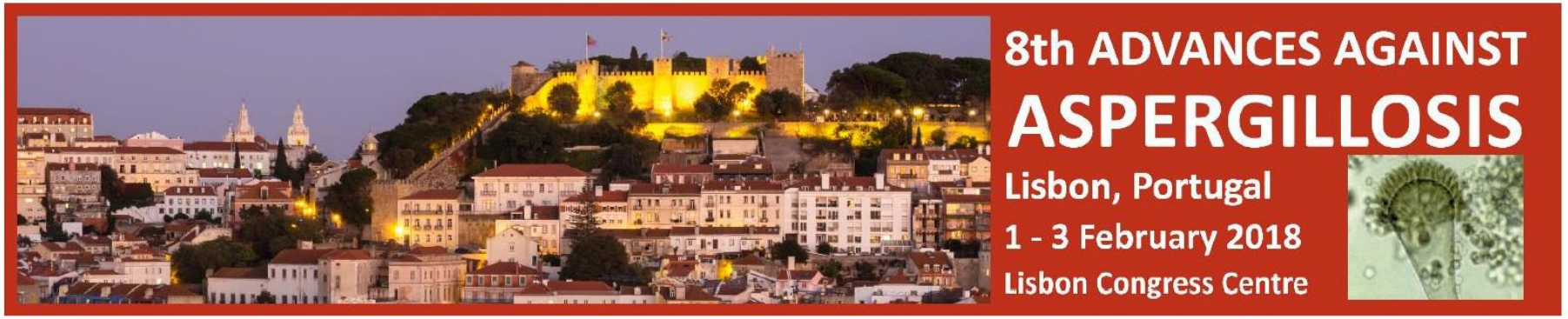
Why does ibrutinib carry a risk of cerebral aspergillosis?



Georgios Chamilos, MD
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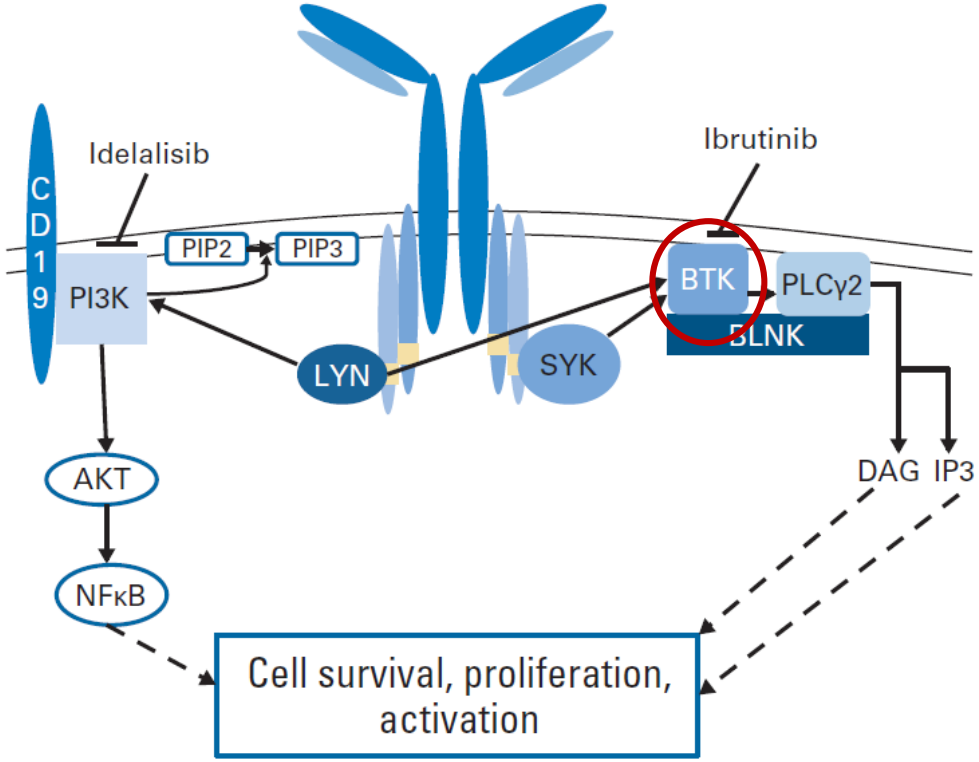
hamilos@imbb.forth.gr

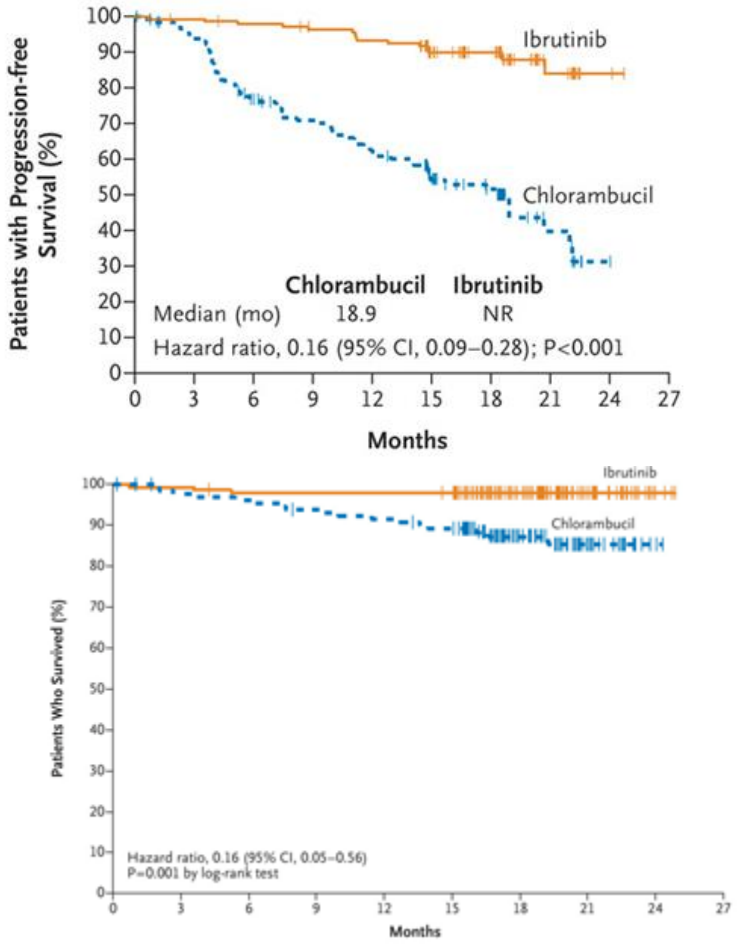
I have no idea!!!

- I asked two experts scientists working on BTK signaling and *Aspergillus*
  - Michalis Lionakis (Cancer Cell, 2017 Jun 12;31(6):833-843.e5)
  - Darius Armstrong-James (EMBO Mol Med. 2015 Mar;7(3):240-58)
- The also had no clue!
- I will try to address the following questions:
  I. Is ibrutinib associated with increased risk for invasive aspergillosis?
  II. Is ibrutinib associated with increased risk for cerebral aspergillosis?
  III. Which are the mechanisms of ibrutinib-associated immunosuppression?
- I will have to make assumptions based on the published literature
- If anyone in the room knows the answer please let me know!

Ibrutinib: a “game-changing drug” in B-cell malignancies (accelerated FDA Approval in 2013)



RESONATE-2 (CLL, frontline ibrutinib)



4 year follow up: only 12% of patients D/C due to AEs (AF, bleeding, infection)

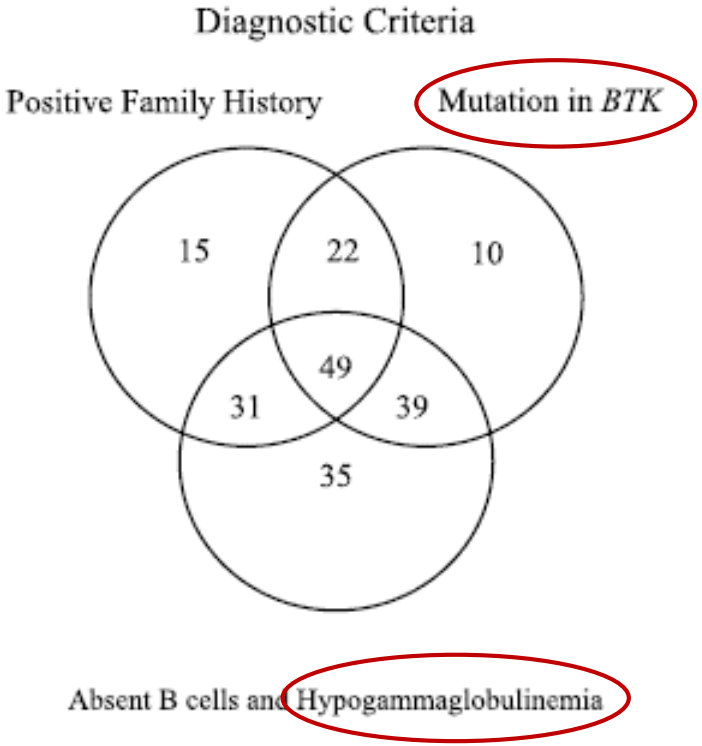
Byrd et al., J Clin Oncol, 2014, 32:3039-3048

Burger JA et al. N Engl J Med 2015;373:2425-2437

X-Linked Agammaglobulinemia

Report on a United States Registry of 201 Patients

Jerry A. Winkelstein, MD, Mary C. Marino, MLS, Howard M. Lederman, MD, PhD, Stacie M. Jones, MD, Kathleen Sullivan, MD, PhD, A. Wesley Burks, MD, Mary Ellen Conley, MD, Charlotte Cunningham-Rundles, MD, PhD, and Hans D. Ochs, MD



Winkelstein JA et al., Medicine, 2006; 85:195-202

Infection	No. of Patients (%)* (n = 201)
Upper respiratory	
Otitis	140 (70)
Sinusitis	119 (59)
Mastoiditis	1
Pneumonia	125 (62)
Chronic/recurrent diarrhea	46 (23)
Conjunctivitis	42 (21)
Pyoderma/cellulitis/subcutaneous abscess	36 (18)
7Meningitis/encephalitis	25 (12)
Sepsis	21 (10)

Organism	No. of Patients (%)* (n = 125)
Pneumococcus	9 (7)
H. influenzae, type b	5 (4)
Pseudomonas spp	3 (2)
Staphylococcus spp	3 (2)
H. parainfluenzae	3 (2)
H. parahemolytica	1 (1)
Klebsiella spp	1 (1)
Mycobacterium avium	1 (1)
Pneumocystic carinii	1 (1)
Measles	1 (1)
Unknown/not reported	105 (84)†

OIs

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-Banacloche[5]

5% PCP

Ibrutinib for Chronic Lymphocytic Leukemia

N ENGL J MED 374;16 NEJM.ORG APRIL 21, 2016

TO THE EDITOR: Burger et al. report promising results of ibrutinib as initial therapy for CLL. After a median follow-up of 18.4 months, three deaths occurred in the ibrutinib group, one from klebsiella infection and two from unknown causes.

We report on brain abscesses due to aspergillosis, a rare occurrence in CLL, which developed during ibrutinib therapy. Invasive aspergillosis developed in three patients with relapsed CLL within 2 months after the initiation of ibrutinib.

Open Forum Infectious Diseases

BRIEF REPORT

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

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

39% IA

94% showed tumor reductions with ibrutinib alone, including patients having PCNSL with *CD79B* and/or *MYD88* mutations, and 86% of evaluable patients achieved complete remission with DA-TEDDi-R. Increased aspergillosis was observed with ibrutinib monotherapy and DA-TEDDi-R. Aspergillosis was linked to BTK-dependent fungal immunity in a murine model. PCNSL is highly dependent on BCR signaling, and ibrutinib appears to enhance the efficacy of chemotherapy.

Lionakis et al., 2017, Cancer Cell *31*, 833–843

Relatively low frequency of Invasive Aspergillosis (IA) in other clinical studies on ibrutinib

Type and Status of Cancer	Type of IFI (No. of Cases)	Frequency of IFI, %	Patients, No.	Median follow-up, mo	Study timing, month/Year	Ref
Relapsed CLL	Cryptococcosis (1)	1.2	85	20.9	5/2010-2/2013	Byrd et al
Relapsed CLL/SLL	IA (2)	0.5	391	9.4	6/2012-11/2013	Byrd et al
Relapsed WM	IA (1)	3.2	31	18.1	8/2014-2/2015	Dimopoulos et al.
Relapsed MCL	Cryptococcosis (1), PJP (1), histoplasmosis (1)	2.7	111	26.7	2/2011-1/2014	Wang et al.
CLL	1l IA, 1 fungal pneumonia	1.6	127	13	7/2010-5/2014	Jain et al.
Relapsed/refractory DLBCL	None	0	80	11.5	5/2012-5/2013	Wilson et al.
Refractory CLL/SLL	PJP (1)	0.7	145	27.6	1/2013-6/2013	O'Brien et al.
Refractory PCNSL	IA (7), PJP (1)	44	18	15.5	8/2014-3/2016	Lionakis et al.
Refractory PCNSL	IA (2)	11	18	N/A	9/2015-8/2016	Choquet et al
Refractory PCNSL	IA (1)	5	20	N/A	N/A	Grommes et al.

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Ibrutinib related infections in clinical practice

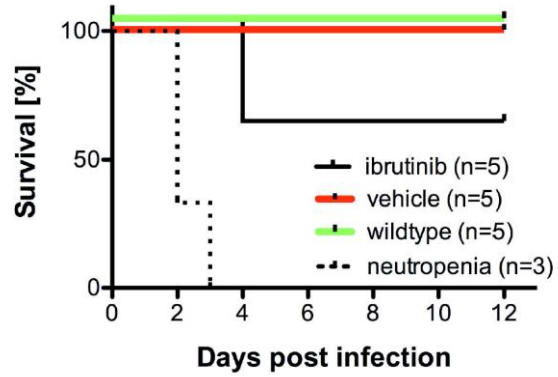
- **Real Word Toxicity**: up to **42%** of 621 relapsed patients D/C ibrutinib due to AEs at a median time of 6 months *(Mato AR, Ann Oncol 2017, 28:1050-1056)*

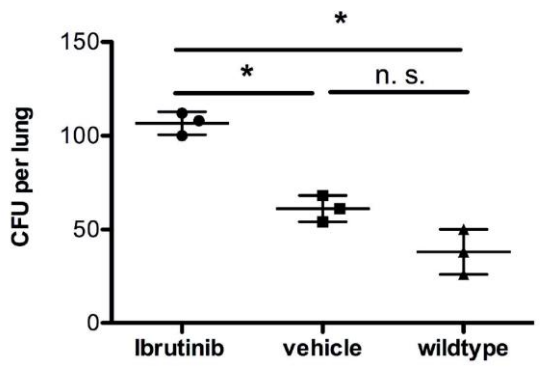
- Phase Ib trial in **relapsed refractory CLL patients**
  - Grade 3+ infection in **51%** of patients (**25%** pneumonia grade 3+), *Byrd JC, N Engl J Med, 2013 Sep 26;369(13):1278-9*

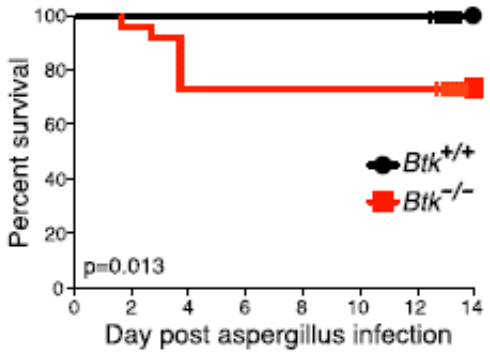
- In 148 malignancy patients (95% CLL), **8.1% OIs** among 148 hematological malignancy patients receiving first-line BTK inhibitors *(Issa N et al., Open Forum Infect Dis 2017l 4 (suppl 1):S699*

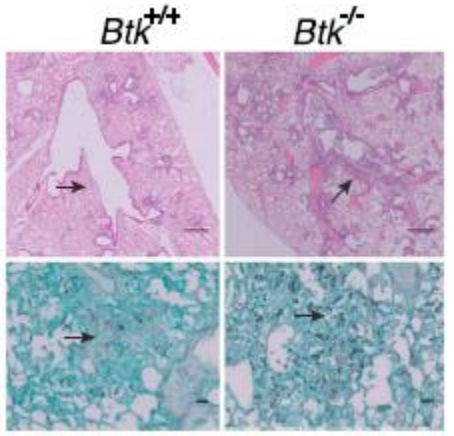
Is ibrutinib therapy associated with increased risk for development of Invasive Aspergillosis?

Increased susceptibility of mice for of IA upon pharmacological of genetic ablation of BTK









Stadler N et al., Haematologica 2017 102:e191-194

Lionakis MS et al.,Cancer Cell 2017 31, 833-843

Is ibrutinib associated with increased risk for cerebral aspergillosis?

Type of IA	Time after treatment	Age/Sex	Type of Cancer	Status of Malignancy	Concomitant steroids	Outcome	Ref
CNS	1 month	N/A	CLL	PD	Yes	Dead	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes		
CNS	2 month	N/A	CLL	PD	Yes		
Lungs	6 wks	62/M	CLL	PD	No		
CNS, lungs	2 wks	76/F	PCNSL	Active	Yes		
CNS, lungs	2 wks	65/M	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	3 months	87/F	PCNSL	Active	Yes	Dead	Lionakis et al.
Lungs	4 months	60/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	2 months	53/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	1 month	64/M	PCNSL	Active	Yes	Alive	Lionakis et al.
CNS, lungs	2 wks	49/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Sinusitis, CNS	3 wks	75/F	CLL	PD	No	Alive	Baron et al.
CNS, lungs	2 months	76/NA	CLL	PD	No	Dead	Jain et al.
Lungs	7 months	67/M	CLL	N/A	No	Dead	Kreiniz et al.

CNS aspergillosis in 9/14 (64%)

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Type of IA	Time after treatment	Age/Sex	Type of Cancer	Status of Malignancy	Concomitant steroids	Outcome	Ref
CNS	1 month	N/A	CLL	PD	Yes	Dead	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
Lungs	6 wks	62/M	CLL	PD	No	Alive	
CNS, lungs	2 wks	76/F	PCNSL	Active	Yes	Dead	
CNS, lungs	2 wks	65/M	PCNSL	Active	Yes	Dead	
CNS, lungs	3 months	87/F	PCNSL	Active	Yes	Dead	Lionakis et al.
Lungs	4 months	60/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	2 months	53/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	1 month	64/M	PCNSL	Active	Yes	Alive	Lionakis et al.
CNS, lungs	2 wks	49/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Sinusitis, CNS	3 wks	75/F	CLL	PD	No	Alive	Baron et al.
CNS, lungs	2 months	76/NA	CLL	PD	No	Dead	Jain et al.
Lungs	7 months	67/M	CLL	N/A	No	Dead	Kreiniz et al.

IA within the first 4 months (> 93%)

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Type of IA	Time after treatment	Age/Sex	Type of Cancer	Status of Malignancy	Concomitant steroids	Outcome	Ref
CNS	1 month	N/A	CLL	PD	Yes	Dead	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes		
Lungs	6 wks	62/M	CLL	PD	No		
CNS, lungs	2 wks	76/F	PCNSL	Active	Yes		
CNS, lungs	2 wks	65/M	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	3 months	87/F	PCNSL	Active	Yes	Dead	Lionakis et al.
Lungs	4 months	60/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	2 months	53/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Lungs	1 month	64/M	PCNSL	Active	Yes	Alive	Lionakis et al.
CNS, lungs	2 wks	49/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Sinusitis, CNS	3 wks	75/F	CLL	PD	No	Alive	Baron et al.
CNS, lungs	2 months	76/NA	CLL	PD	No	Dead	Jain et al.
Lungs	7 months	67/M	CLL	N/A	No	Dead	Kreiniz et al.

45% of cases of CNS aspergillosis in pts with brain pathology

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Type of IA	Time after treatment	Age/Sex	Type of Cancer	Status of Malignancy	Concomitant steroids	Outcome	Ref
CNS	1 month	N/A	CLL	PD	Yes	Dead	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
Lungs	6 wks	62/M	CLL	PD	No	Alive	Arthus et al.
CNS, lungs	2 wks	76/F	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	2 wks	65/M	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	3 months	87/F	PCNSL	Active	Yes		
Lungs	4 months	60/M	PCNSL	Active	Yes		
Lungs	2 months	53/M	PCNSL	Active	Yes		
Lungs	1 month	64/M	PCNSL	Active	Yes	Alive	Lionakis et al.
CNS, lungs	2 wks	49/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Sinusitis, CNS	3 wks	75/F	CLL	PD	No	Alive	Baron et al.
CNS, lungs	2 months	76/NA	CLL	PD	No	Dead	Jain et al.
Lungs	7 months	67/M	CLL	N/A	No	Dead	Kreiniz et al.

Refractory of relapsed malignancy in 100% of patients

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Type of IA	Time after treatment	Age/Sex	Type of Cancer	Status of Malignancy	Concomitant steroids	Outcome	Ref
CNS	1 month	N/A	CLL	PD	Yes	Dead	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
CNS	2 month	N/A	CLL	PD	Yes	Alive	Ruchlemer et al.
Lungs	6 wks	62/M	CLL	PD	No	Alive	Arthus et al.
CNS, lungs	2 wks	76/F	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	2 wks	65/M	PCNSL	Active	Yes	Dead	Lionakis et al.
CNS, lungs	3 months	87/F	PCNSL	Active	Yes	Dead	
Lungs	4 months	60/M	PCNSL	Active	Yes	Alive	
Lungs	2 months	53/M	PCNSL	Active	Yes	Alive	
Lungs	1 month	64/M	PCNSL	Active	Yes	Alive	Lionakis et al.
CNS, lungs	2 wks	49/M	PCNSL	Active	Yes	Alive	Lionakis et al.
Sinusitis, CNS	3 wks	75/F	CLL	PD	No	Alive	Baron et al.
CNS, lungs	2 months	76/NA	CLL	PD	No	Dead	Jain et al.
Lungs	7 months	67/M	CLL	N/A	No	Dead	Kreiniz et al.

71% of patients also received corticosteroids

Clin Infect Dis. 2018 Jan 6;66(1):140-148

blood®
Prepublished online February 1, 2018;
doi:10.1182/blood-2017-11-818286

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

David Ghez, Anne Calleja, Caroline Protin, Marine Baron, Marie-Pierre Ledoux, Gandhi Damaj, Mathieu Dupont, Brigitte Dreyfus, Emmanuelle Ferrant, Charles Herbaux, Kamel Laribi, Ronan Le Calloch, Marion Malphettes, Franciane Paul, Laetitia Souchet, Malgorzata Truchan-Graczyk, Karen Delavigne, Caroline Dartigeas and Loïc Ysebaert

- Retrospective surveillance (French Innovative Leukemia Organization for CLL)
- 33 cases of IFI from 16 Cancer Centers from 2013-2017
- Invasive aspergillosis in 27/33 (81%) within 3 months of ibrutinib treatment
- **CNS aspergillosis in 11/27 (40%)**
- All r**efractory/relapsed** disease
- Additional predisposing factors in most of patients (**steroids in 7**, neutropenia in 5)

Conclusions

- Ibrutinib treatment increases the risk for development of IA
- CNS dissemination is a frequent event in ibrutinib-related aspergillosis
- Ibrutinib-associated IA occurs in the setting of additional immunosuppressive conditions:
  - ✓Corticosteroids
  - ✓Refractory/relapsed hematological malignancy
  - ✓Brain pathology due to the underling disease (microglia?)
- Environmental exposures and other epidemiological factors could be also implicated in ibrutinib-associated aspergillosis

Lessons from primary immunodeficiencies predisposing to Aspergillus

- **Functional defects in myeloid cells**
  - Job's syndrome (STAT3)
  - **CGD (NADPH oxidase)**
  - Pulmonary alveolar proteinosis (GM-CSF signaling)
- **Defects in myeloid cell numbers (including chemotaxis)**
  - MonoMAC syndrome (GATA2)-**numbers**
  - Severe congenital neutropenia (ELA2, HAX1)-**numbers**
  - Leucocyte adhesion deficiency (CD18)-**trafficking**
  - **CARD9 deficiency (ONLY IMMUNODEFICIENCY LINKED TO CEREBRAL ASPERGILLOSIS)-defect in neutrophil chemotaxis** (Rieber N et al., JCI Insight. 2016 Oct 20;1(17):e89890)

Lionakis MS et al., JCI Insight. 2017 Jun 2;2(11). pii: 93156t

Unique predisposing factors for CNS aspergillosis

- Case series (14 cases, MGH: 2000-2011) and literature review
- Lung was the primary focus (11/14)
- Predisposing factors
  - **Corticosteroids (10/14, 71%)**
  - Neutropenia (6/14, 43%)
  - Metabolic diseases

  ✓Diabetes mellitus in 3 (21%),hepatic insufficiency in 3 (21%)
- **Previous brain pathology in 8/14 (57%)**

Kourkoumpetis TK et al., Medicine 2012;91: 328Y336

Literature review of 123 additional cases of CNS aspergillosis

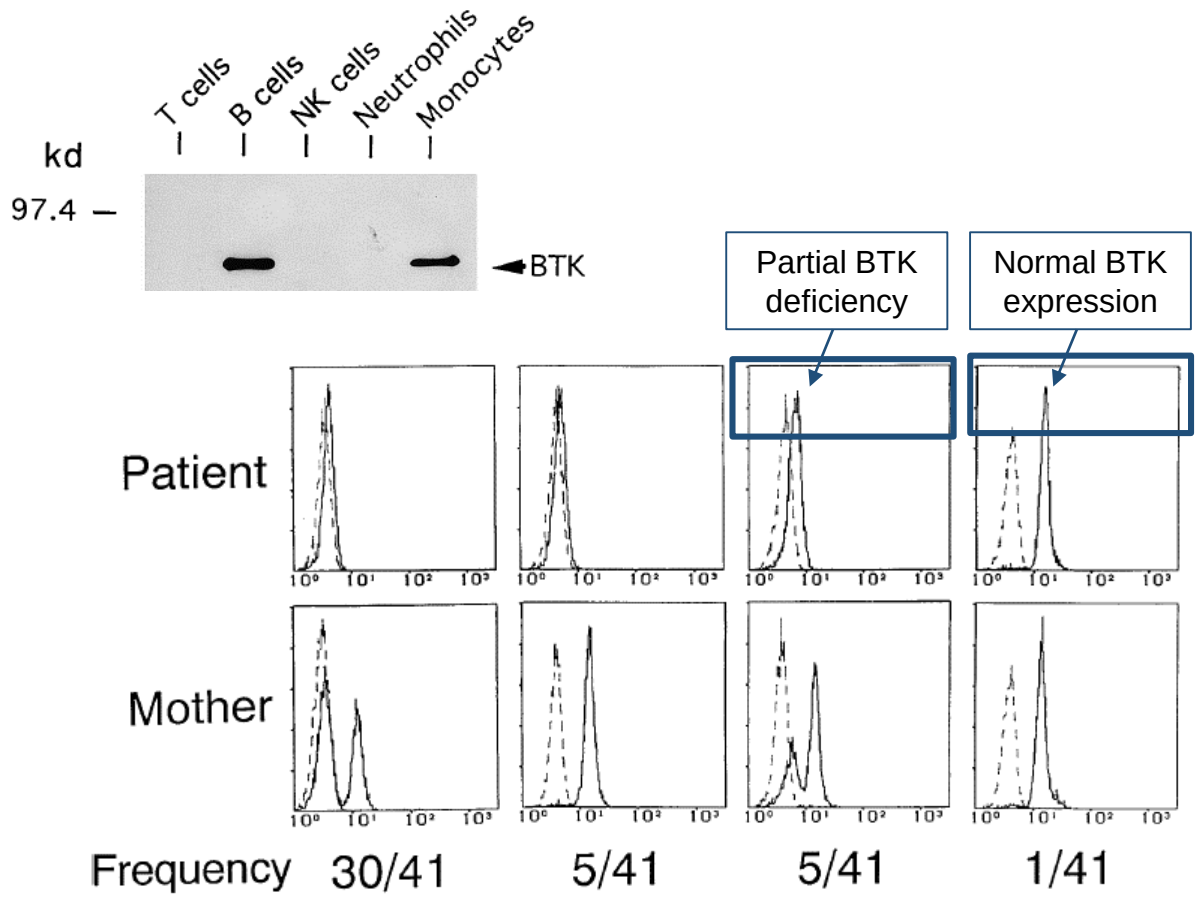
- Literature review of 123 cases
- 60 (49%) patients on immunosuppressive therapy
  - **C/steroids (22%), CsA** (4.1%), Tacrolimus (1%), anti-TNF (1%)
- **No underlying disease in 23/123 (24%)**
- **Diabetes mellitus in 18% of patients (paranasal involvement)**
- 5% of patients had **previous brain pathology**
- *A. fumigatus* (33.3%), *A. flavus* (6%)

Kourkoumpetis TK et al., Medicine 2012;91: 328Y336

Potential mechanisms of ibrutinib-related IA

- Defect(s) in myeloid cell function(s)?

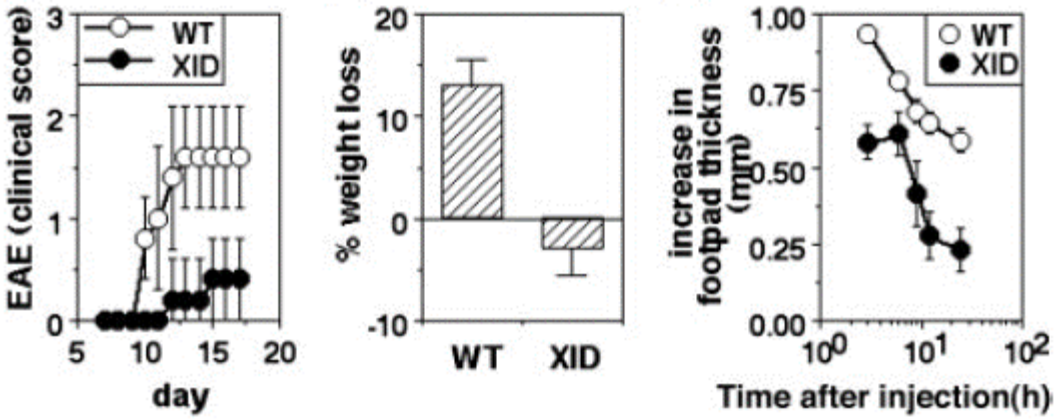
Defects in BTK expression in monocytes of XLA patients



Blood, Vol 91, No 2 (January 15), 1998: pp 595-602

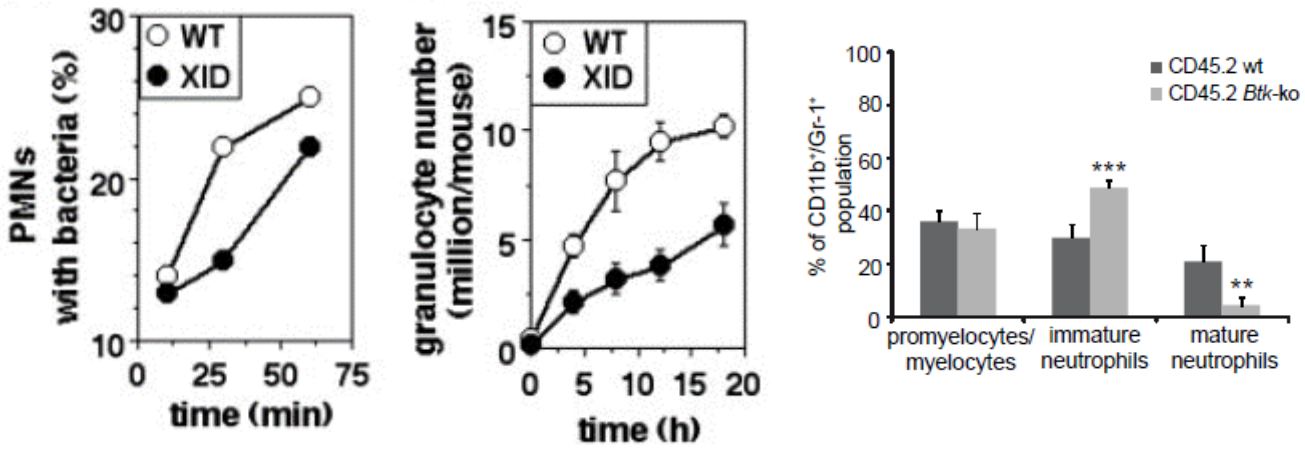
BTK deficiency results in broad immune defects in myeloid cells: **PMNs**

CNS Inflammation



Mangla A et al., Blood. 2004 Aug 15;104(4):1191-7. Epub 2004 Apr 29.

PMN phagocytosis, chemotaxis and differentiation

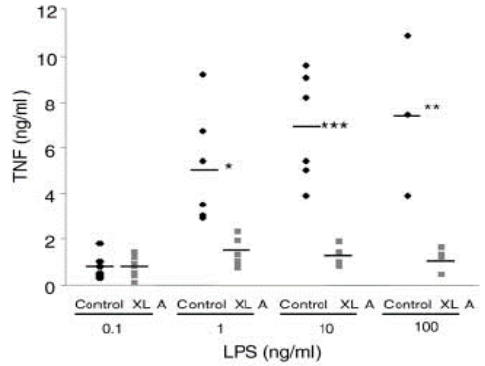


Fiedler K, et al, Blood. 2011 Jan 27;117(4):1329-39.

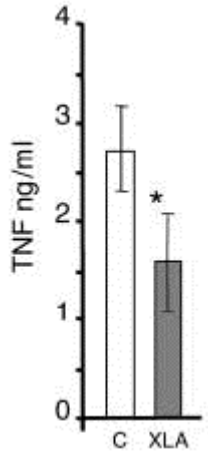
BTK deficiency results in broad immune defects in myeloid cells: **Macrophages**

TNF production in Macrophages

PBMCs

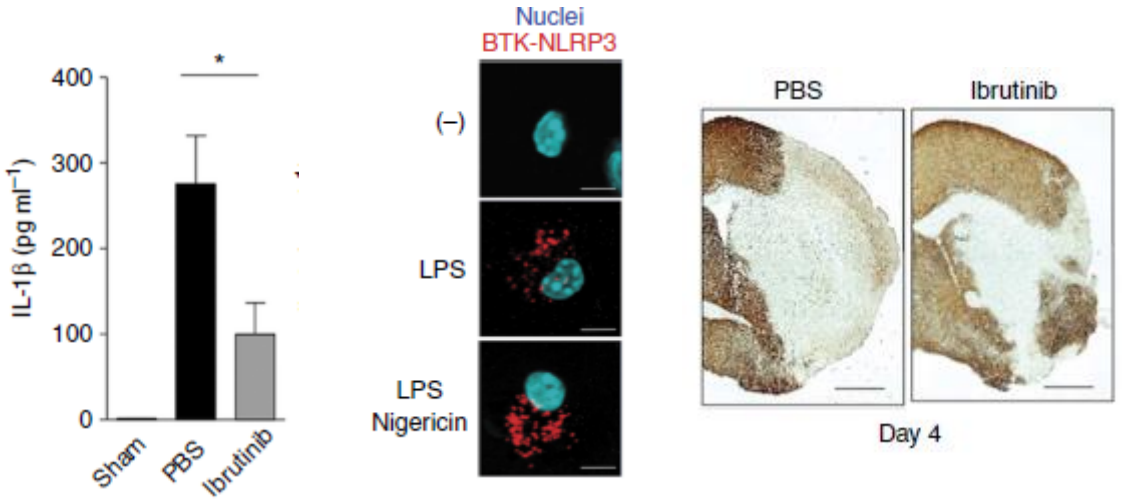


Macrophages



Horwood NJ et al., Exp Med. 2003 Jun 16;197(12):1603-11

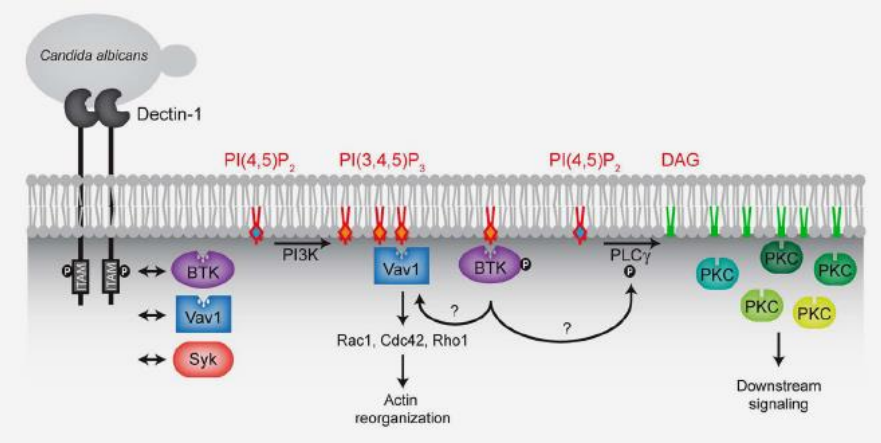
Inflammasome activation in Macrophages



Ito M et al., Nat Commun. 2015 Jun 10;6:7360

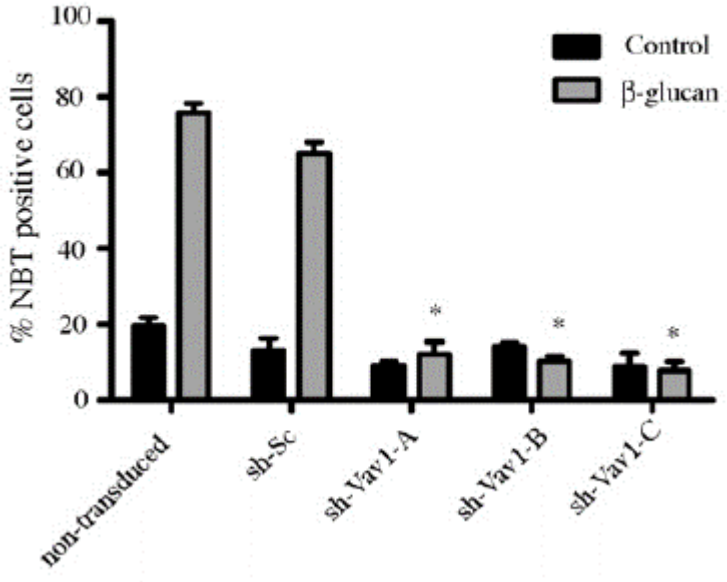
BTK deficiency results in broad immune defects in myeloid cells: **Microglia**

VaV/BTK dependent phagocytosis



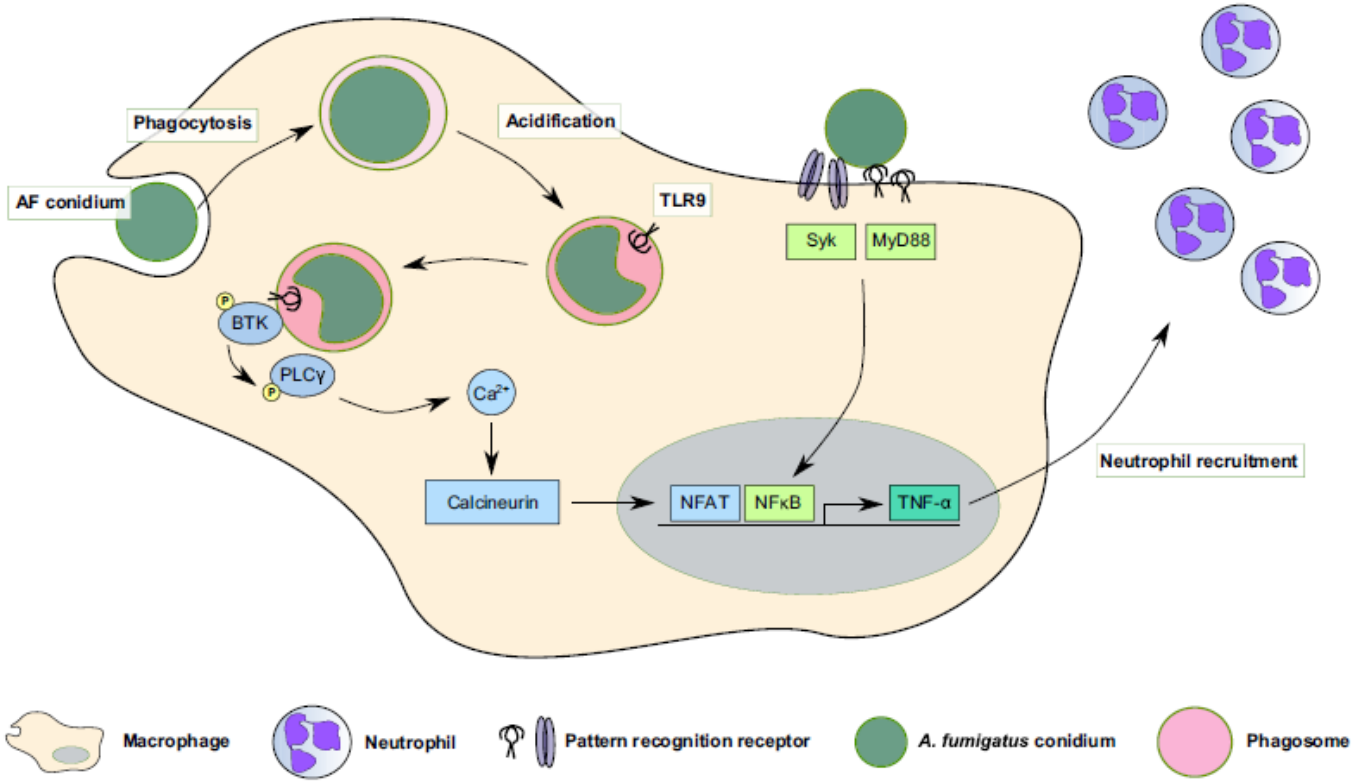
Strijbis K et al., PLoS Pathog 2013

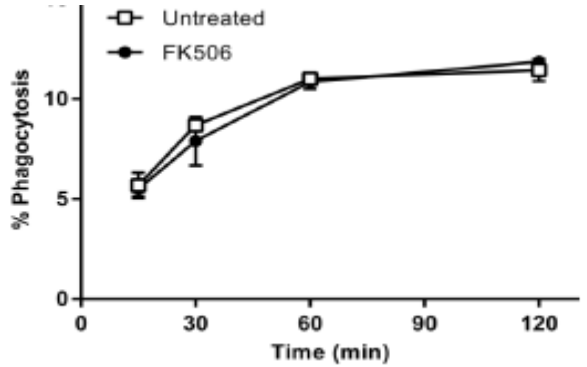
VaV dependent ROS production

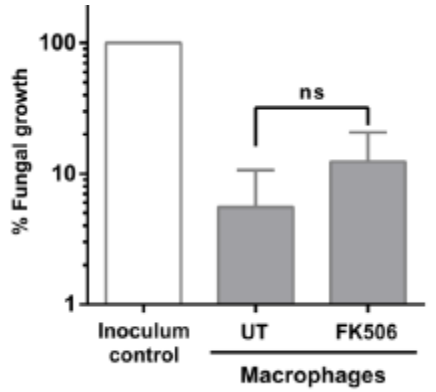


Shah VB et al., Molecular Immunology 46 (2009) 1845–1853

BTK/Calcineurin signaling activation during *Aspergillus* infection in macrophages







Herbst S et al., EMBO Mol Med. 2015 Mar;7(3):240-58; Armstrong-James D et al., PLoS Pathog. 2018 Jan 4;14(1):e1006627

Physiological Immune Response against *Aspergillus*

Shlezinger N, et al., Science. 2017 Sep 8;357(6355):1037-1041
Clark HL, et al., J Immunol, 2016 196:336-44
Jhingran A et al., PLoS Pathog 2015 11:e1004589
Espinosa V et al., PLoS Pathog 10:e1003940
Hohl T et al., Cell Host Microbe 2009 6:470-81
Hohl TM PLoS Pathog 2005 1 e30
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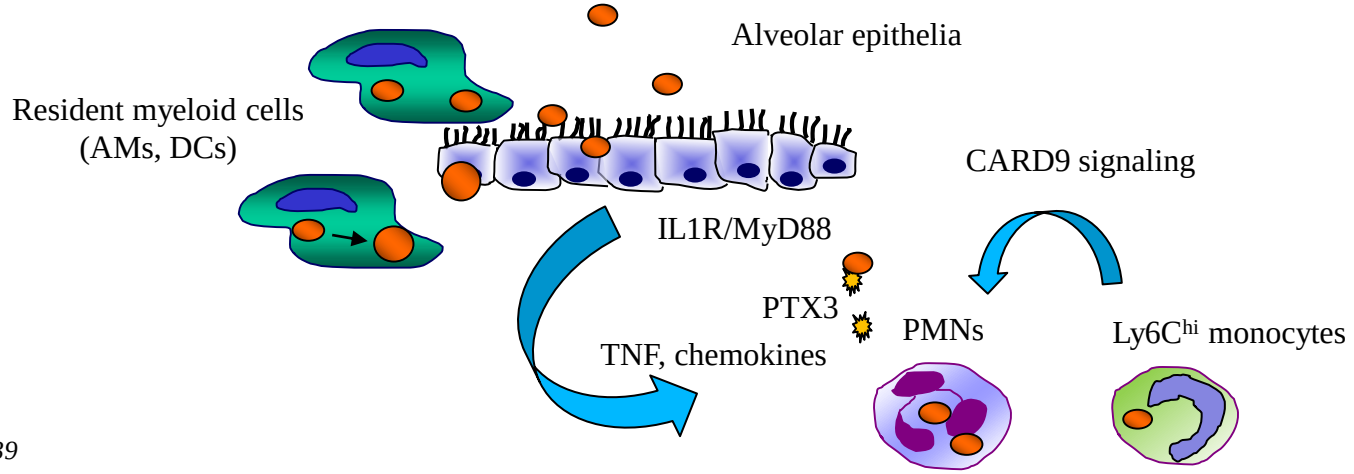
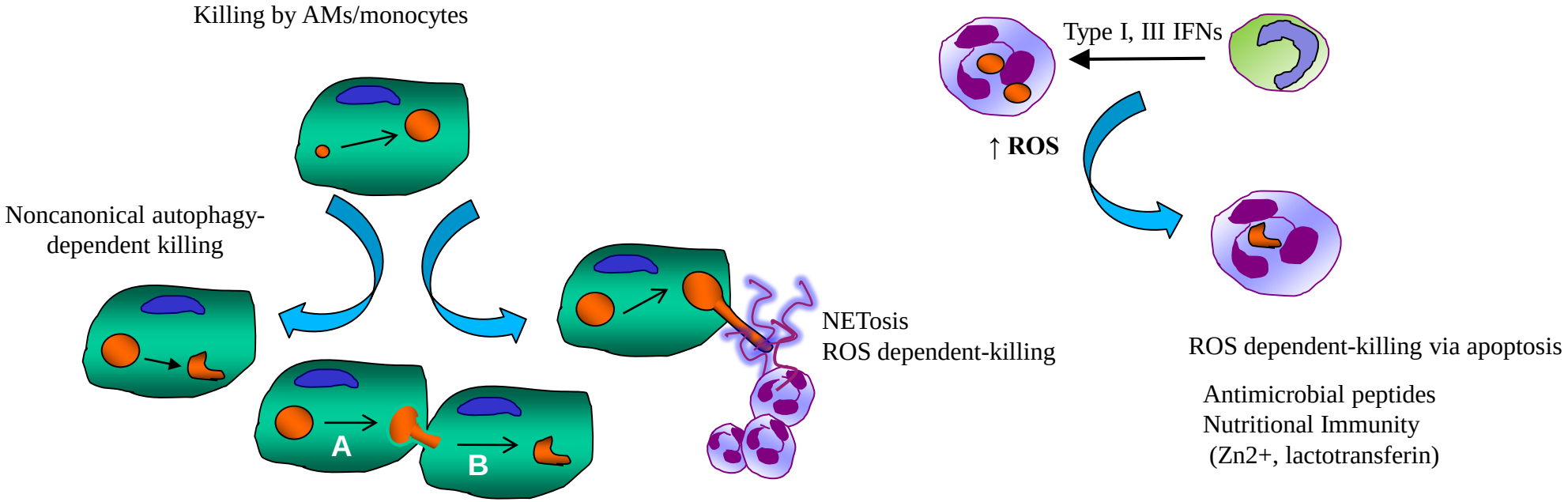
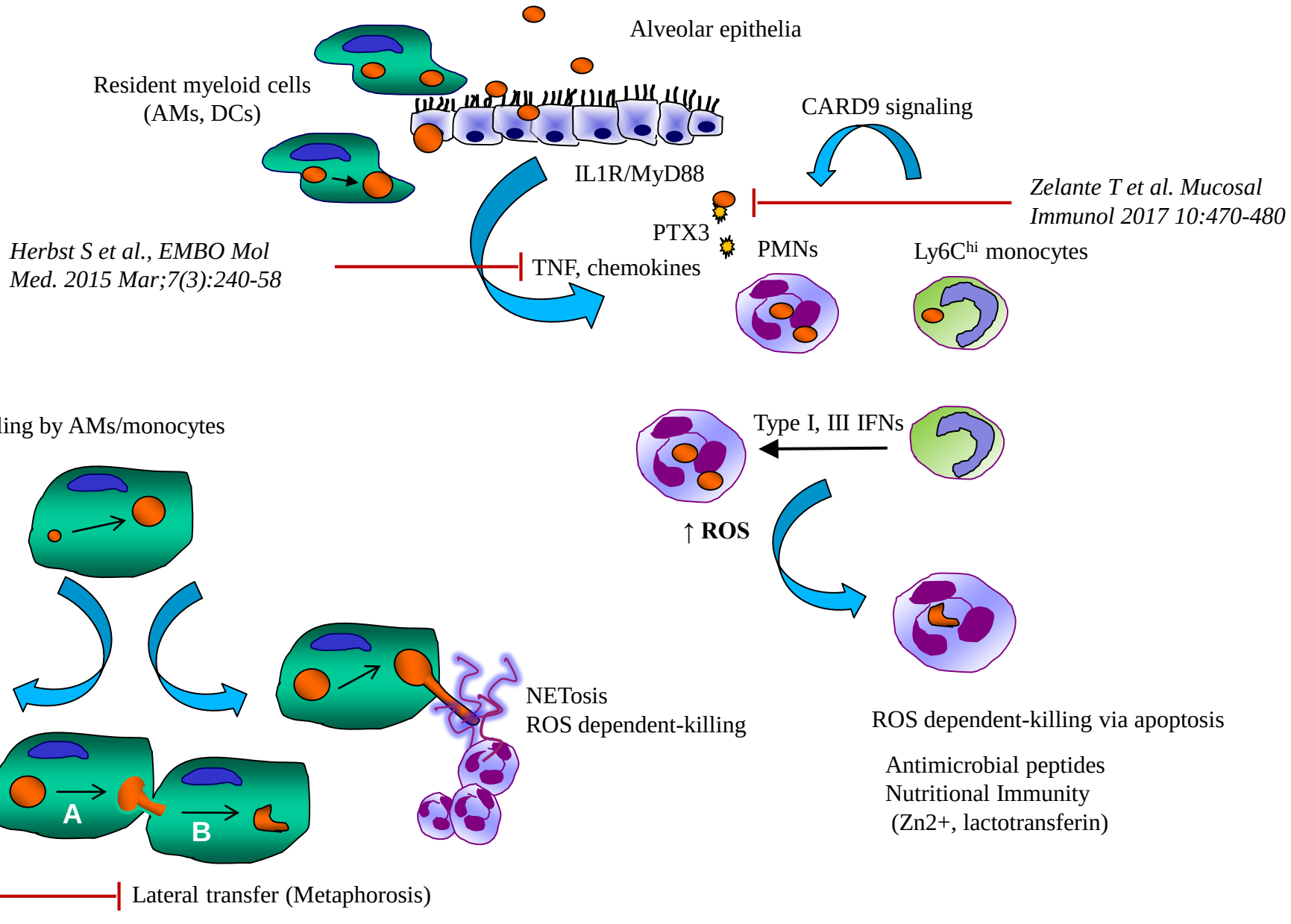


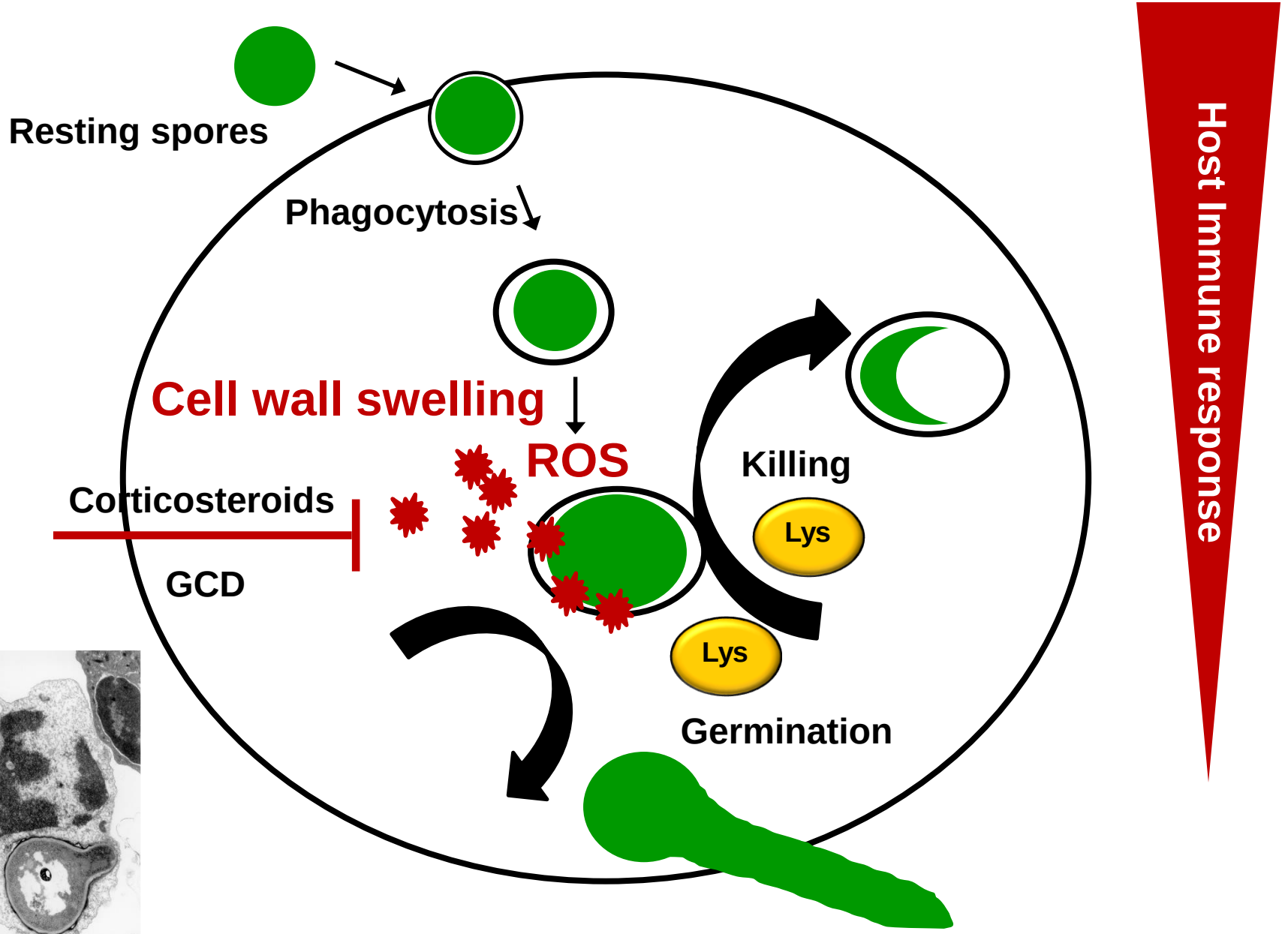


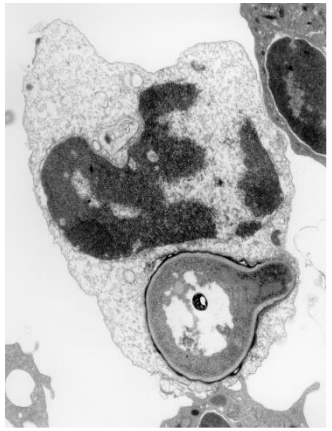
Potential immune defects caused by inhibition of BTK



Additive immunosuppressive action of corticosteroids on BTK inhibition?

Killing of *Aspergillus* inside macrophages





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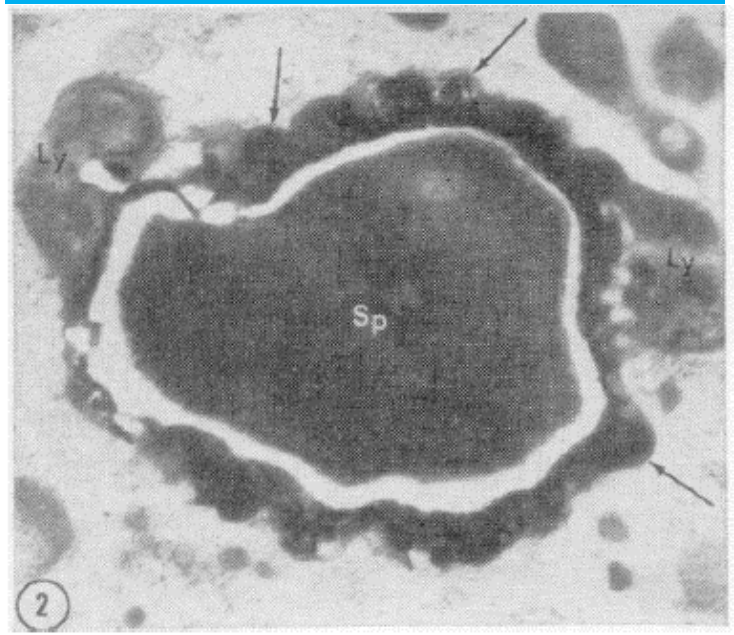
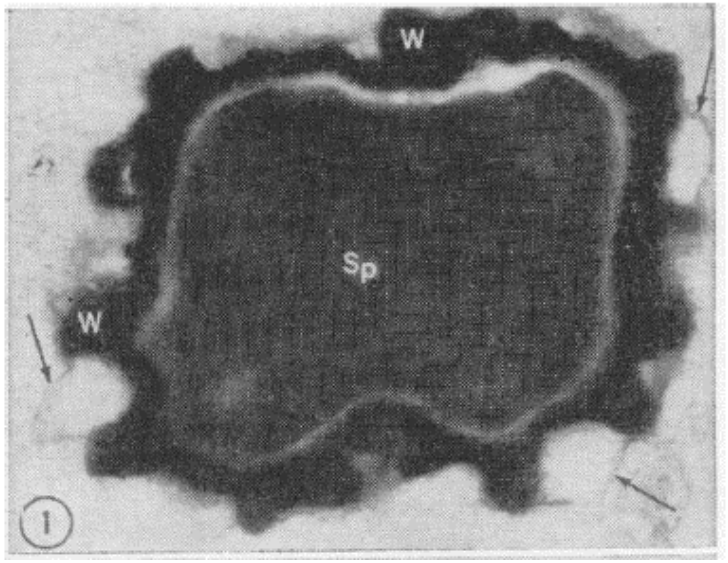
Corticosteroid-induced immunosuppression is characterized by broad defects in phagosome biogenesis

Lysosomal Stability during Phagocytosis of Aspergillus flavus Spores by Alveolar Macrophages of Cortisone-Treated Mice

Control



Cortisone-treated



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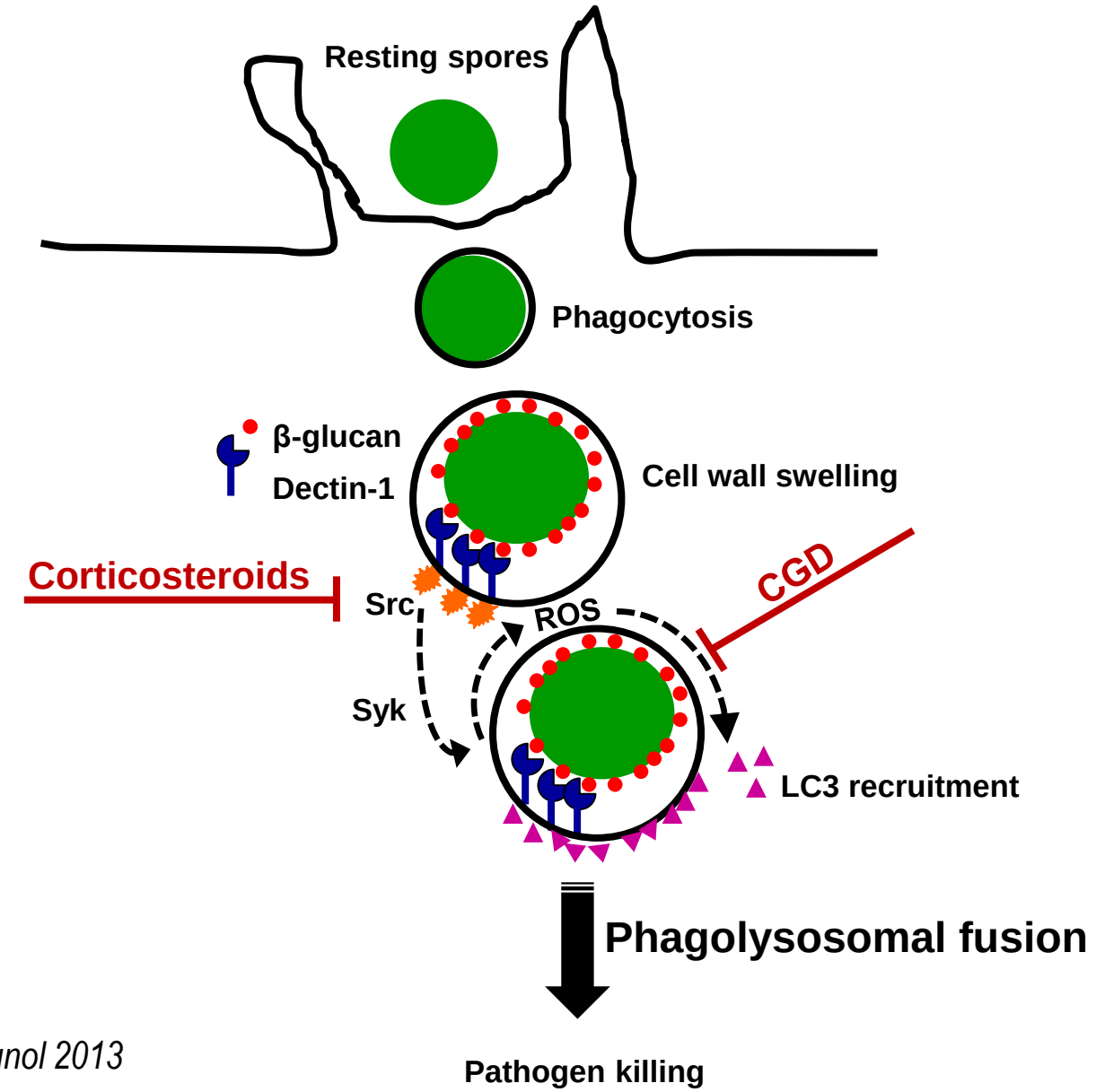
LC3 associated phagocytosis (LAP) regulates *Aspergillus* killing by phagocytes



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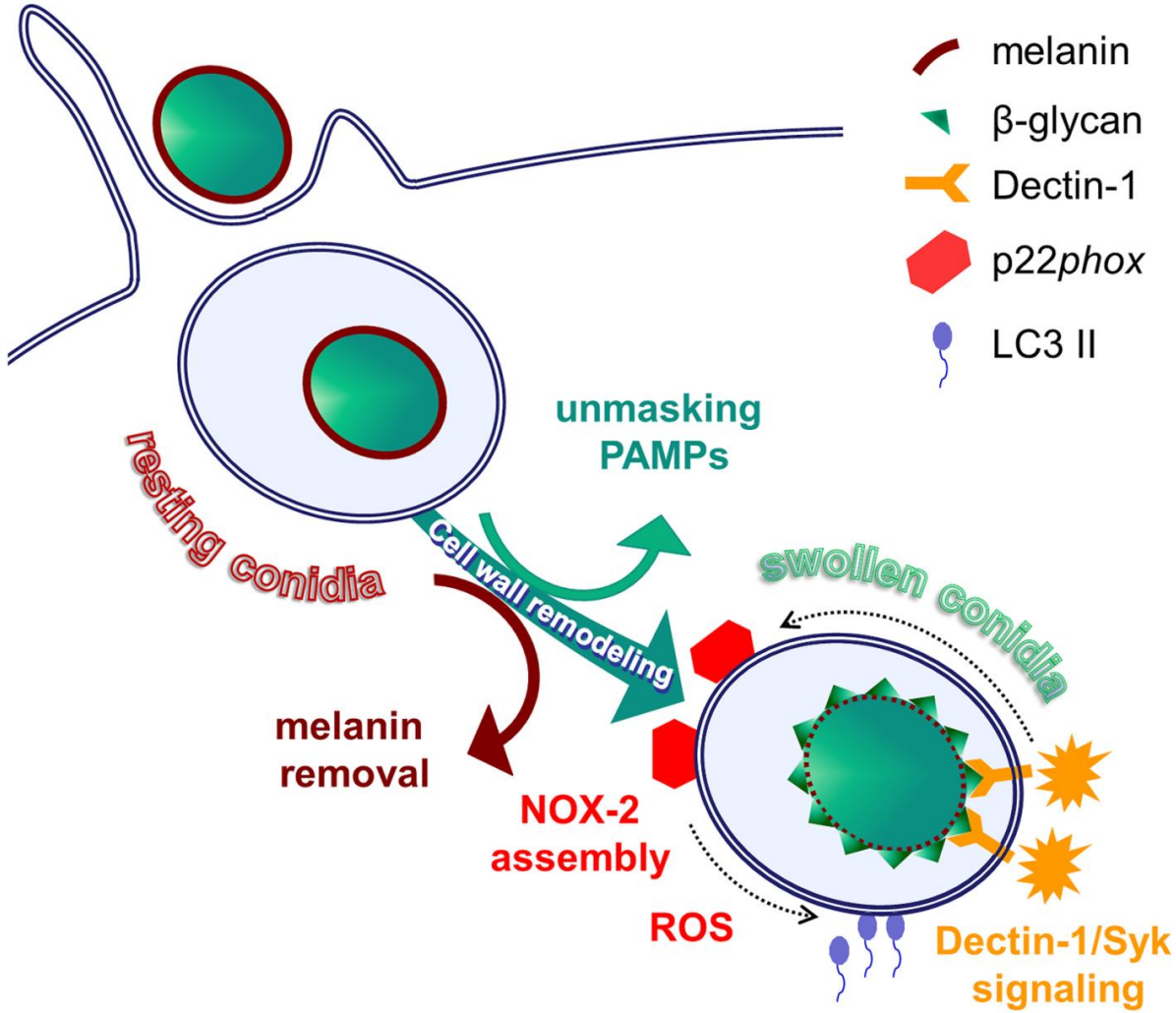
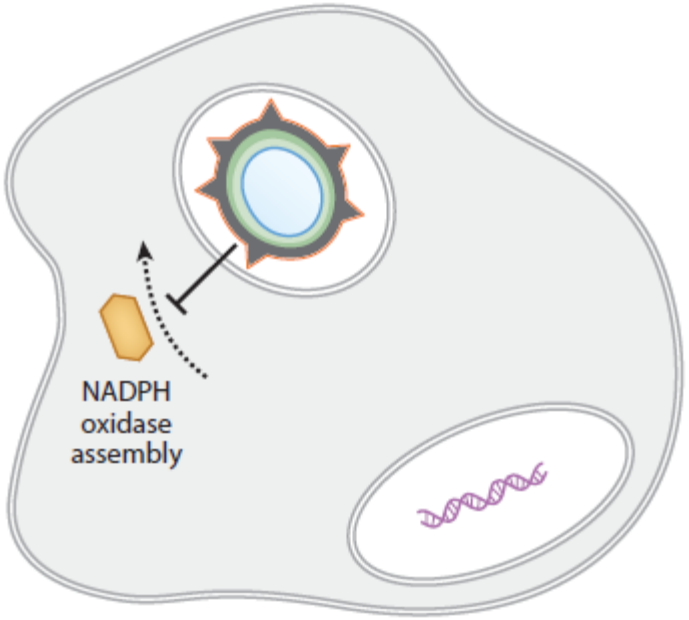
*Aspergillus m*elanin targets LAP to promote pathogenicity



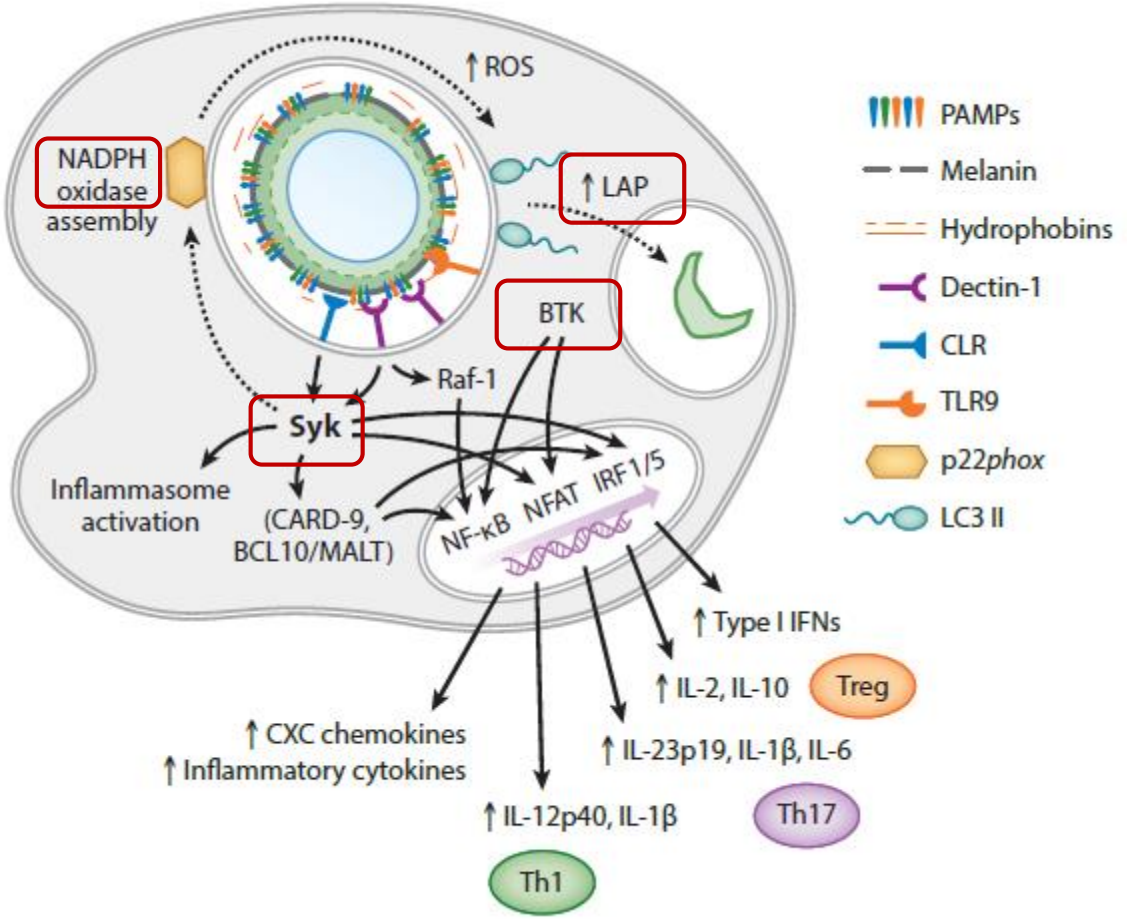
Akoumianaki T et al., Cell Host Microbe, 2016

Signaling pathways regulating immunity against *Aspergillus* inside macrophages

Dormant conidia



Swollen conidia



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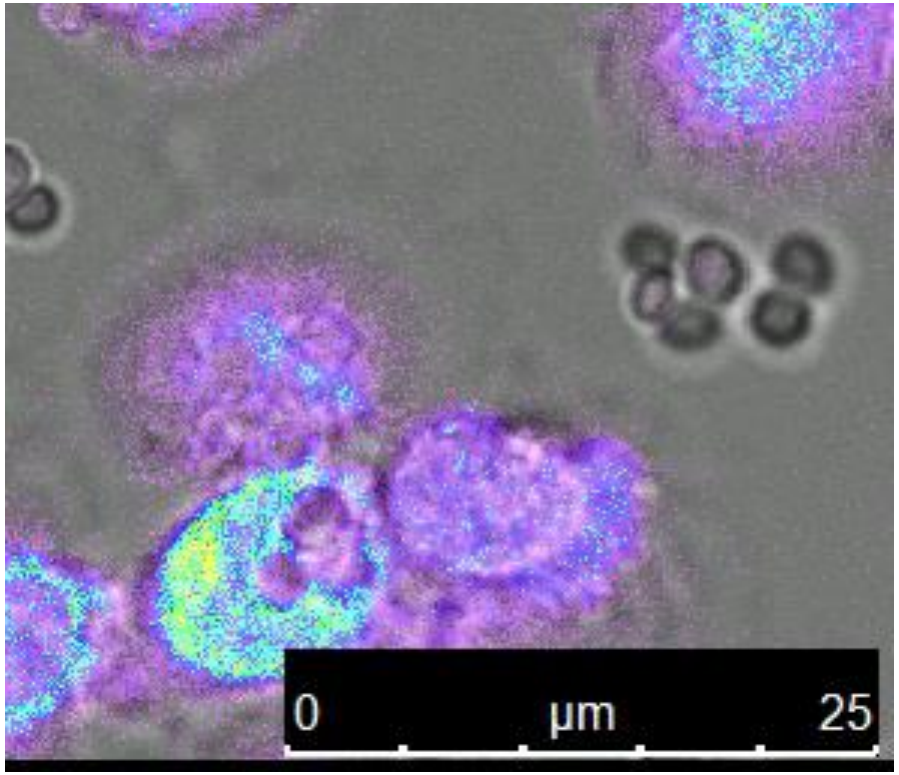
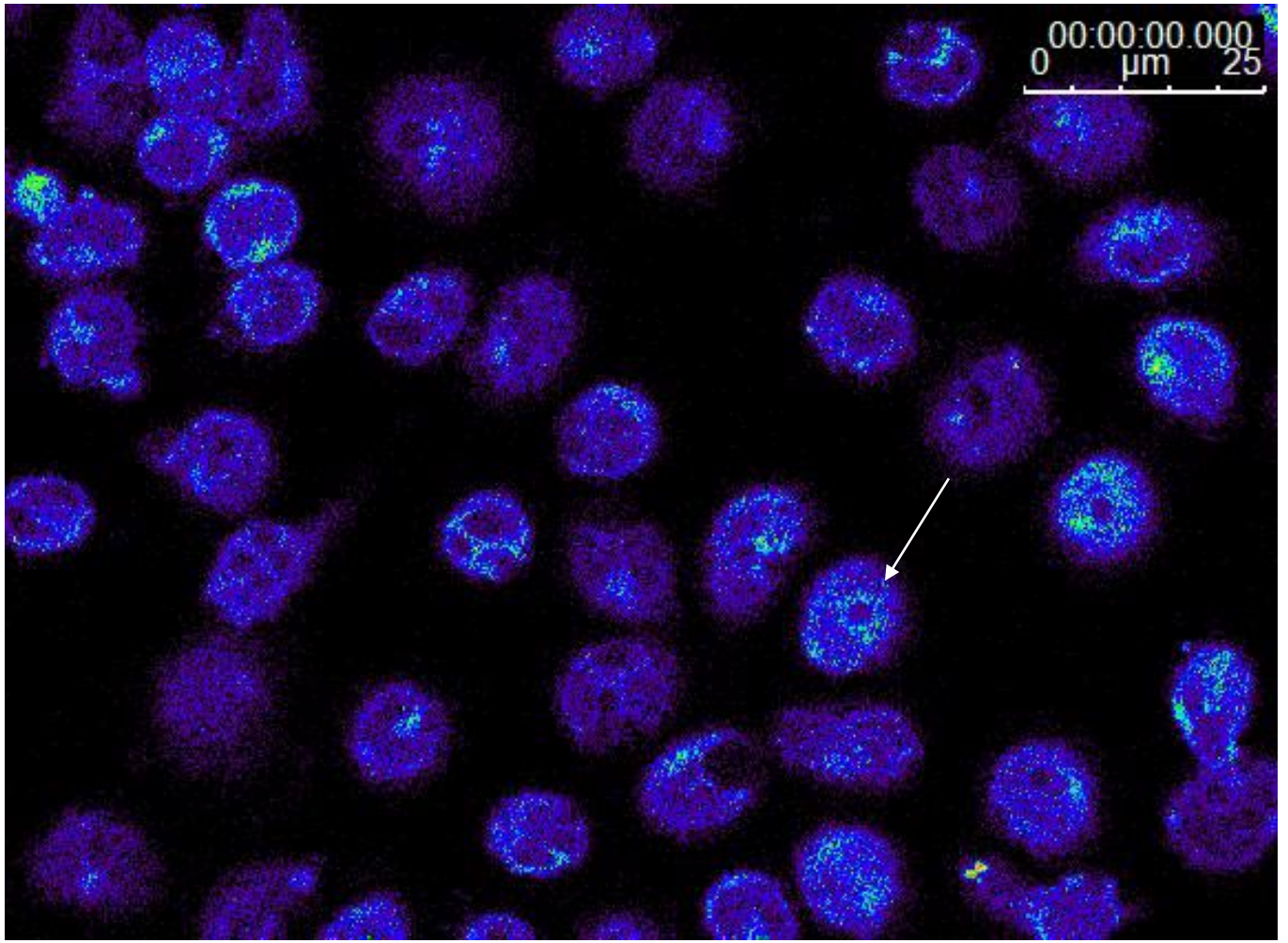
A specialized Ca2+ signaling pathway regulates LAP

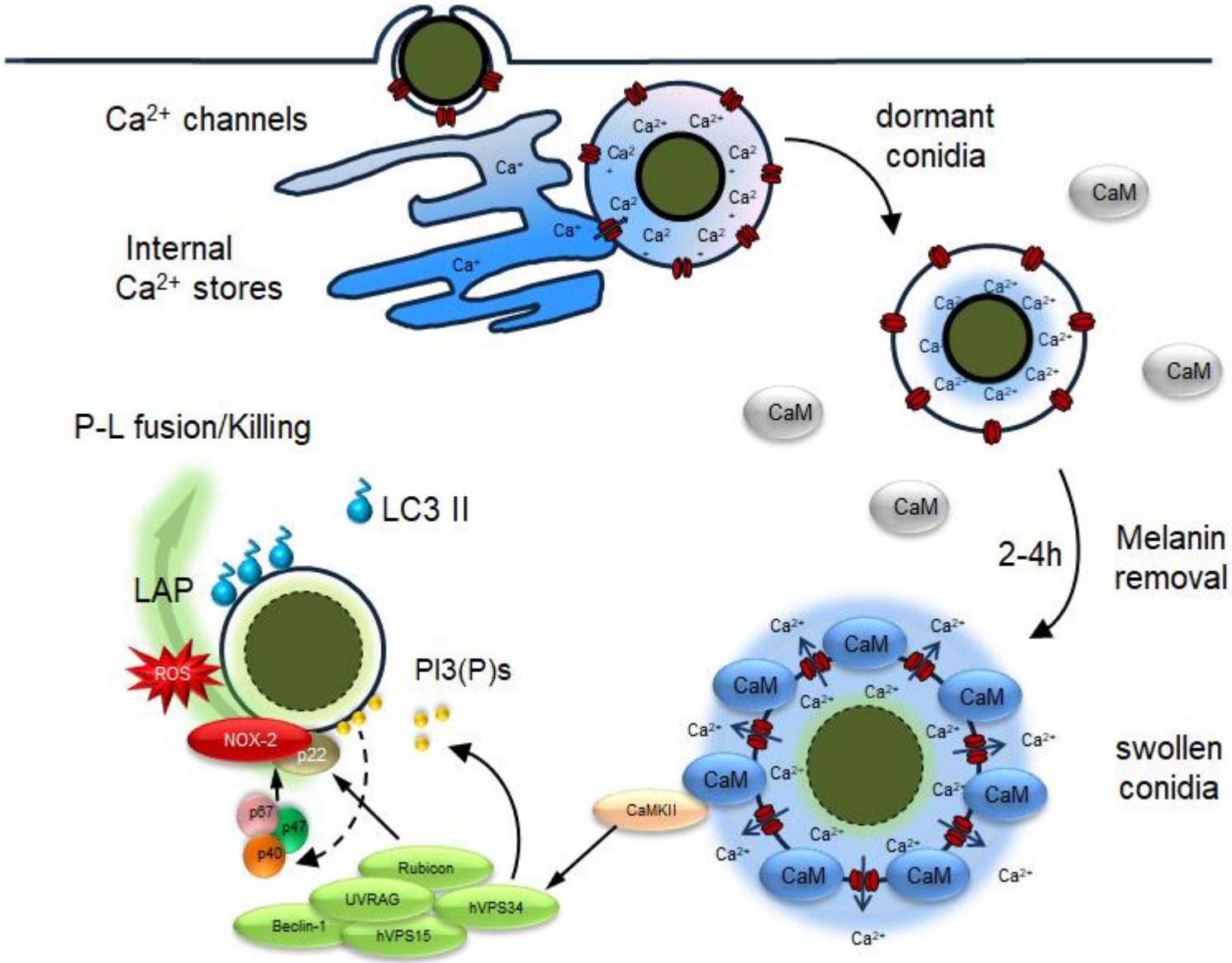


Kyrmizi et al., (under review)



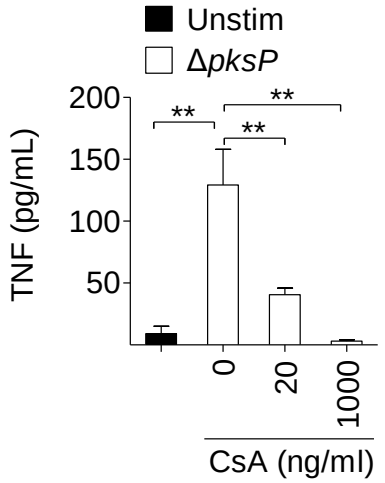
Kyrmizi et al., (under review)

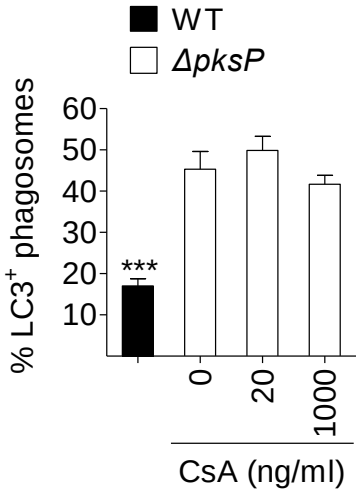
A specialized Ca2+/Calmodulin (CaM) signaling regulates LAP

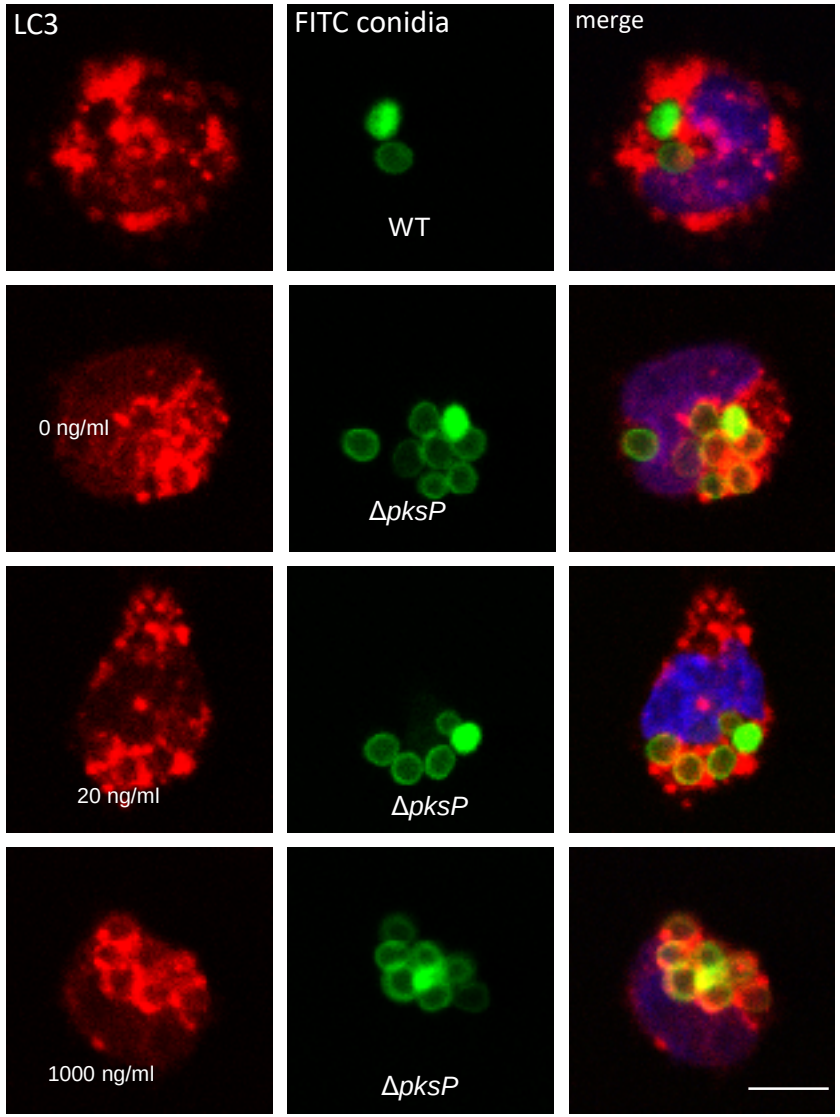


Kyrmizi et al., (under review)

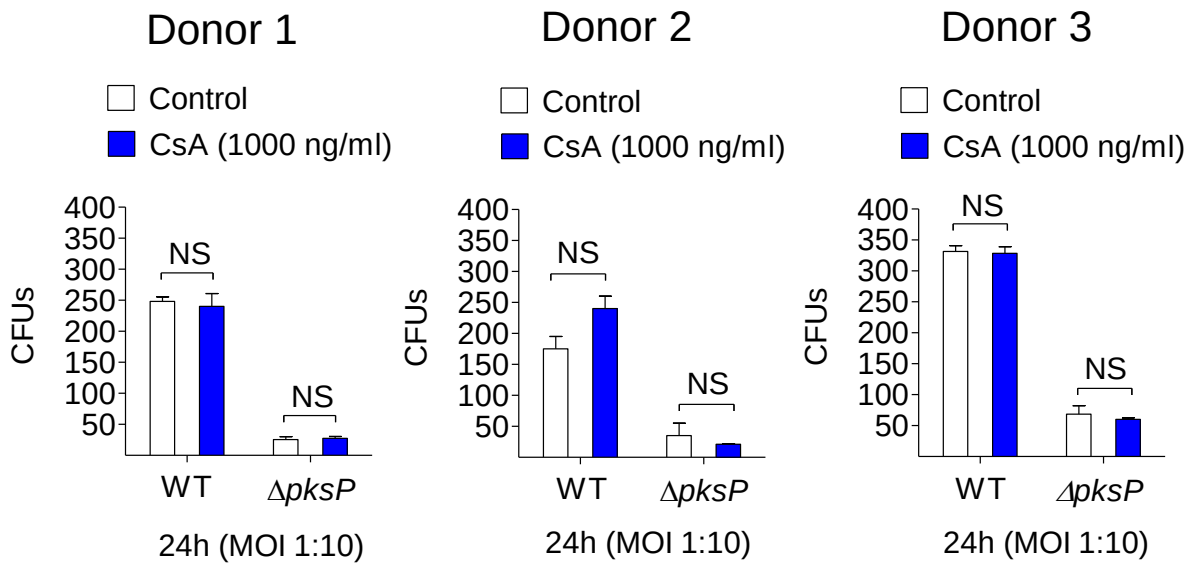
Calcineurin inhibitors do not inhibit *Aspergillus* LAP



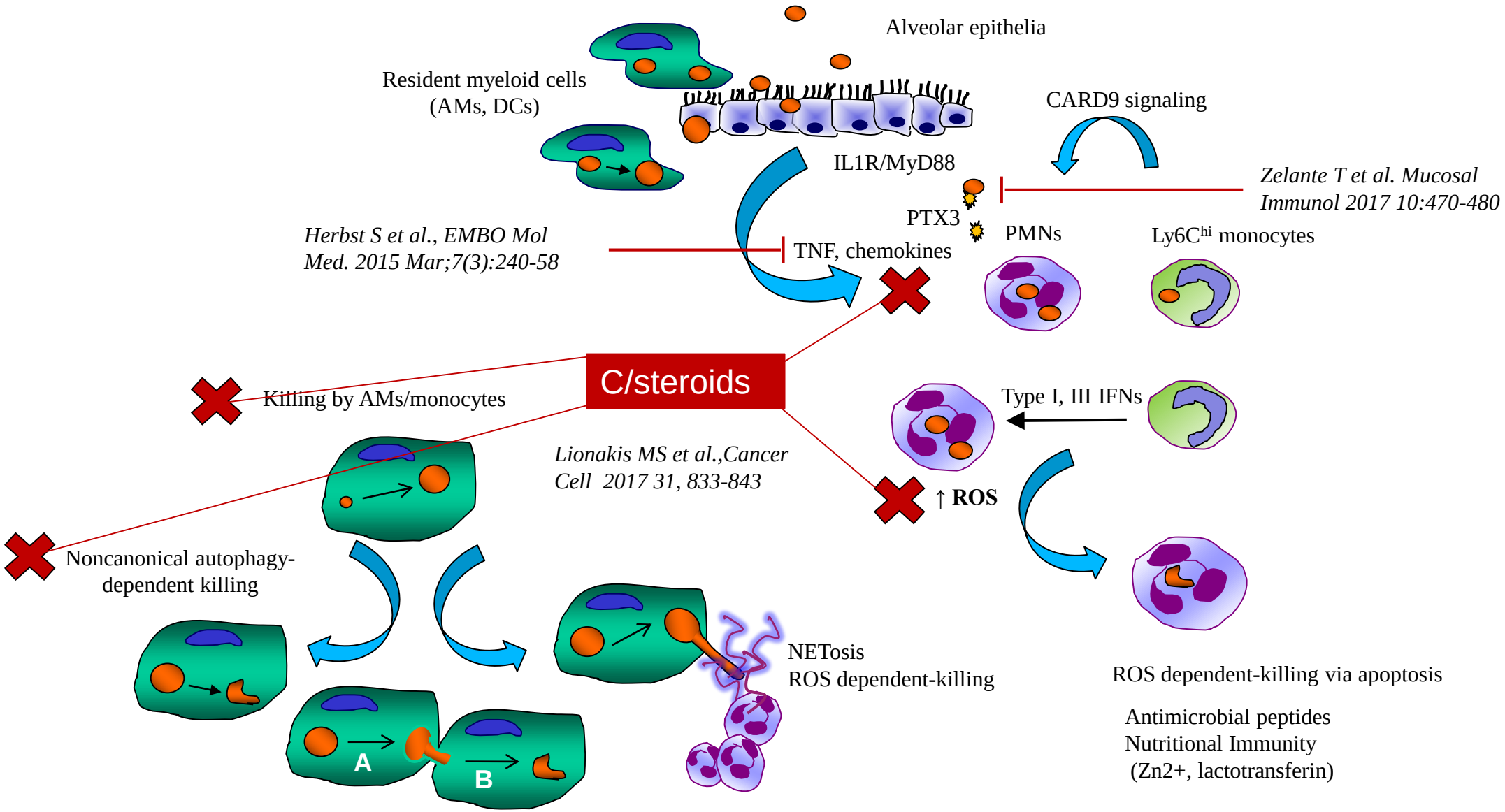




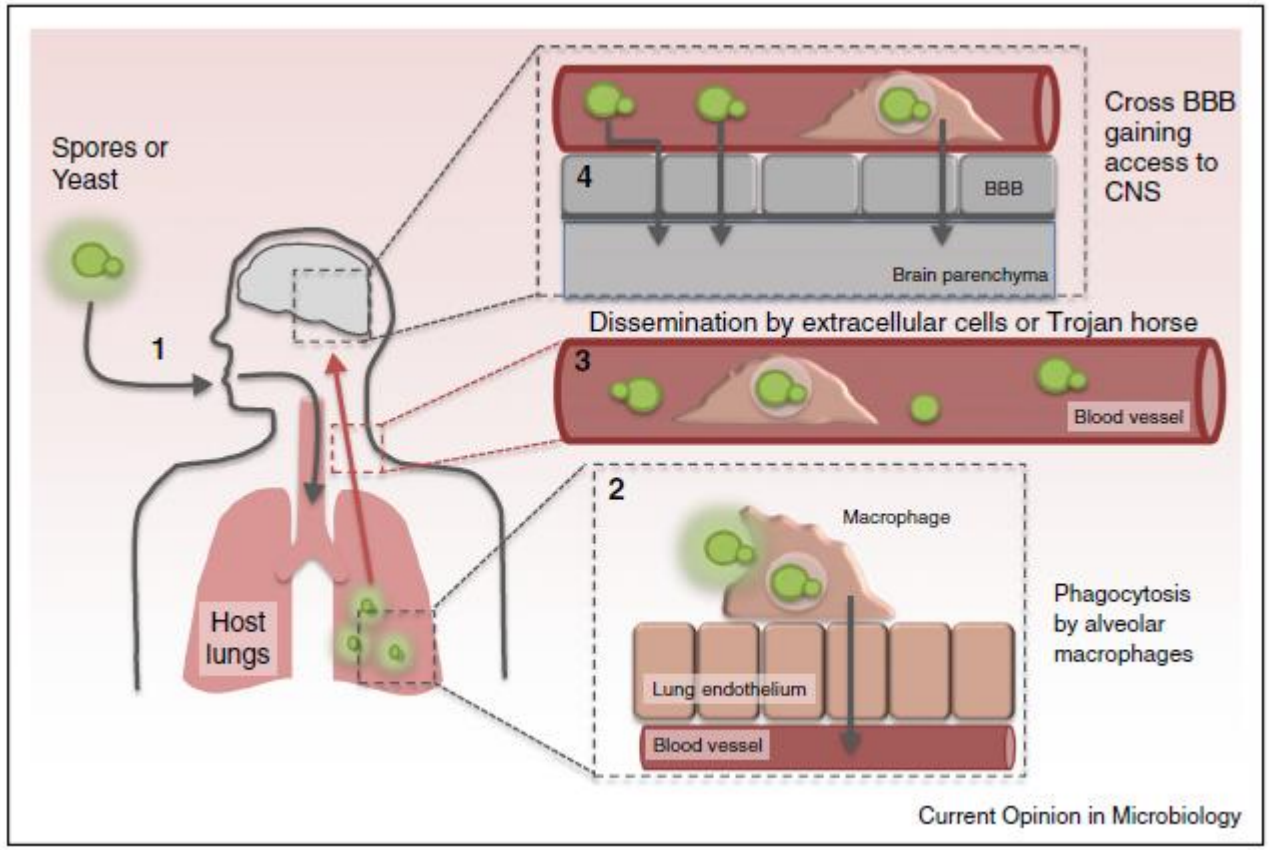
Scale bar 6µm



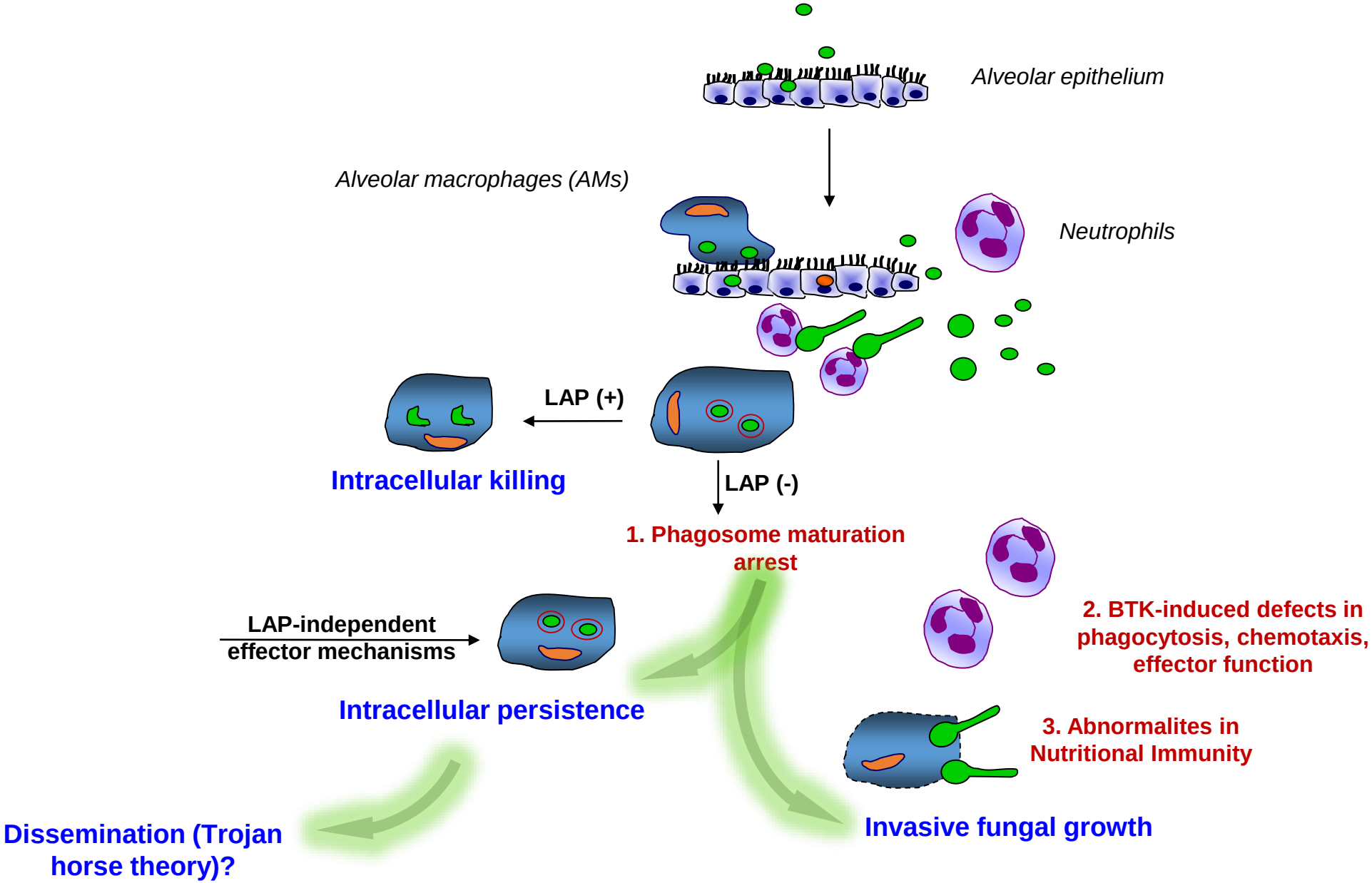
Additive immunosuppressive action of corticosteroids on BTK inhibition



CNS dissemination of *Cryptococcus*: a Trojan horse hypothesis



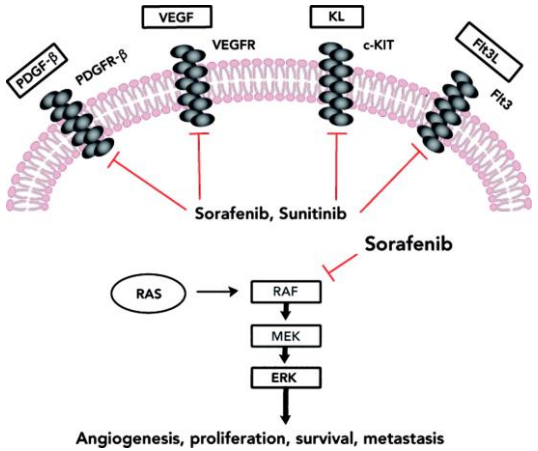
A “Trojan horse” hypothesis on *Aspergillus* persistence and CNS dissemination?



Additional risk factors in cases of ibrutinib-associated CNS aspergillosis?

- Immunodeficiency related to status and type of underlying malignancy
- Patient specific environmental exposures
- Off target effects?
- Genetic predisposition to IA
- Immune defects related to previous sepsis episodes
- Immunosuppressive effects of other drugs
- Pharmacogenomic and drug-drug interactions
- Uncharacterized pathogen-associated risk factors

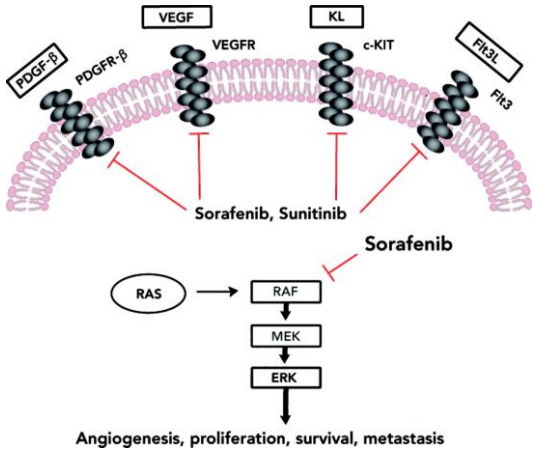
Other SMKIs are associated invasive aspergillosis: the sorafenib story



Type of IFI	Sites of infection	Type of cancer	Age/Sex	Concomitant corticosteroids	Comorbidities
Subacute invasive aspergillosis*	lung	Hepatocellular carcinoma	64/M	No	DM, Asthma

**Bazaz R & DW Denning, Clin Infect Dis 2018 Jan 23*

Other SMKIs are associated invasive aspergillosis: the sorafenib story



Type of IFI	Sites of infection	Type of cancer	Age/Sex	Concomitant corticosteroids	Comorbidities
Subacute invasive aspergillosis*	lung	Hepatocellular carcinoma	64/M	No	DM, Asthma
Invasive aspergillosis	pneumonia	Thyroid cancer	N/A	Yes	N/A
Invasive aspergillosis	pneumonia	Salivary gland carcinoma	N/A	No	N/A
Talaromyces marneffei infection	disseminated	AML	67/M	No	N/A

**Bazaz R & DW Denning, Clin Infect Dis 2018 Jan 23*
Chamilos G, Lionakis MS, Kontoyiannis DP, Clin Infect Dis 2018

Can we make predictions on the risk of treatment with certain SMKIs for IA?

Aspergillus fumigatus Induces Innate Immune Responses in Alveolar Macrophages through the MAPK Pathway Independently of TLR2 and TLR4[1]

J Immunol 2006; 177:3994-4001

Marc Dubourdeau,* Rafika Athman,† Viviane Balloy,‡ Michel Huerre,§ Michel Chignard,‡ Dana J. Philpott,† Jean-Paul Latgé,* and Oumaïma Ibrahim-Granet[2]*

CARD9 mediates Dectin-1–induced ERK activation by linking Ras-GRF1 to H-Ras for antifungal immunity

J. Exp. Med. 2014 Vol. 211 No. 11 2307-2321

Xin-Ming Jia,[1] Bing Tang,[2] Le-Le Zhu,[1] Yan-Hui Liu,[1] Xue-Qiang Zhao,[3] Sara Gorjestani,[3] Yen-Michael S. Hsu,[3] Long Yang,[1] Jian-Hong Guan,[1] Guo-Tong Xu,[1] and Xin Lin[3]

The future of IMIs in the era of targeted therapies for malignant and autoimmune diseases?

- A surge of therapies with SMKIs targeting antifungal immune signaling pathways
  - BTK inhibitors
  - PI3K inhibitors
  - Syk inhibitors
  - NOX inhibitors
  - MAPK inhibitors
  - JAK/STAT inhibitors

- Additional IA cases associated with biological therapies
  - TNF inhibitors
  - eculizumab

Clin Infect Dis. 2018 Jan 6;66(1):140-148

Which should be the top priorities in research of IA associated with small molecule kinase inhibitors (SMKIs)?

- Better epidemiology tools and increased surveillance to capture **Missed Aspergillosis Cases**
- Mandatory report of IMIs in Clinical Trials
- Better risk stratification tools in low-risk patients
- Urgent need for development of novel biomarkers of immunodeficiency
- Preclinical studies on the risk of SMKIs for development of IMIs
- Basic research on IMI immunology and pathogenesis
- Basic research on understanding molecular mechanisms of immunodeficiency

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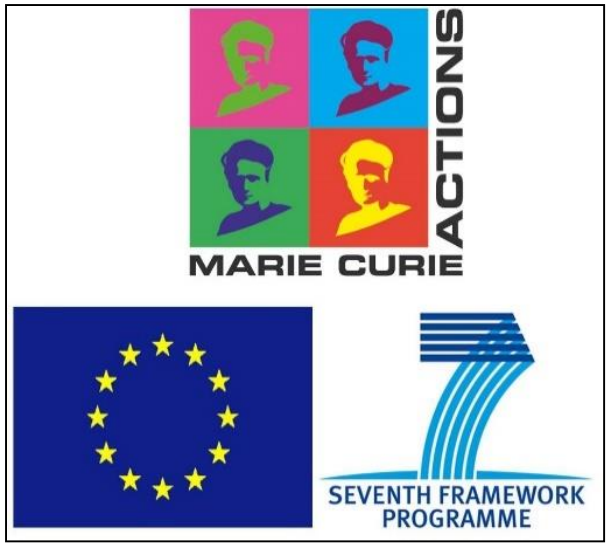
MARIE CURIE ACTIONS
SEVENTH FRAMEWORK PROGRAMME


Ευρωπαϊκή Ένωση
Ευρωπαϊκό Κοινωνικό Ταμείο
ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ
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επένδυση στην κοινωνία της γνώσης
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ΕΣΠΑ 2007-2013
πρόγραμμα για την ανάπτυξη
ΕΥΡΩΠΑΪΚΟ ΚΟΙΝΩΝΙΚΟ ΤΑΜΕΙΟ
Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης


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ΙΚΥ


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Thank you!!!