

Current research in understanding pathogenesis and host immunity toward developing treatment options

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Bench to Bedside Program in Fungal Pathogenesis

Inherited disorders
(Fungi a “signature” pathogen)
(~1000 patients)

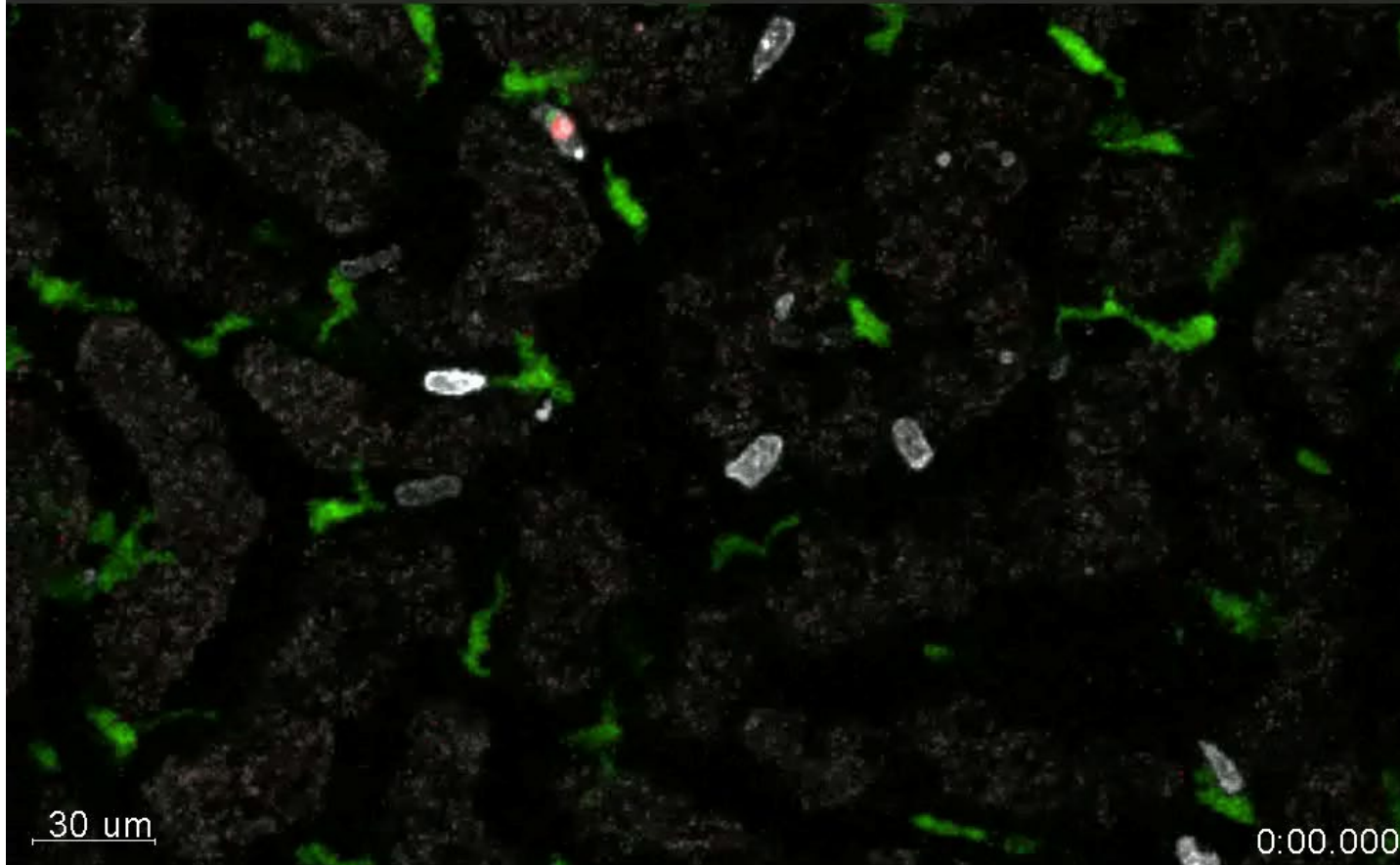
**BASIC/TRANSLATIONAL
STUDIES**

Innate & adaptive
immune mechanisms

CANDIDA
ASPERGILLUS

CLINICAL STUDIES

Acquired/iatrogenic
(ibrutinib, danirixin
eculizumab, antibiotics
fostamatinib)

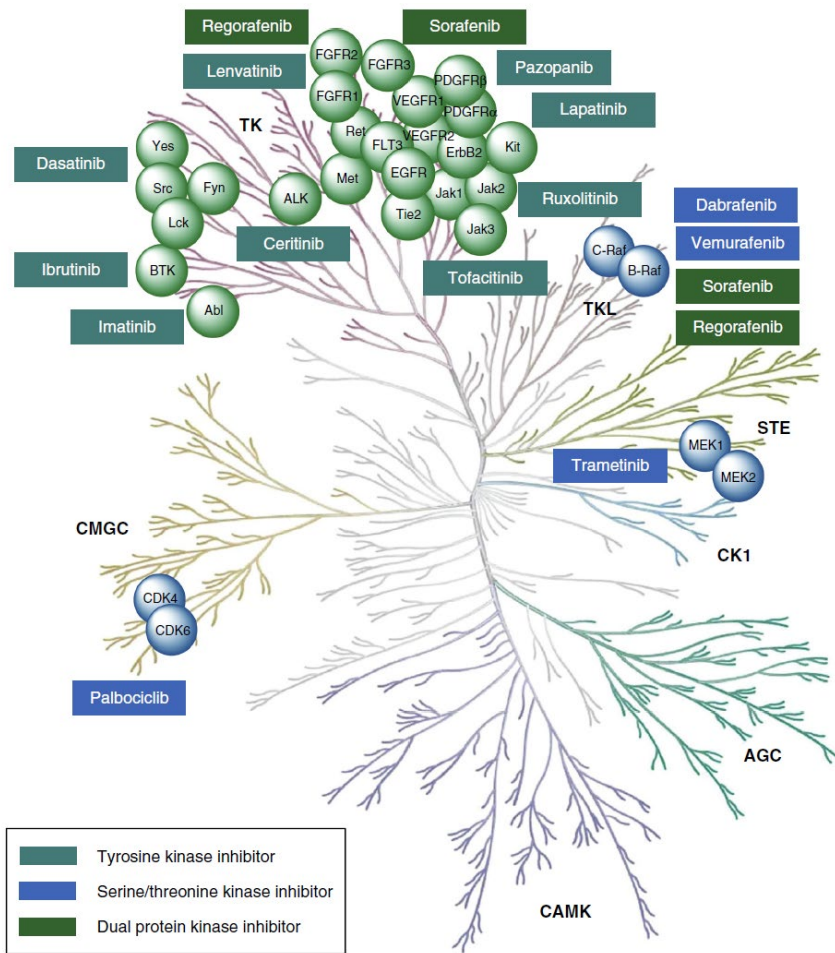


**Red: dTomato-
*C. albicans***

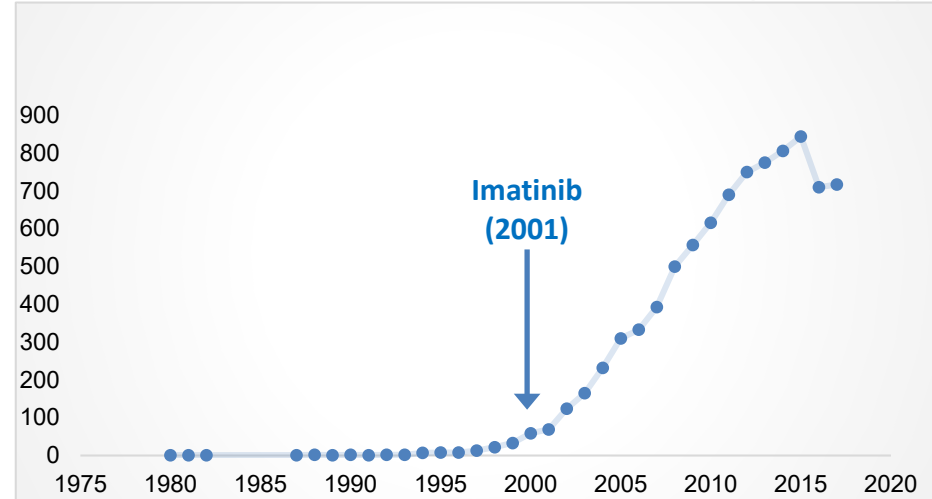
**Green: Cx3cr1
(macrophages)**

**Grey: Ly6G
(neutrophils)**

An Expanded Universe of At-risk Patients



PUBMED RESEARCH: Small Molecule Kinase Inhibitors (SMKIs)



FDA-Approved Updated Medication Guide

MEDICATION GUIDE

SOLIRIS® (so-leer-is)

(eculizumab)

injection, for intravenous use

What is the most important information I should know about SOLIRIS?

SOLIRIS is a medicine that affects your immune system. SOLIRIS can lower the ability of your immune system to fight infections.

- **SOLIRIS increases your chance of getting serious and life-threatening meningococcal infections.** Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

SOLIRIS may also increase the risk of other types of serious infections. If your child is treated with SOLIRIS, make sure that your child receives vaccinations against **Streptococcus pneumoniae and Haemophilis influenza type b (Hib).** Certain people may be at risk of serious infections with gonorrhea. Talk to your doctor about whether you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing. **Certain fungal infections (aspergillus)** may also happen if you take SOLIRIS and have a weak immune system or a low white blood cell count.

What are the ingredients in SOLIRIS?

Active ingredient: eculizumab

Inactive ingredients: polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, and Water for Injection

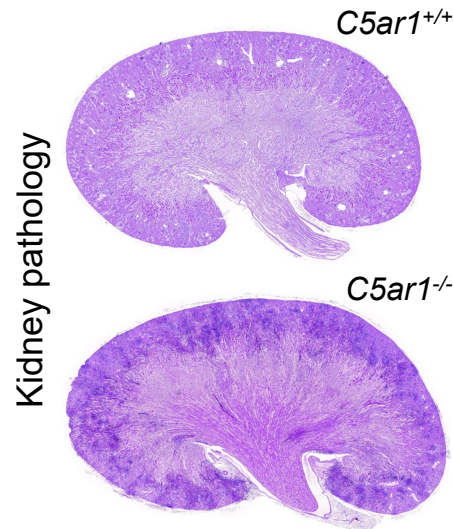
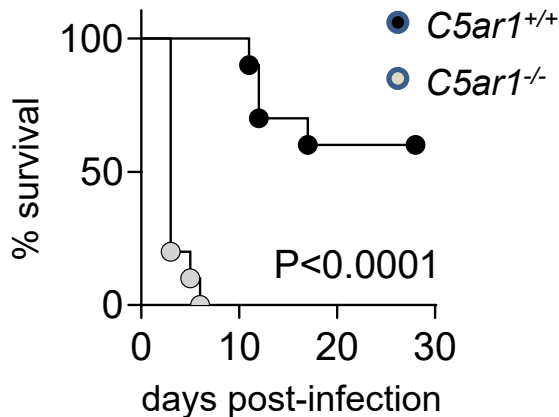
Manufactured by Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210 USA. US License Number 1743

This Medication Guide has been approved by the U.S. Food and Drug Administration

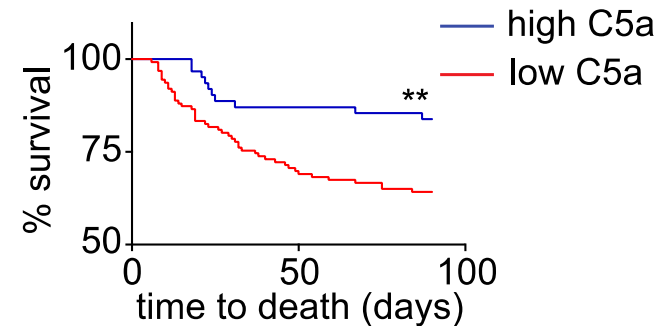
Revised: 07/2018

Complement C5a is critical for protection against invasive candidiasis

Mice with invasive candidiasis



ICU patients with invasive candidiasis



Chemoattractant Receptors Modulate Immunity in Systemic Candidiasis via Differential Mechanisms

RECEPTOR

CX3CR1

Lionakis et al., JCI, 2013
Collar et al., JCI Insight, 2018

CX₃CR1-M280



Macrophage survival

CCR1

Lionakis et al., PLoS Pathog, 2012
Lionakis et al., AAC, 2017



Neutrophil recruitment

CXCR1

Swamydas et al, Science Transl Med, 2016

CXCR1-T276



Neutrophil degranulation

CCR7

Tim Break, unpublished



Renal tubular cell survival

CXCR2

Lekha Swamydas, unpublished



Neutrophil fungal killing

C5AR1

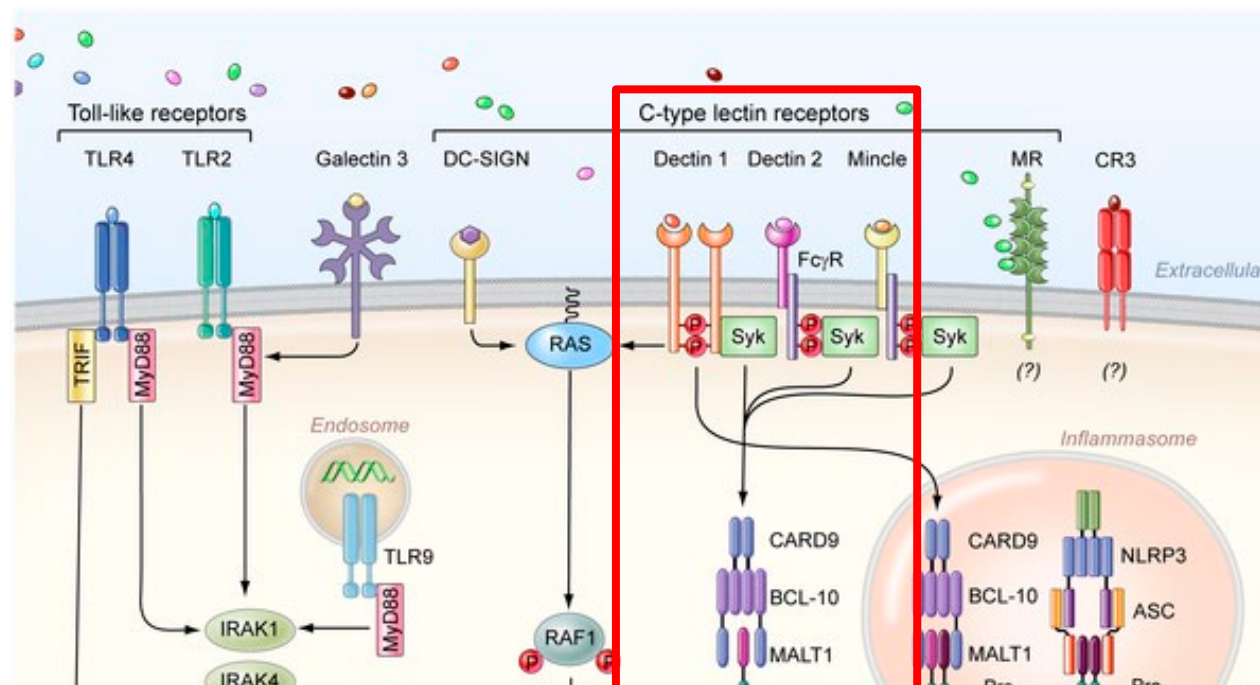
Jigar Desai, under review

C5 SNPs



Monocyte/macrophage fungal killing

SYK-CARD9 are Centrally Positioned in Antifungal Immune Pathways



Fostamatinib
>50 trials in
ClinicalTrials.gov

- RA
- AML
- GvHD
- Lymphomas
- Solid tumors
- Autoimmune
cytopenias
- COVID-19

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

ESTABLISHED IN 1812

SEPTEMBER 30, 2010

VOL. 363 NO. 14

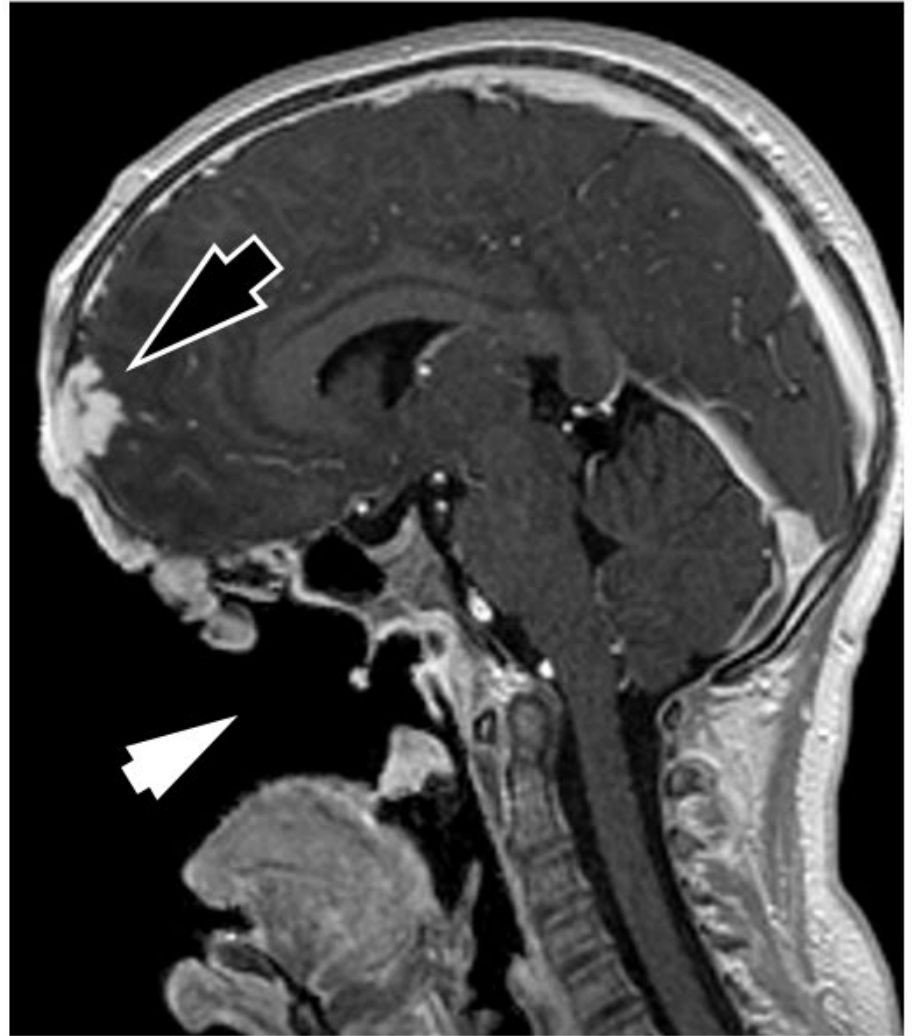
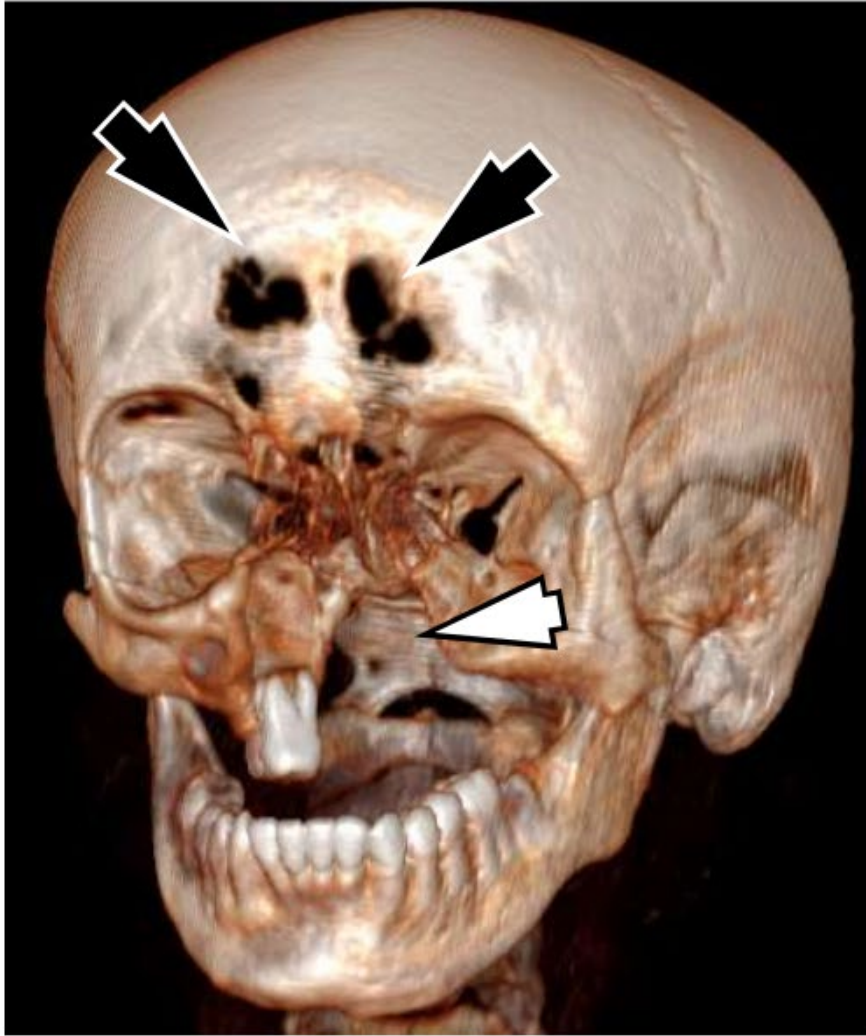
An Oral Spleen Tyrosine Kinase (Syk) Inhibitor
for Rheumatoid Arthritis



Corynespora Infection and CARD9 Deficiency



Corynespora Infection and CARD9 Deficiency



Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma

Michail S. Lionakis,^{1,7} Kieron Dunleavy,^{2,7} Mark Roschewski,² Brigitte C. Widemann,³ John A. Butman,⁴ Roland Schmitz,² Yandan Yang,² Diane E. Cole,³ Christopher Melani,² Christine S. Higham,³ Jigar V. Desai,² Michele Ceribelli,⁵ Lu Chen,⁵ Craig J. Thomas,^{2,5} Richard F. Little,⁶ Juan Gea-Banacloche,³ Sucharita Bhaumik,³ Maryalice Stetler-Stevenson,³ Stefania Pittaluga,³ Elaine S. Jaffe,³ John Heiss,³ Nicole Lucas,² Seth M. Steinberg,³ Louis M. Staudt,^{2,8,*} and Wyndham H. Wilson^{2,8,*}

Lionakis et al., 2017, Cancer Cell 31, 1–11
June 12, 2017 Published by Elsevier Inc.
<http://dx.doi.org/10.1016/j.ccell.2017.04.012>

CellPress

Atypical *Pneumocystis jirovecii* pneumonia in previously untreated patients with CLL on single-agent ibrutinib

BLOOD, 13 OCTOBER 2016 • VOLUME 128, NUMBER 15

Inhye E. Ahn,^{1,*} Theresa Jerussi,^{2,*} Mohammed Farooqui,³ Xin Tian,⁴ Adrian Wiestner,³ and Juan Gea-Banacloche⁵

Open Forum Infectious Diseases

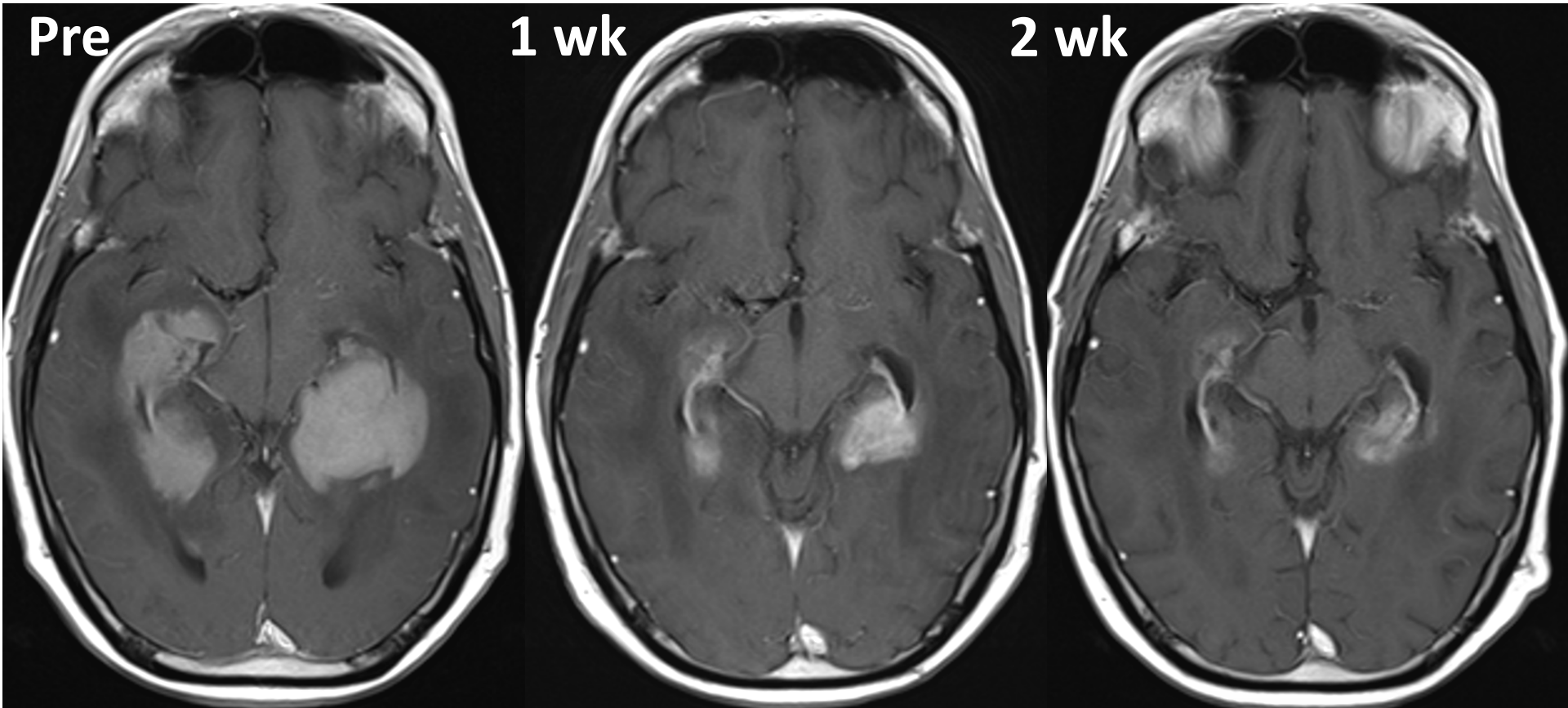
BRIEF REPORT

Disseminated Cryptococcosis With Brain Involvement in Patients With Chronic Lymphoid Malignancies on Ibrutinib

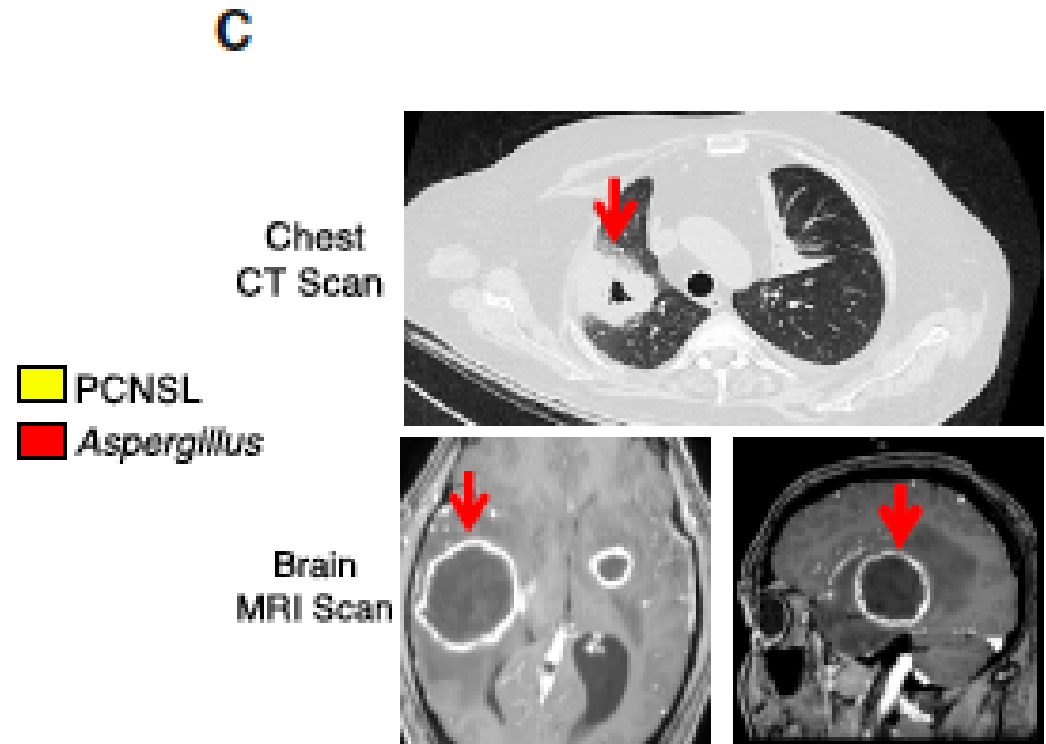
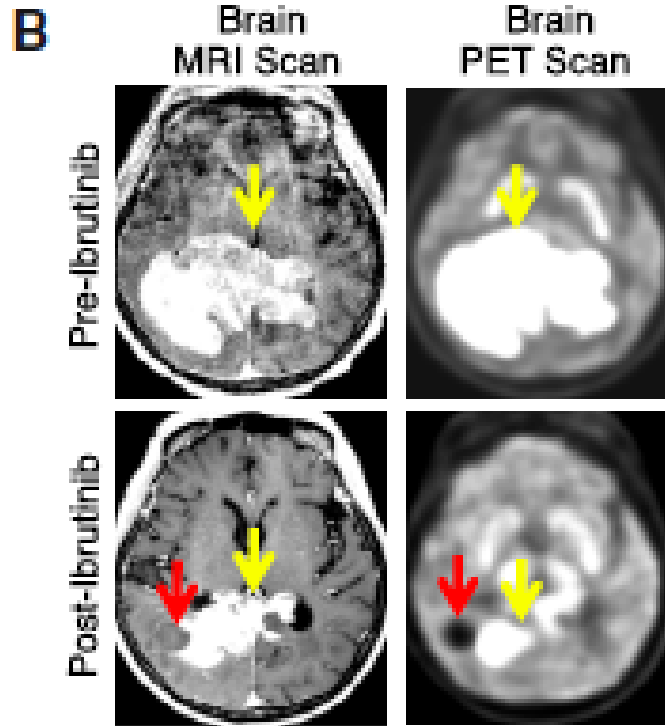
Julia A. Messina,¹ Eileen K. Maziarz,¹ Andrej Spec,² Dimitrios P. Kontoyiannis,³ and John R. Perfect¹

¹Department of Medicine, Duke University, Durham, North Carolina; ²Division of Infectious Disease, Washington University, St. Louis, Missouri; ³University of Texas MD Anderson Cancer Center, Houston

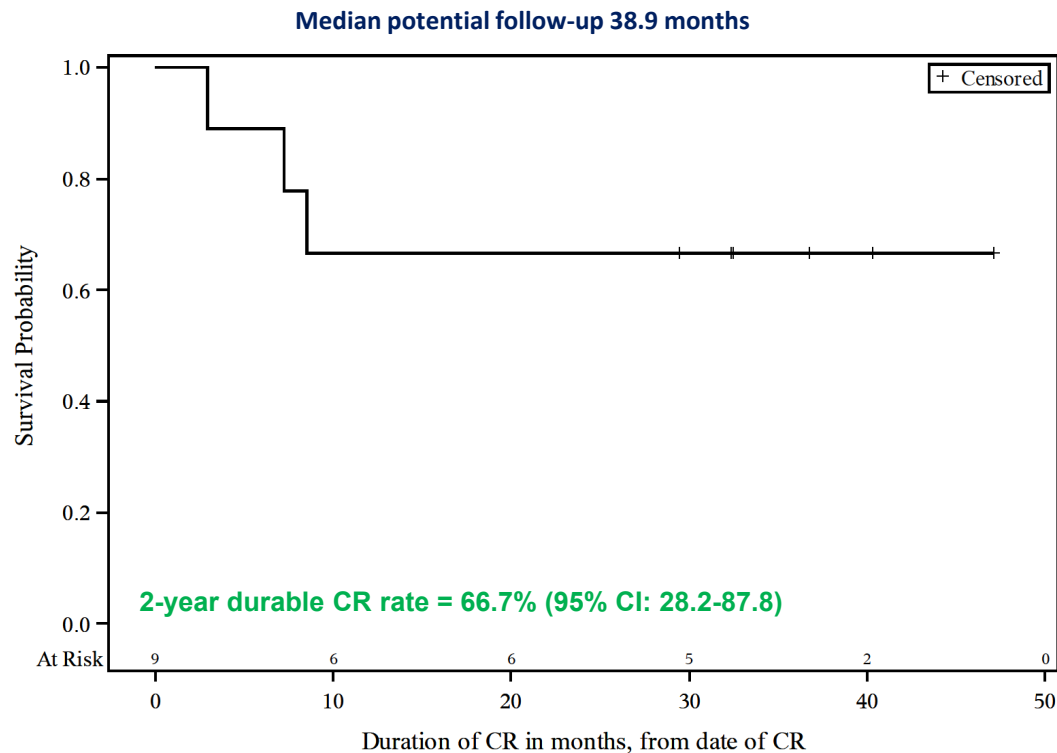
Ibrutinib over 2 weeks for CNS lymphoma



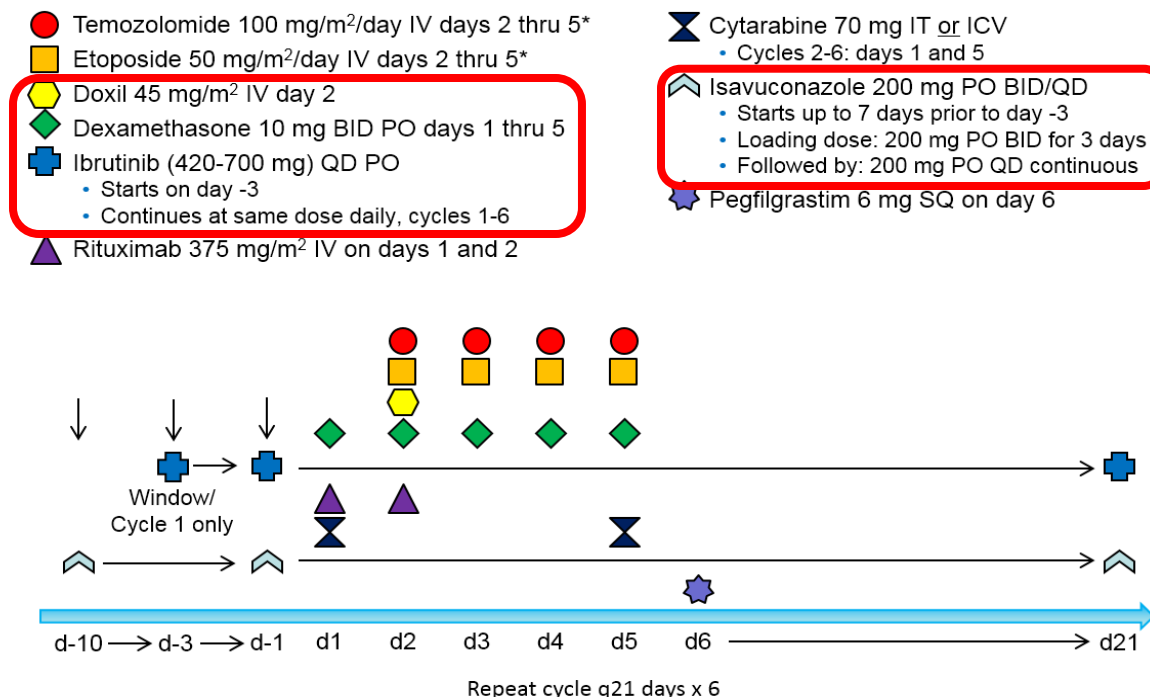
An unexpected emergence of aspergillosis



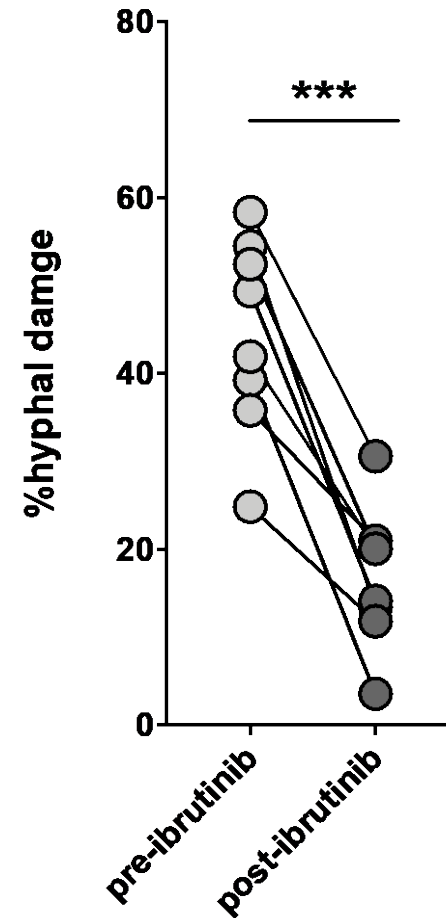
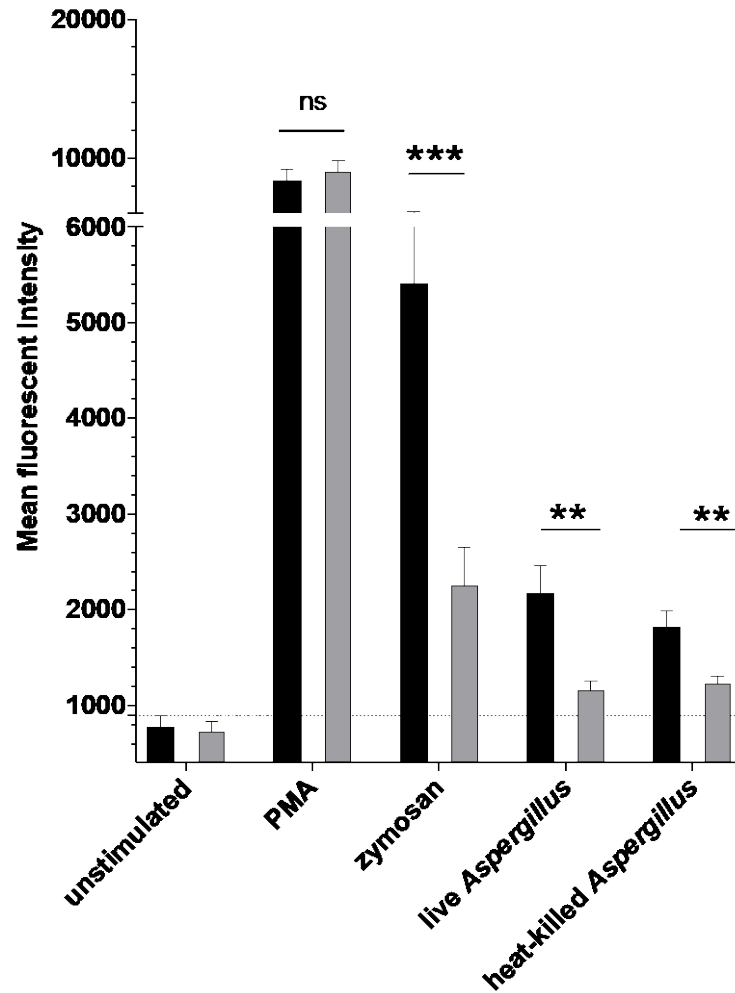
Durable Remissions in Refractory PCNSL



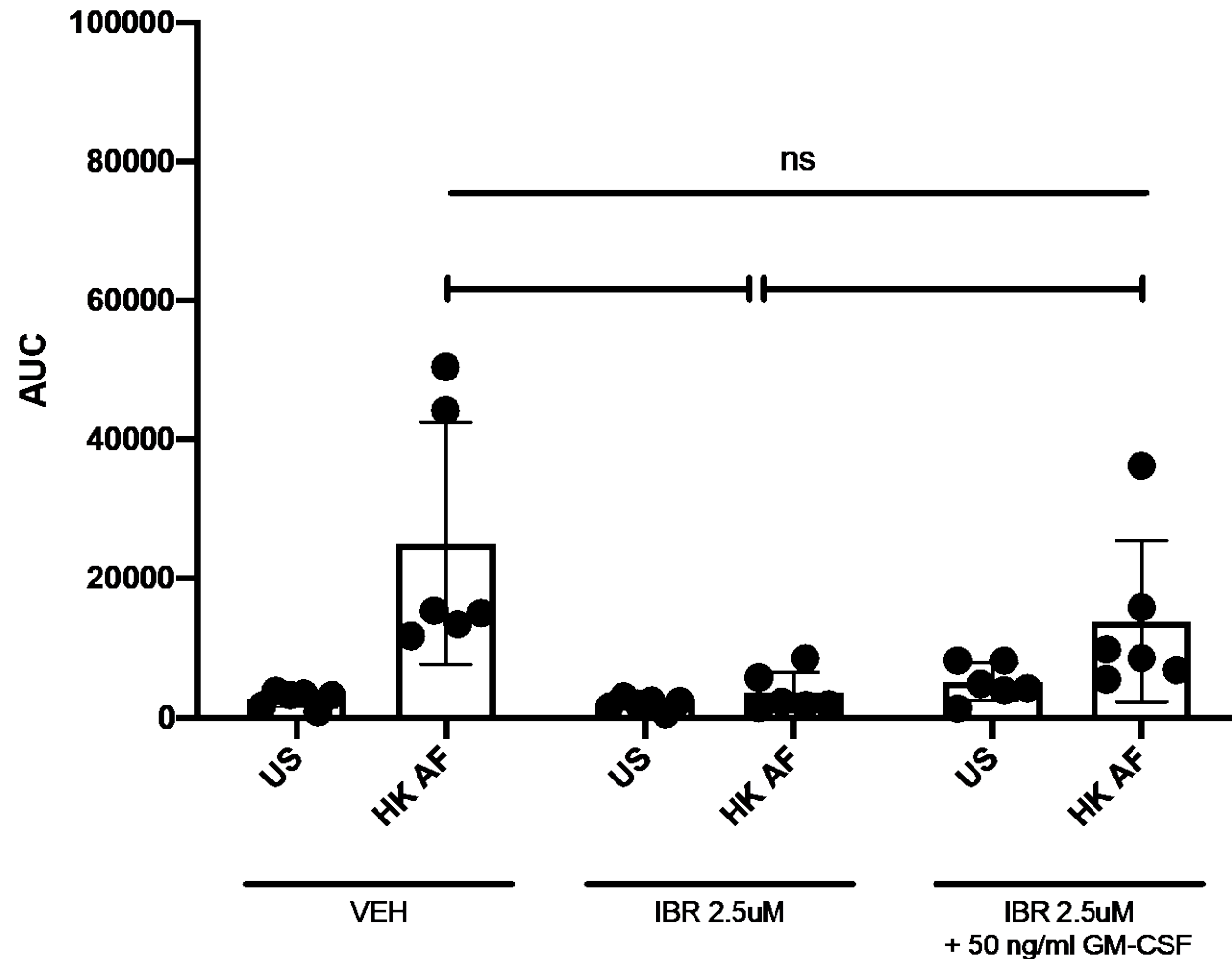
TEDDi-R v2.0 for PCNSL and SCNSL



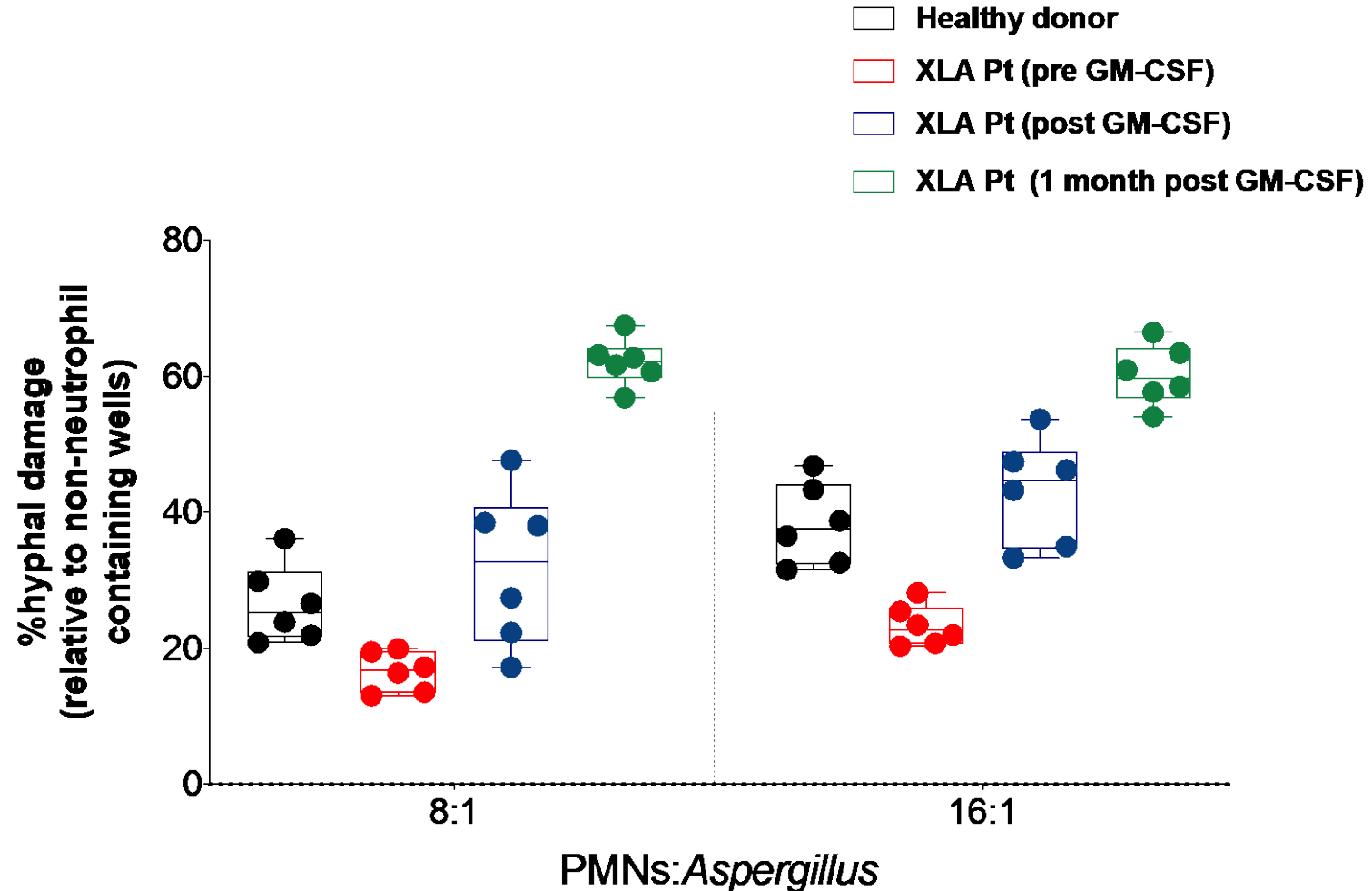
Ibrutinib impairs ROS production and fungal killing by human neutrophils *in vivo*



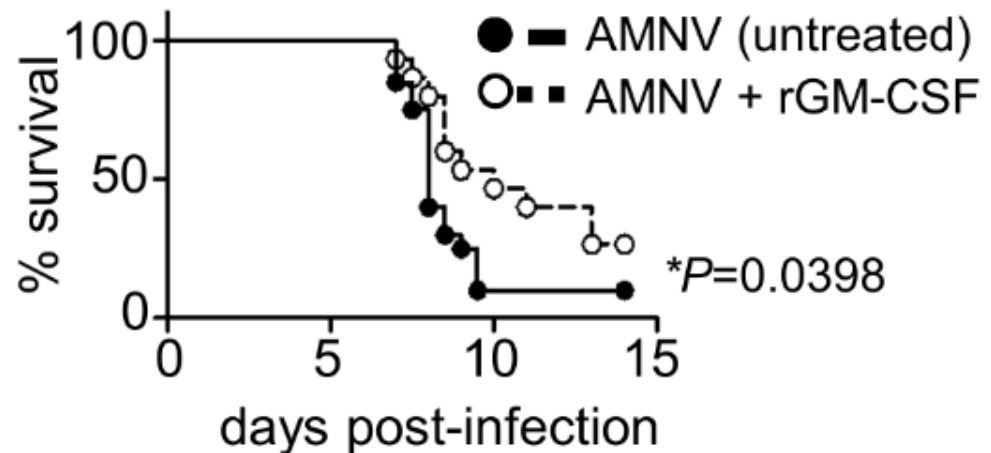
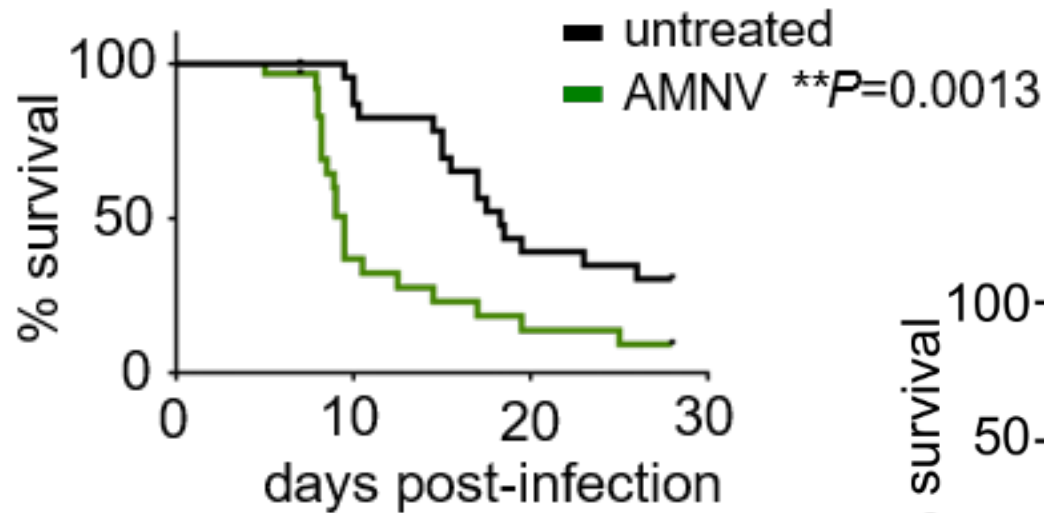
GM-CSF rescues the BTK inhibition-induced ROS defect in human neutrophils



GM-CSF rescues the BTK inhibition-induced neutrophil defect in an XLA patient



Antibiotics Enhance Susceptibility of WT mice to Systemic Candidiasis



The New England Journal of Medicine

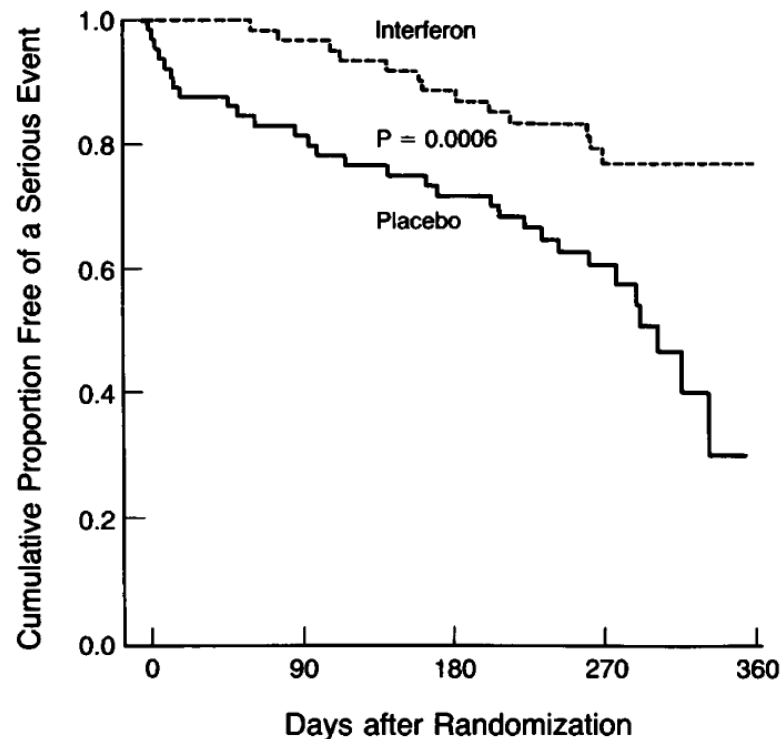
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Volume 324

FEBRUARY 21, 1991

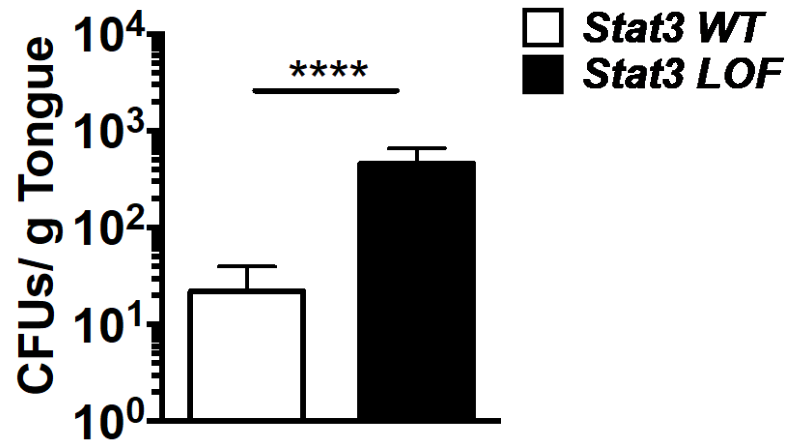
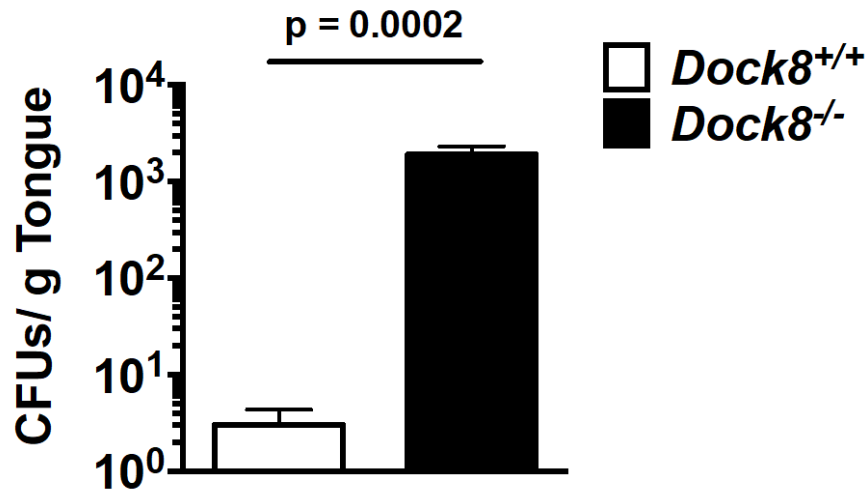
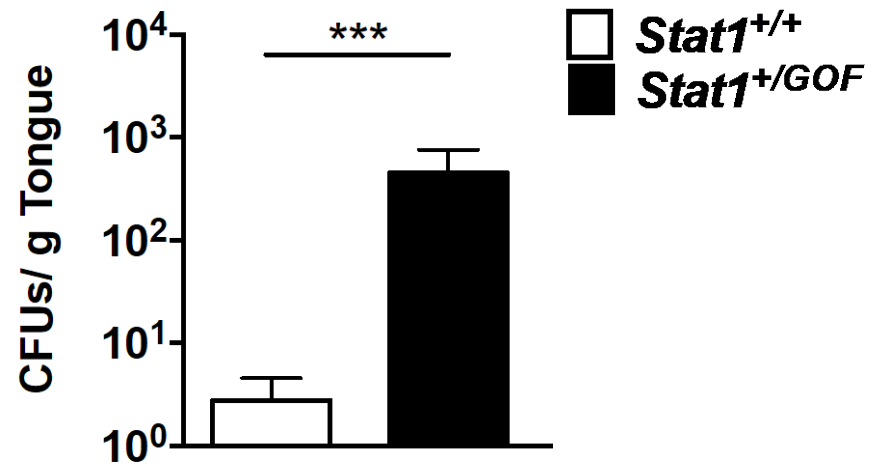
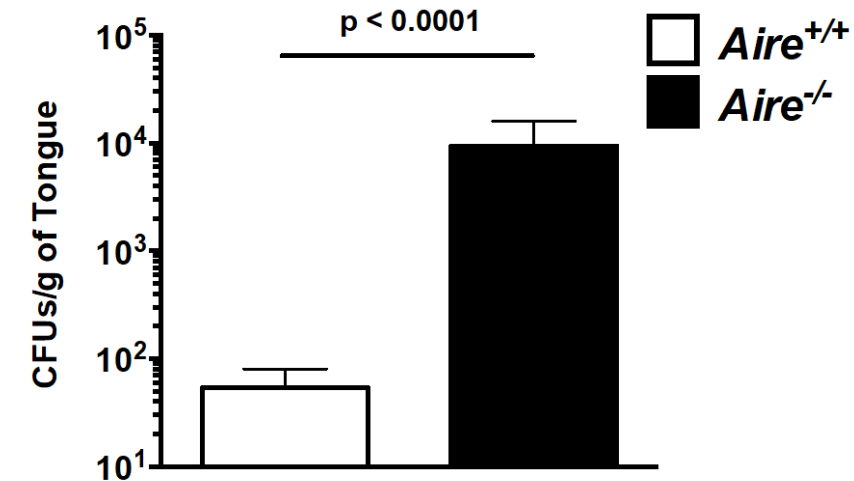
Number 8

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

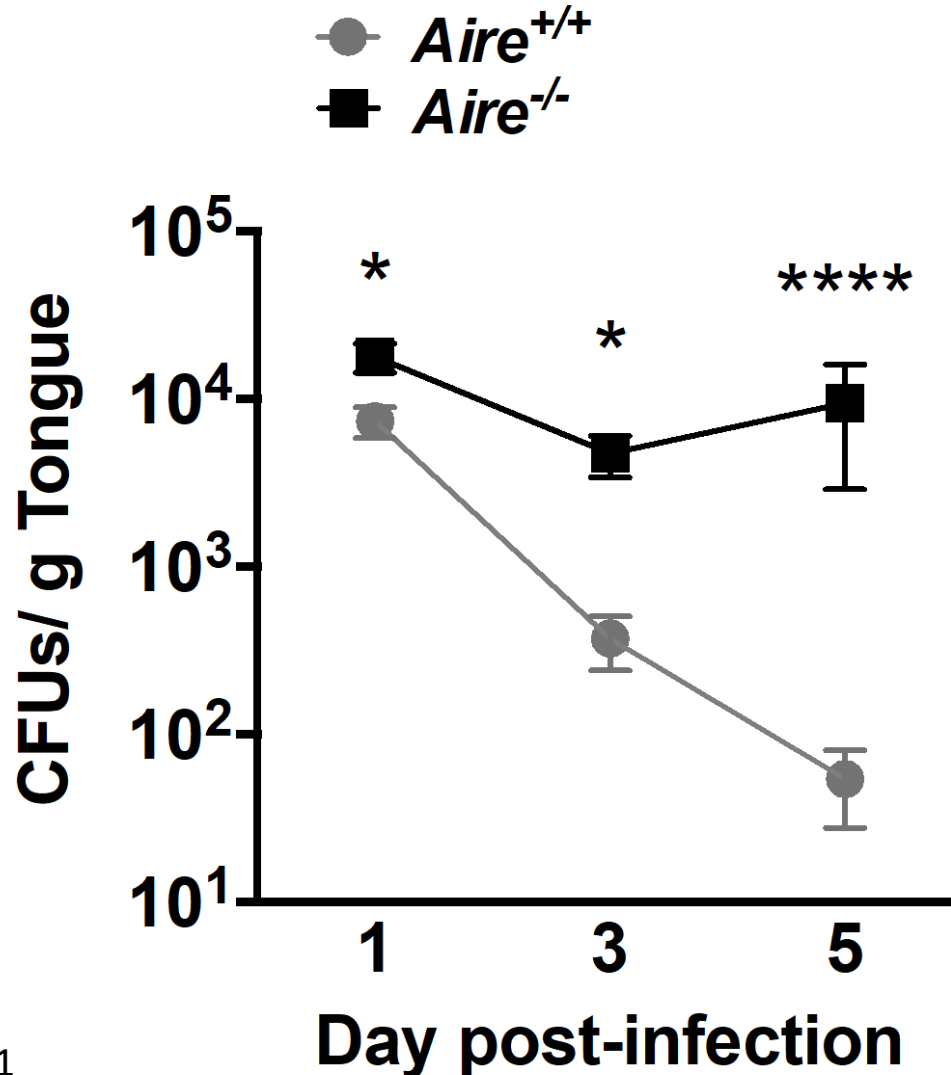


**How about strategies that dampen the
immune response to combat fungal
disease?**

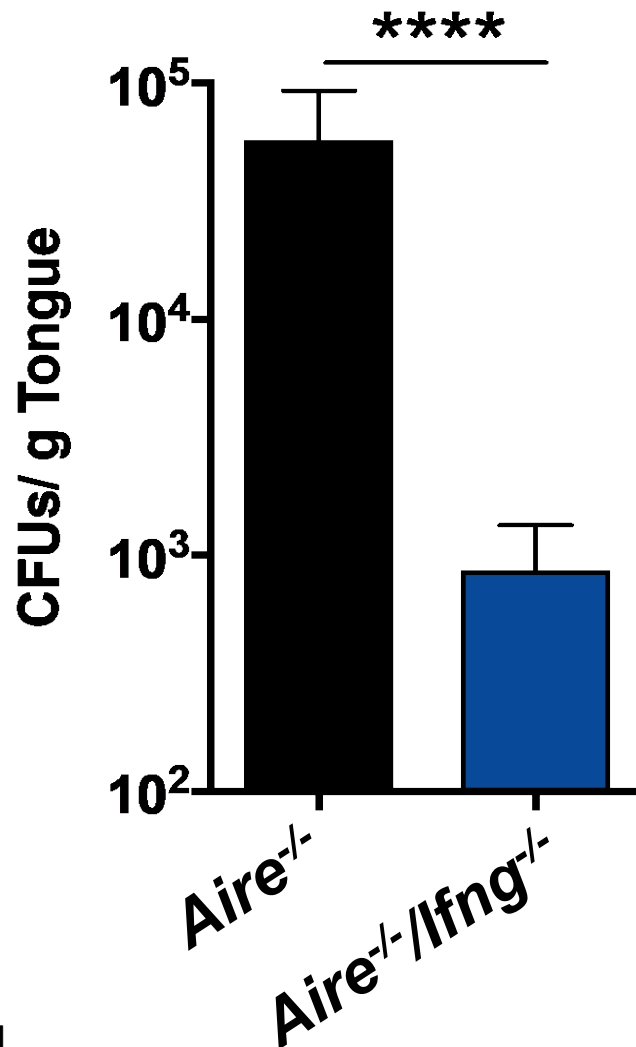
Phenocopying Syndromes of Human CMC in Mice



Development of the First Model of Oral Candidiasis in *Aire*^{-/-} Mice



Inhibition of Interferon- γ in *Aire*^{-/-} Mice Decreases Mucosal Fungal Burden



Similar results with:

- IFN- γ Ab neutralization
- Ruxolitinib (JAK/STAT inhibitor)

**** $P < 0.0001$

Mucosal Antifungal Defense: IL-17-Driven Protection and IFN- γ -Driven Immunopathology

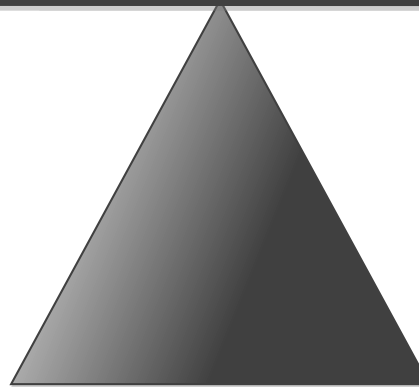
APPROPRIATE
ANTIMICROBIAL
ACTIVITY
(RESISTANCE)

IL-17

IMMUNOPATHOLOGY

IFN- γ

STAT1 GOF
JAK1 GOF
Down syndrome
RVVC
Oral GvHD
HIV/AIDS



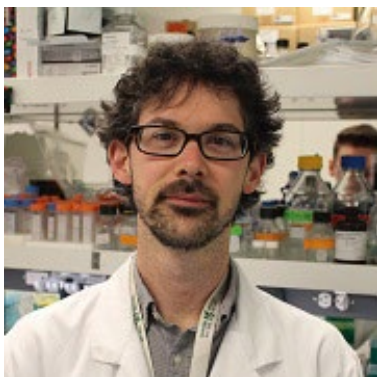
Understanding host-fungal interactions

Personalized risk stratification and
prognostication strategies

Targeted prophylaxis strategies

Immune-based adjunct therapies

Brendan Snarr



R. Drummond



Elise Ferre



Monica Schmitt



Ashira Lubkin



Vas Oikonomou



Tim Break



Mike Abers



Sebastian Ochoa



Jigar Desai



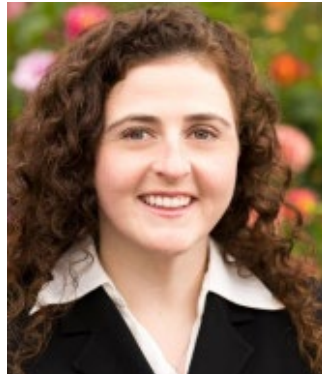
Marissa Zarakas



Andrew Wishart



Ahnika Kline



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Acknowledgements

Intramural collaborators

Steve Holland	Niki Moutsopoulos
Gigi Notarangelo	Yasmine Belkaid
Josh Milner	Jason Brenchley
Phil Murphy	Wyndham Wilson
Harry Malech	Louis Staudt
June Kwon-Chung	Bill Gahl
Kat Mayer-Barber	Dan Barber
Heather Hickman	Adrian Zelazny
Mike Lenardo	Kathy Calvo
Pam Schwartzberg	Ken Olivier
Julie Segre	Kevin Fennelly
Sergio Rosenzweig	Amy Hsu
Peter Burbelo	David Kleiner
Rachel Caspi	Colleen Sweeney
Uli Siebenlist	Karen Winer
Vanja Lazarevic	Theo Heller
Morgan Similuk	Magda Walkiewicz

Extramural collaborators

John Perfect	Mark Anderson
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Tobias Hohl	Silvio Gutkind
Yoichiro Iwakura	Scott Filler
Sergio Lira	Dusan Bogunovic
Julian Naglik	Dimitrios
Bernie Hube	Kontoyiannis
Robb Cramer	David Perlin
Brian Schaefer	Peter Pappas
Dinos Mikelis	Taco Kuipers
Jean Lim	Tom Chiller

Thank you!