherited CARD9 Deficiency in 2 Unrelated Patients With Invasive *Exophiala* Infection

Fanny Lantermier,^{1,2,3} Elisa Barbati,^{1,2} Ulrich Meinzer,^{4,5} Luyan Liu,^{1,2} Vincent Pedergnana,^{1,2} Mélanie Migaud,^{1,2}
Sébastien Héritier,^{2,6} Maryline Chomton,^{2,6} Marie-Louise Frémond,^{2,6} Emmanuel Gonzales,¹³ Caroline Galeotti,¹⁴
Serge Romana,⁸ Emmanuel Jacquemin,¹³ Adela Angoulvant,¹⁵ Valeska Bidault,¹⁶ Danielle Canioni,⁷ Julie Lachenaud,¹⁷
Davood Mansouri,¹⁸ Seyed Alireza Mahdaviani,¹⁹ Parvaneh Adimi,²⁰ Nahal Mansouri,¹⁸ Mahin Jamshidi,²¹
Marie-Elisabeth Bougnoux,^{2,9,11} Laurent Abel,^{1,2,22} Olivier Lortholary,^{2,3,12} Stéphane Blanche,^{2,6}
Jean-Laurent Casanova,^{1,2,6,22,a} Capucine Picard,^{1,2,6,10,a} and Anne Puel^{1,2}

JID, 2015

**CARD9 mutations linked to subcutaneous
phaeohyphomycosis and T_H17 cell deficiencies**

JACI, 2014

IFI Susceptibility – Take Home

Autoantibodies to IFN γ and GM-CSF

Mutations in IFN γ R1, IL-12R β 1 and IL-12R β 2

Mutations in *GATA2*, *STAT1* (GOF), *CARD9*

Hyper-IgE syndrome (*STAT3*, *DOCK8*)

Severe mycoses should prompt investigation for host defects

Great opportunities to gain insight in antifungal immunity

Adjunct immunotherapy and/or transplantation lessons

Thank you!