Μηχανισμοί άμυνας σε ενδοκυττάρια παθογόνα

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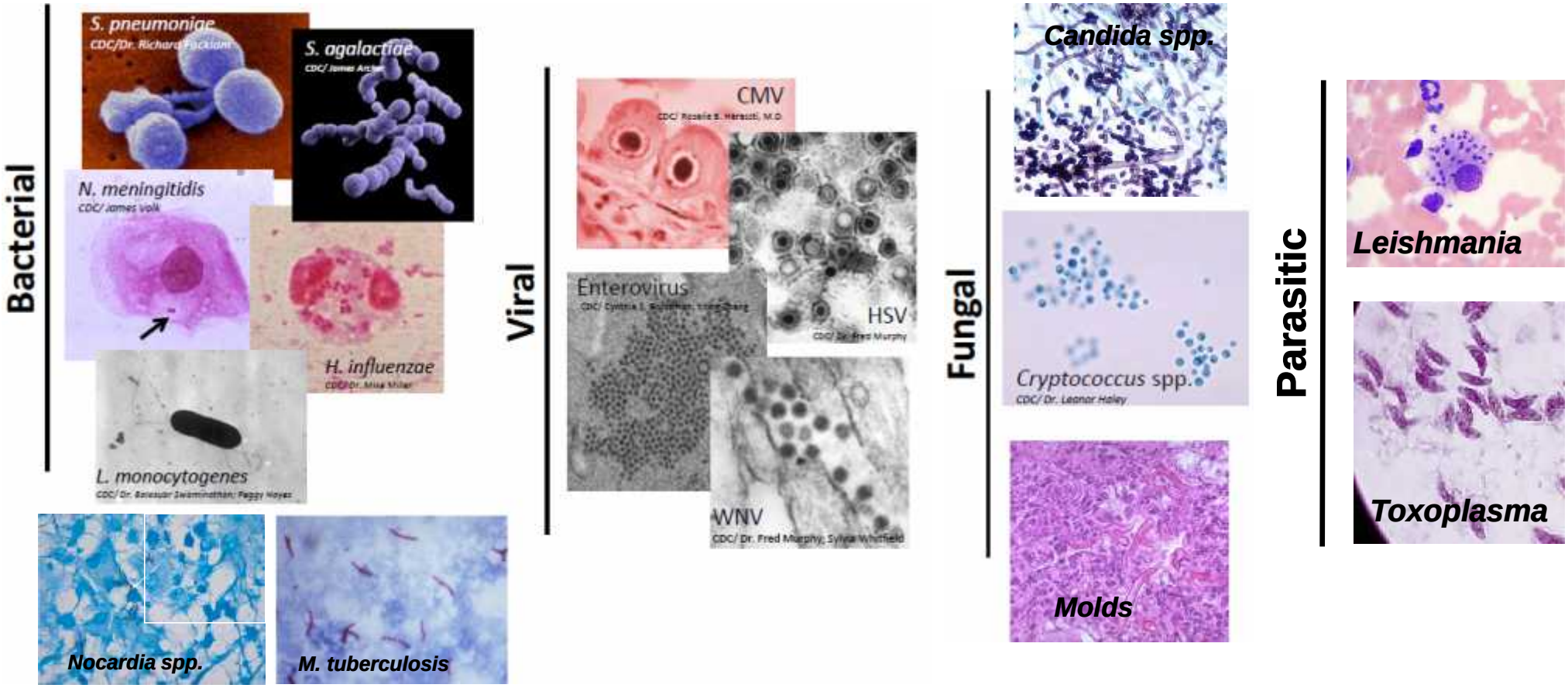
Microbiological classification of infectious diseases



SCIENCE SOURCE

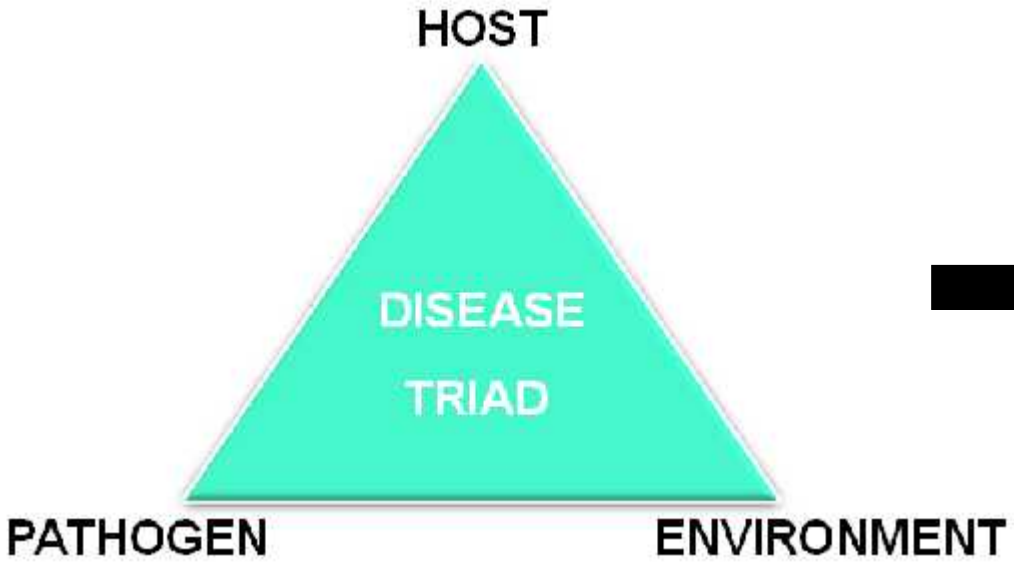
Casadevall A, Pirofski LA Nature 2014; 11; 516:165-6

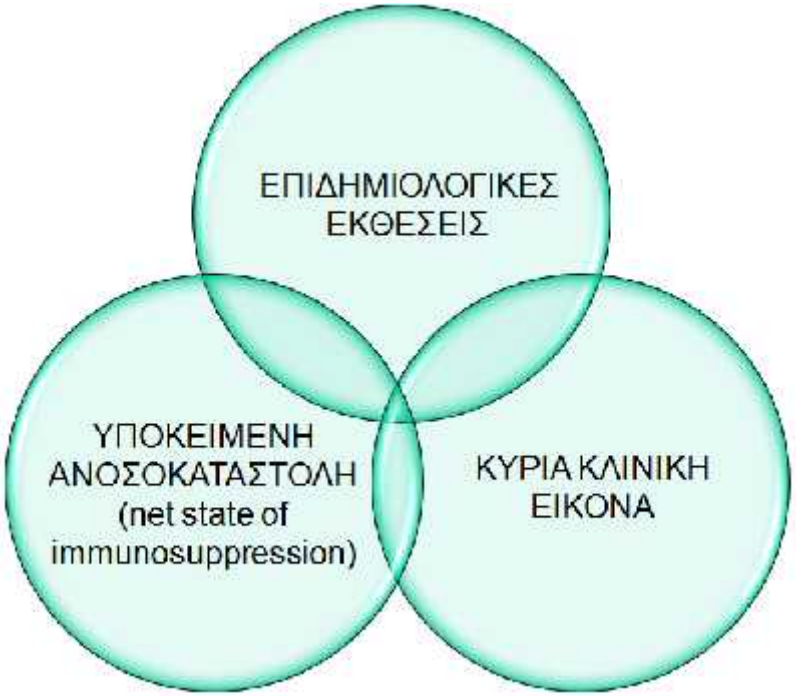
The often harmless fungus *Aspergillus fumigatus* can cause severe pulmonary disease in people with leukaemia.

Ditch the term pathogen

Disease is as much about the host as it is the infectious agent — the focus on microbes is hindering research into treatments, say **Arturo Casadevall** and **Liise-anne Pirofski**.

Rationale Diagnostic Approach



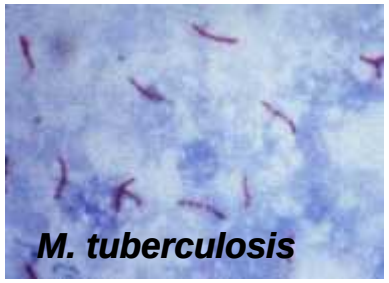


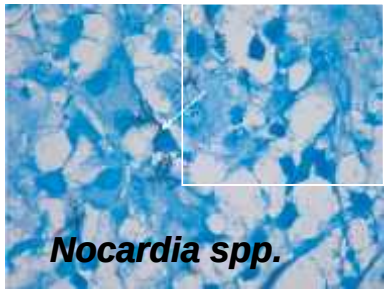
Classification of infectious diseases based on **immunopathogenesis**

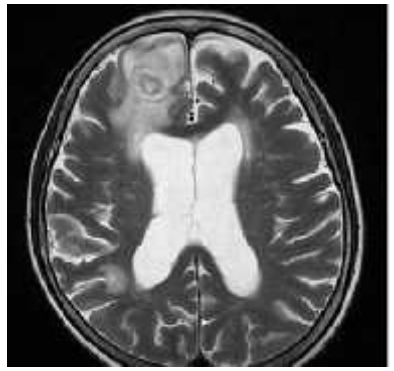
- **Acute** infections: sepsis syndromes (e.g., pneumonia, UTI), **extracellular** pathogens
- **Opportunistic infections (OIs)**
  - ✓ **Subacute clinical course**
  - ✓ **Intracellular** pathogens**-**granulomatous infections (e.g., *Cryptococcus*, TB, NTMB, parasites)
  - ✓ **Extracellular** pathogens (e.g., *Candida*, molds)
- **Mixed** (polymicrobial) infections

OIs share **common clinical features**

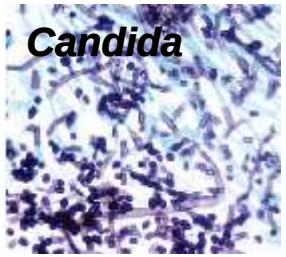
Bacterial



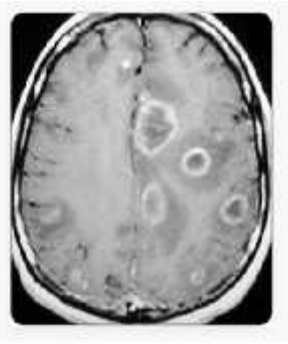




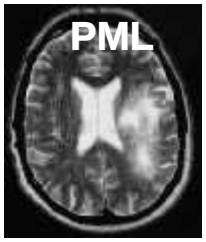
Fungal (+ Endemic fungi)

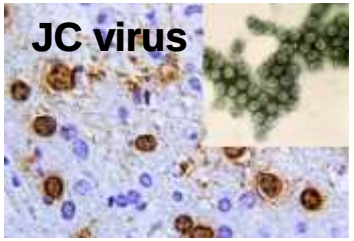


Parasitic

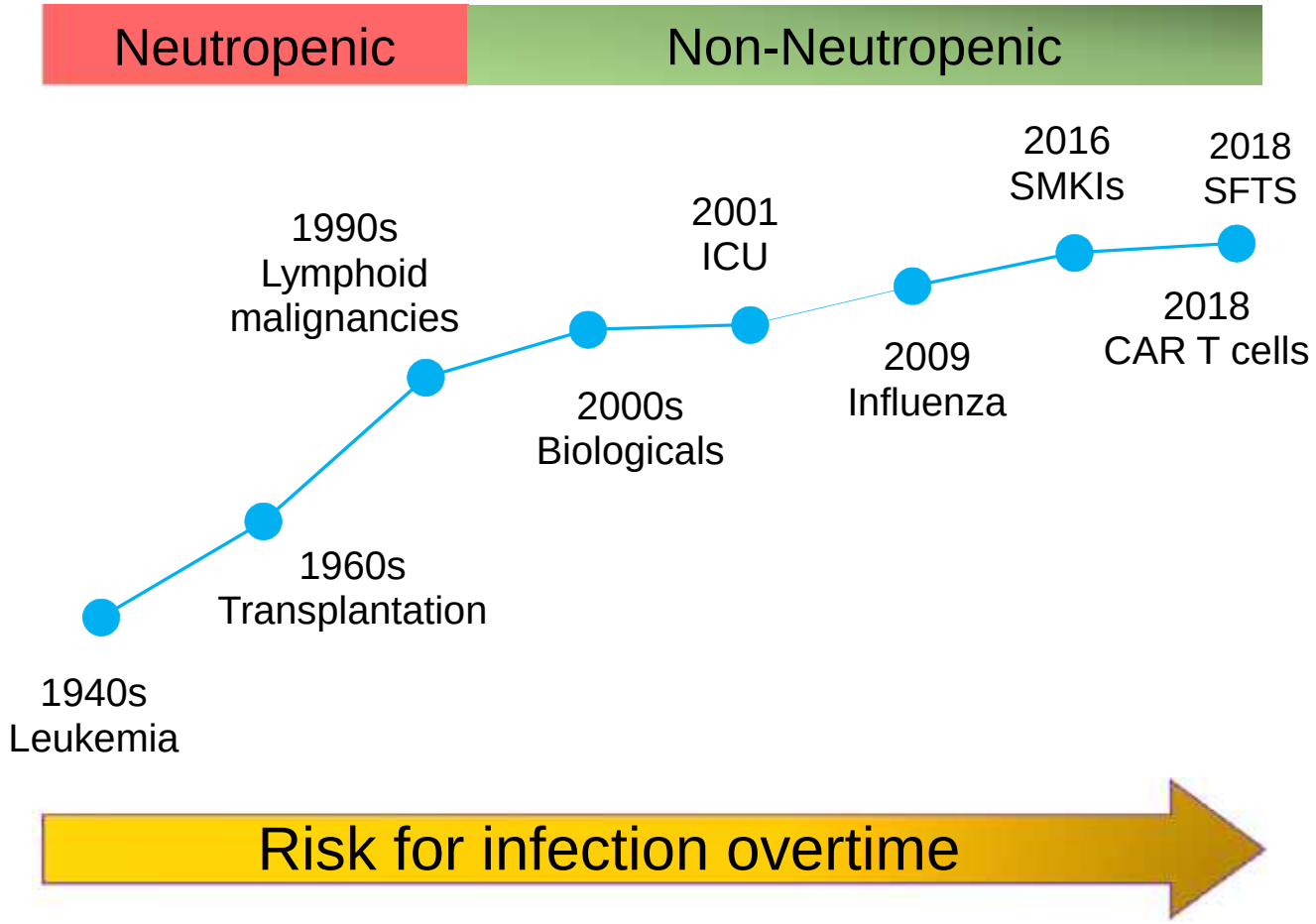


Viral

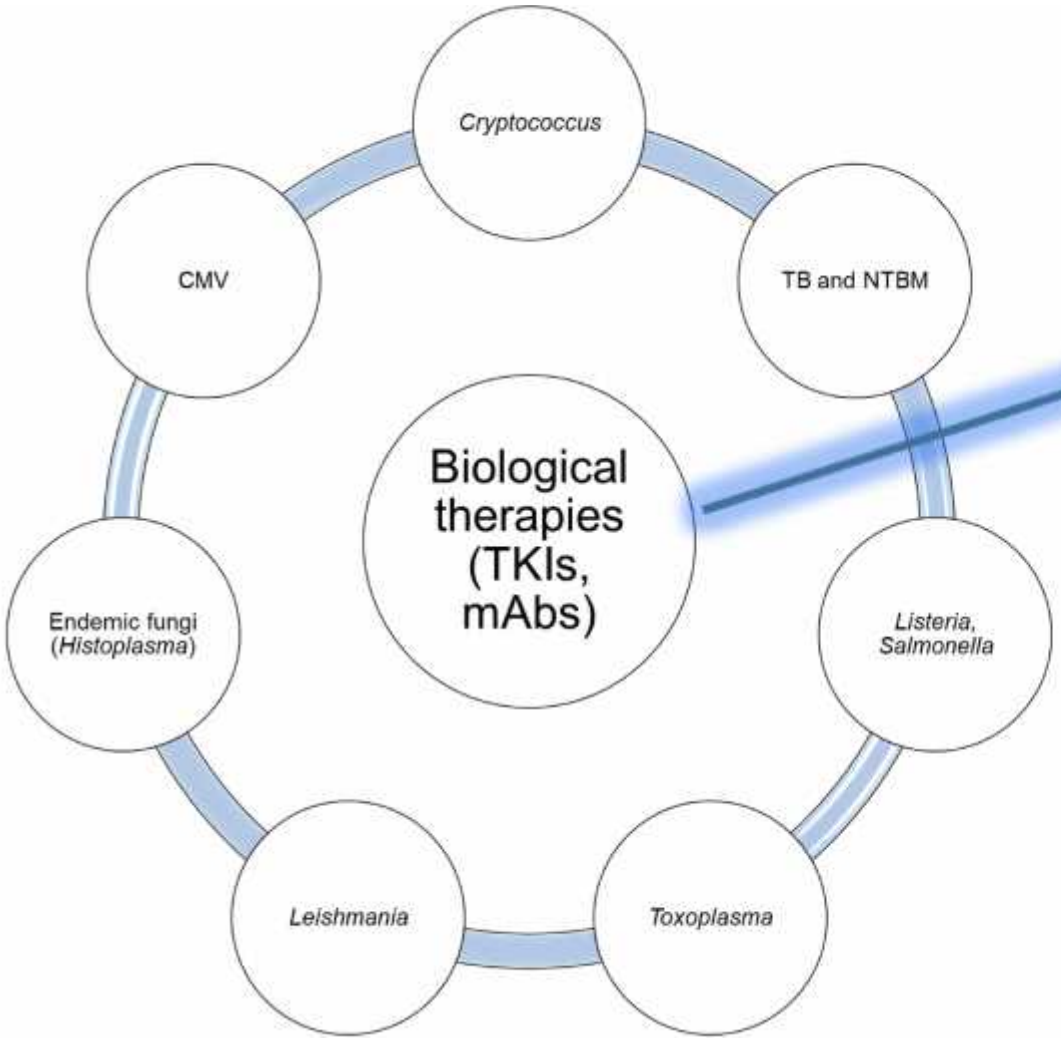




The evolving epidemiology of OIs

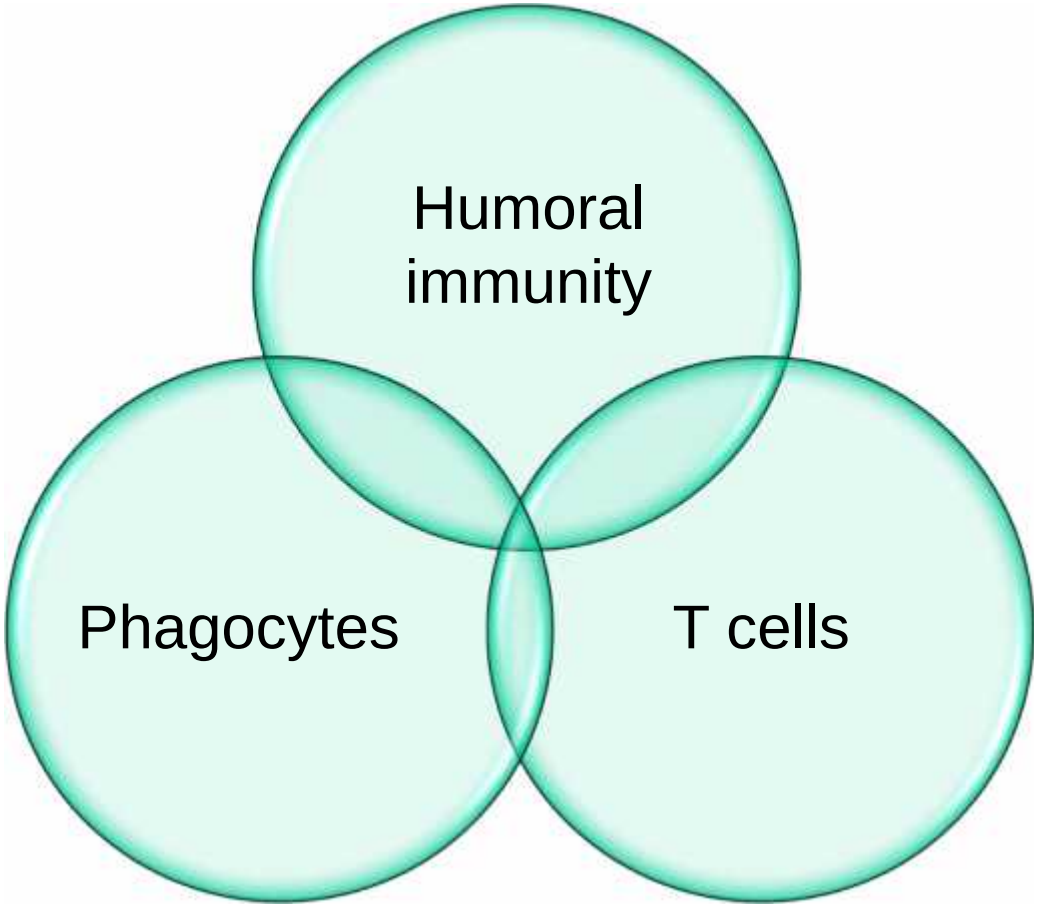


Latge & Chamilos Clin Microbiol Rev (In Press)

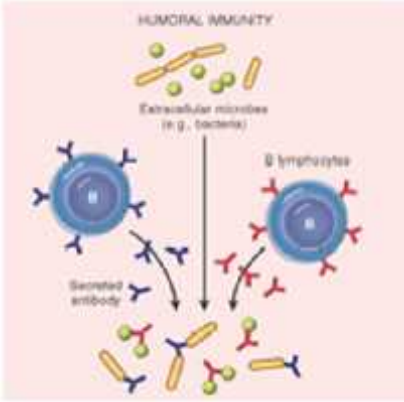


Why certain biological therapies are associated with **increased risk for specific OIs**?

Mechanism of Immunodeficiency



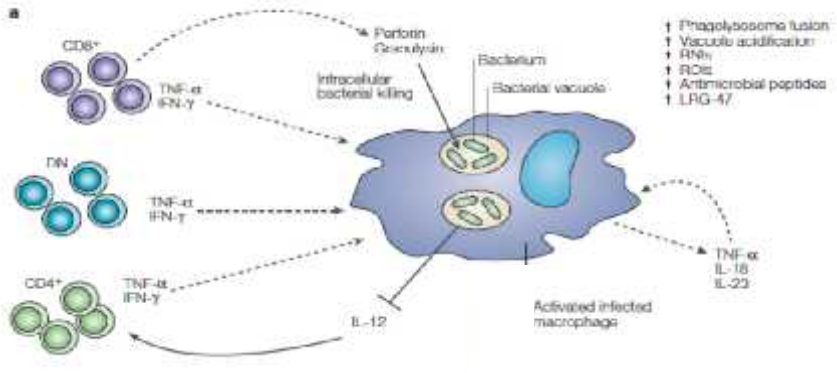
HUMORAL IMMUNITY: B cells, complement



Neutralization
Lysis (complement)
Phagocytosis (PMNs, Macrophages)
Phagosome maturation

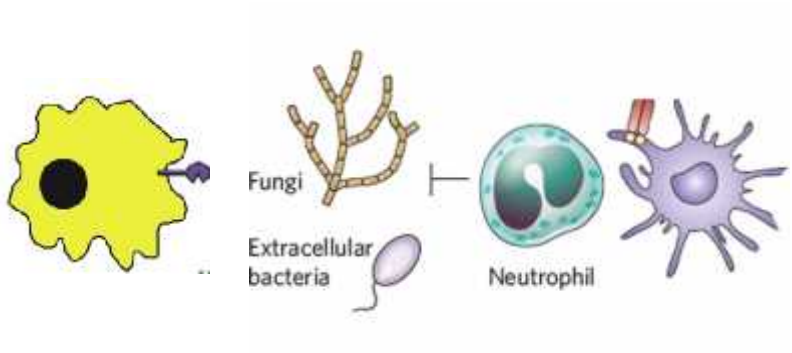
Immune deficit	Predisposing condition	Related Pathogens
B lymphocyte deficiency	MM, leukemia, anti-CD20, c/steroids	Encapsulated bacteria, Giardia, Salmonella, Campylobacter, Enteroviruses
Spleen	Splenectomy, SCD, SLE	Encapsulated bacteria, Capnocytophaga
Complement	Congenital, acquired (SLE)	Encapsulated bacteria, S.aureus

CELLULAR IMMUNITY: T cells



Immune deficit	Predisposing condition	Related Pathogens
T lymphocyte deficiency	AIDS, lymphoma, chemotherapy, transplantation, c/steroids	Intracellular Pathogens Latent viruses: CMV Bacteria: Listeria, TB,NTBM, Nocardia Fungi: PCP, Cryptococcus Parasites: Toxoplasma, Leishmania

CELLULAR IMMUNITY: Phagocytes

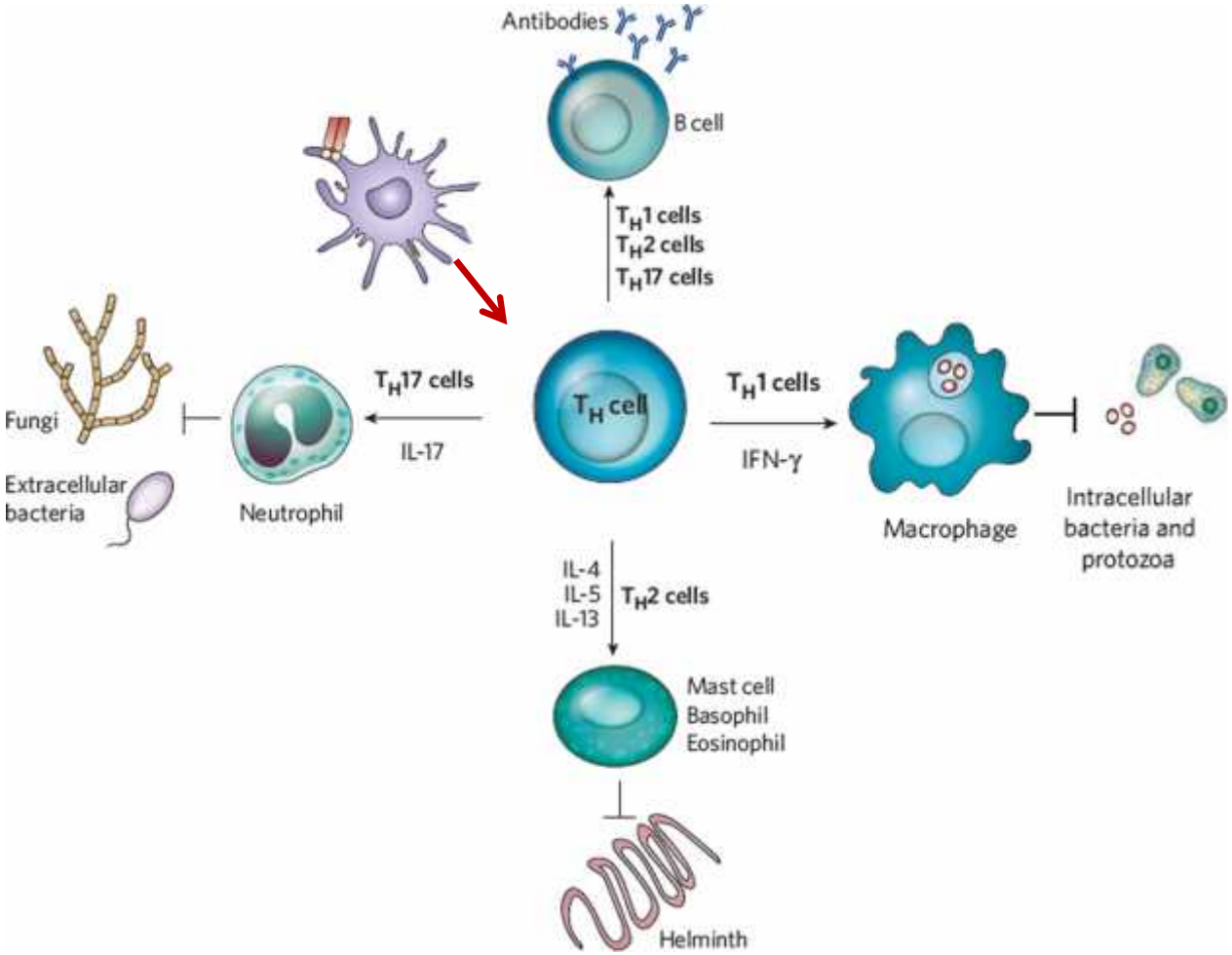


Immune deficit	Predisposing condition	Related Pathogens
Neutropenia	Chemotherapy, leukemia	Gram negative, S. aureus, Streptococci, Fungi: Candida, molds
Neutrophil chemotaxis	DM, cirrhosis, alcoholism, uremia, trauma, burn, steroids	S. aureus, Streptococci, Fungi: Candida, molds
Functional defects	CGD, MPO deficiency, c/steroids	S. aureus, E. coli, Fungi: Candida, molds

Ενα διαφορετικό μοντέλο ανοσολογικής απάντησης

- Sensing of danger (damage)
- Functional Specialization
- Division of Labor-Co-operative activity
- Memory: Adaptive Immunity
- Communication: Cross-Talk
- Redundancy: many effectors
- Plasticity: Epigenetic reprogramming-trained immunity
- Tolerance: Balanced Response ➡ Infection Clearance vs. Resolution of inflammation

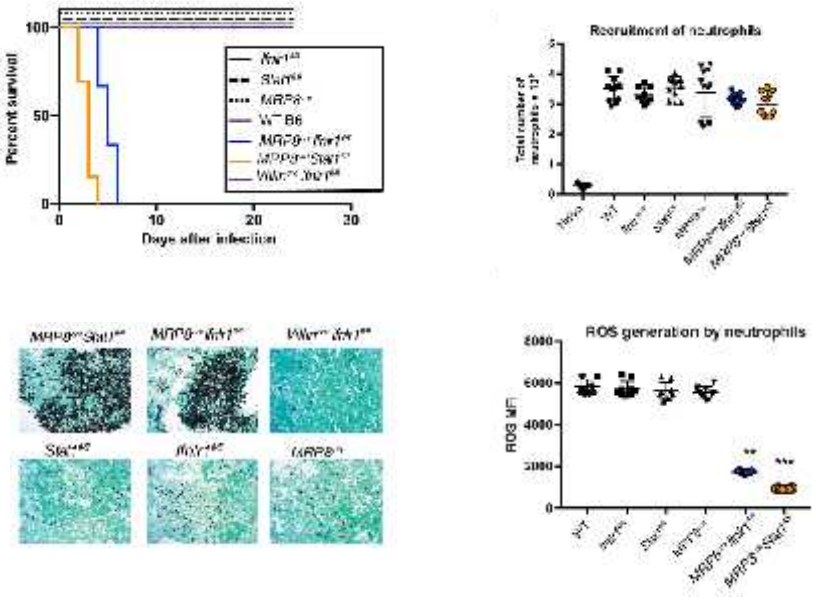
Η αμφίδρομη σχέση της επίκτητης με την ενδογενή ανοσία (Memory and Cross talk of immune system)



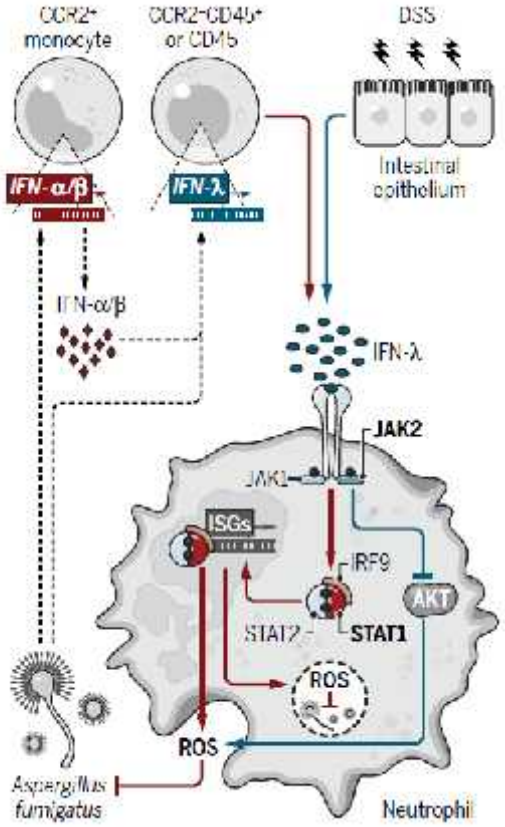
Η πολυεπίπεδη δομή της ανοσολογικής απάντησης (Redundancy)

- Epithelia: sensing, secretion of cytokines/chemokines, AMPs, cross-talk with immune cells, programmed cell death
- Microbiome: Competition for growth, natural antibiotics, metabolites
- Soluble PRRs: collectins, pentraxins
- Serum: complement, Abs, nutritional immunity
- Phagocytes: oxidative and non-oxidative mechanisms of killing
  - PMNs: NETosis, sequestration of essential nutrients
- Other immune cells (NK cells, pDCs, CTL): direct cytotoxicity (granulysin, perforins), cross talk with adaptive and innate effectors
- Cytokines/chemokines: orchestrate immune response, direct antimicrobial action

Immune cell cross-talk

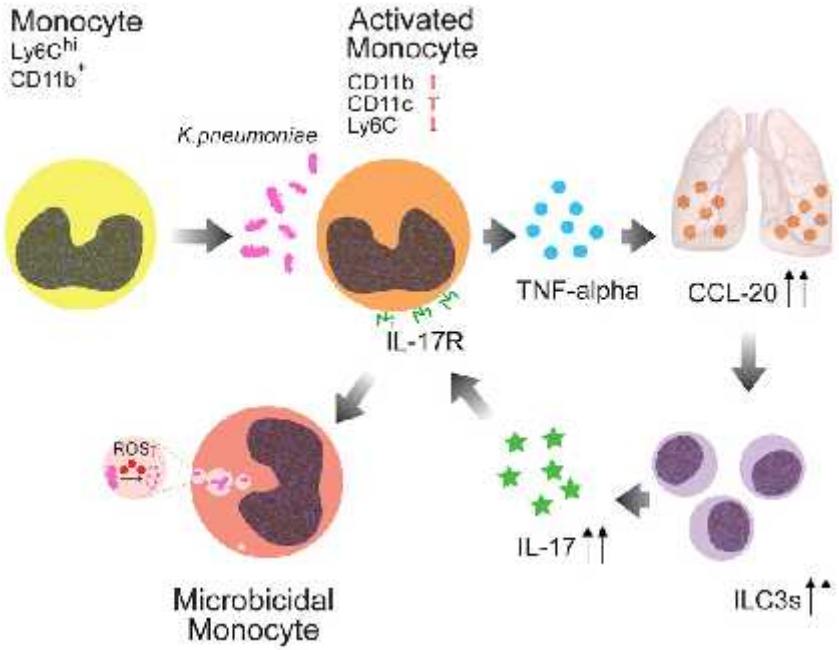


Espinosa *et al.*, *Sci. Immunol.* **2**, eaan5357 (2017)



Innate Lymphocyte/Ly6C^{hi} Monocyte Crosstalk Promotes *Klebsiella Pneumoniae* Clearance

Huizhong Xiong,[1,2] James W. Keith,[1,2,3] Dane W. Samilo,[1,5] Rebecca A. Carter,[1,2] Ingrid M. Leiner,[1,2] and Eric G. Pamer[1,2,4,*]



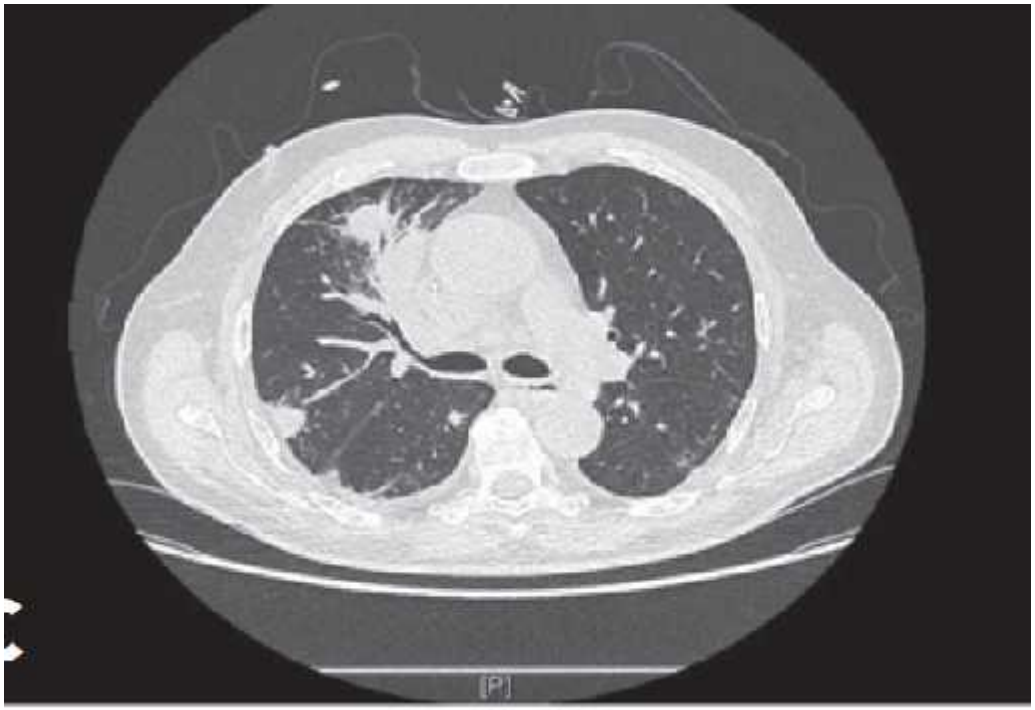
Cell *165*, 679–689, April 21, 2016

Biological therapies associated with ***increased risk for OIs caused by extracellular pathogens***

Κλινική Περίπτωση #1

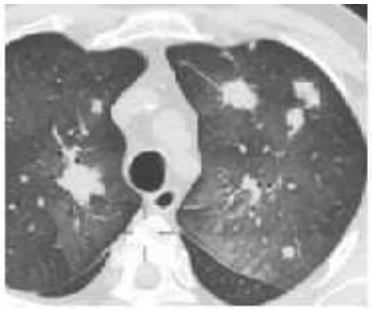
- 67 y/o white male, asymptomatic CLL diagnosed in 2010
- In 2017 started **on oral BTK inhibitor (ibrutinib)**
- Four months later admitted in the ER with fever, shortness of breath and dry cough
- **CT chest**: bilateral infiltrates
- Started on broad spectrum antibiotics (Pip/Tazo + Levofloxacin + TMP/SMX) + fluconazole + oselatamivir

Chest CT findings



Specificity of chest CT in diagnosis of infections in Hematological Malignancy Patients?

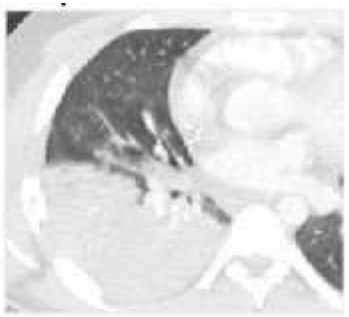
P. aeruginosa



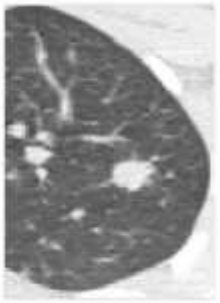
Aspergillus

K. pneumoniae

Mold

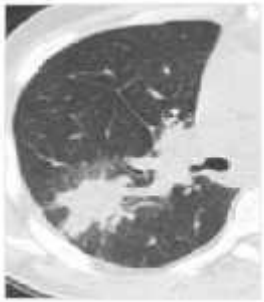


Nocardia

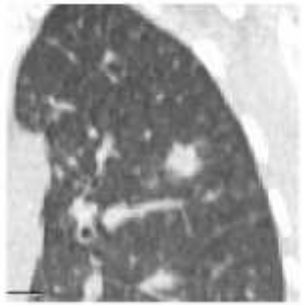


Mold

Lymphoma



CMV



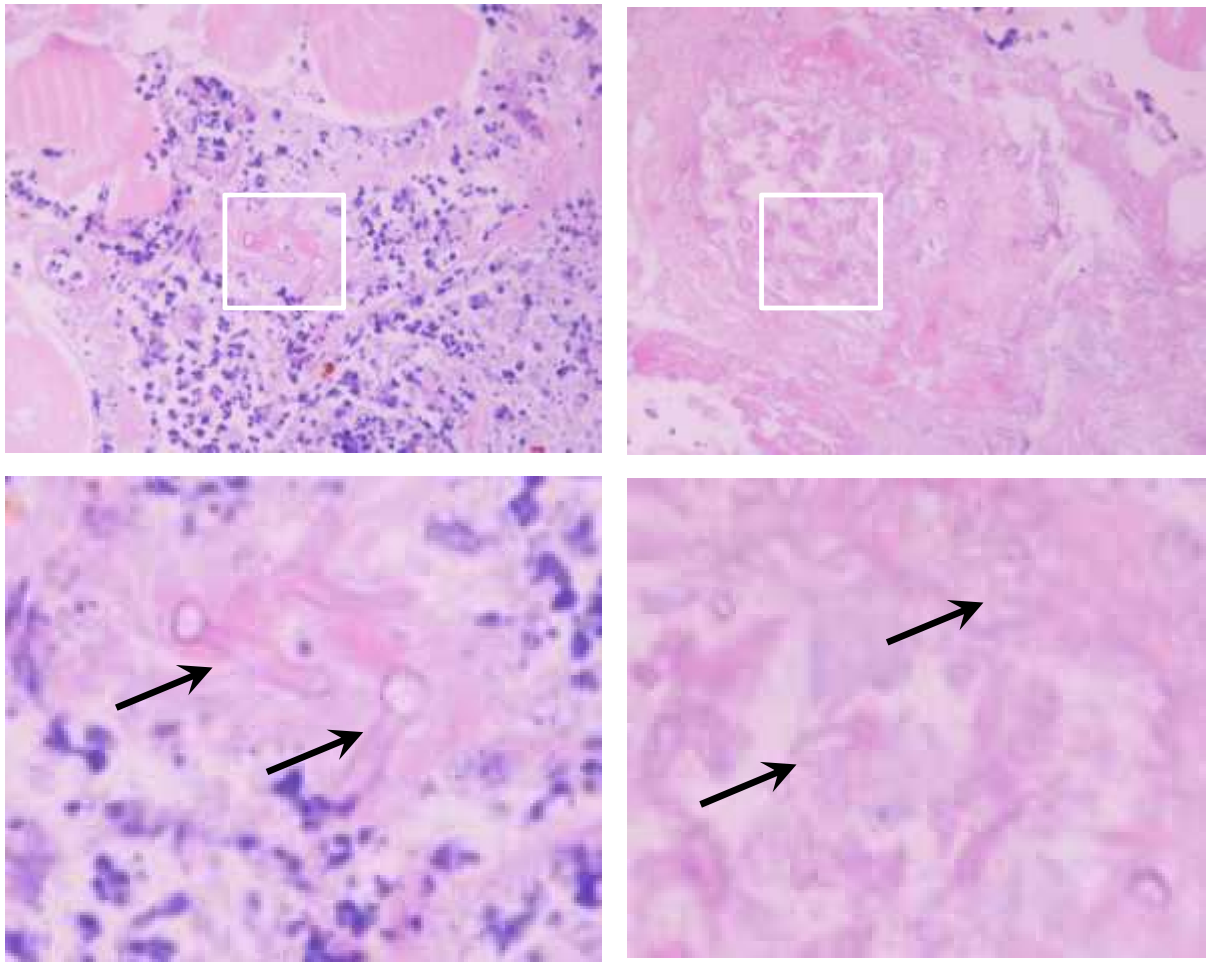
Cryptococcus

Lionakis MS, Lewis RE, Kontoyiannis DP, Clin Infect Dis 2018

Ποιο από τα παρακάτω είναι σωστό στη διαγνωστική προσέγγιση:

1. CT staging (CT lung +/- sinus +/- brain)
2. Early bronchoscopy (within 48-72h)
3. BAL fluid Cx, GM Ag, PCR
4. Biopsy, histology and culture of lesions if feasible
5. Empirical antifungal coverage for IMI (including non-Aspergillus molds)
6. All of the above

Biopsy: Mucormycosis



Αναπάντητα Ερωτήματα…..

1. Αιτιολογική συσχέτιση της μυκητίασης με την έναρξη του αναστολέα BTK?
   - ✓ Ρόλος υποκείμενης νόσου, προηγούμενων θεραπειών?
2. Συσχέτιση αναστολέα BTK με άλλες μυκητιακές λοιμώξεις?
3. Μηχανισμός επαγόμενης ανοσοκαταστολής?
4. Άλλες αναδυόμενες ομάδες ασθενών με αυξημένο κίνδυνο για 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.

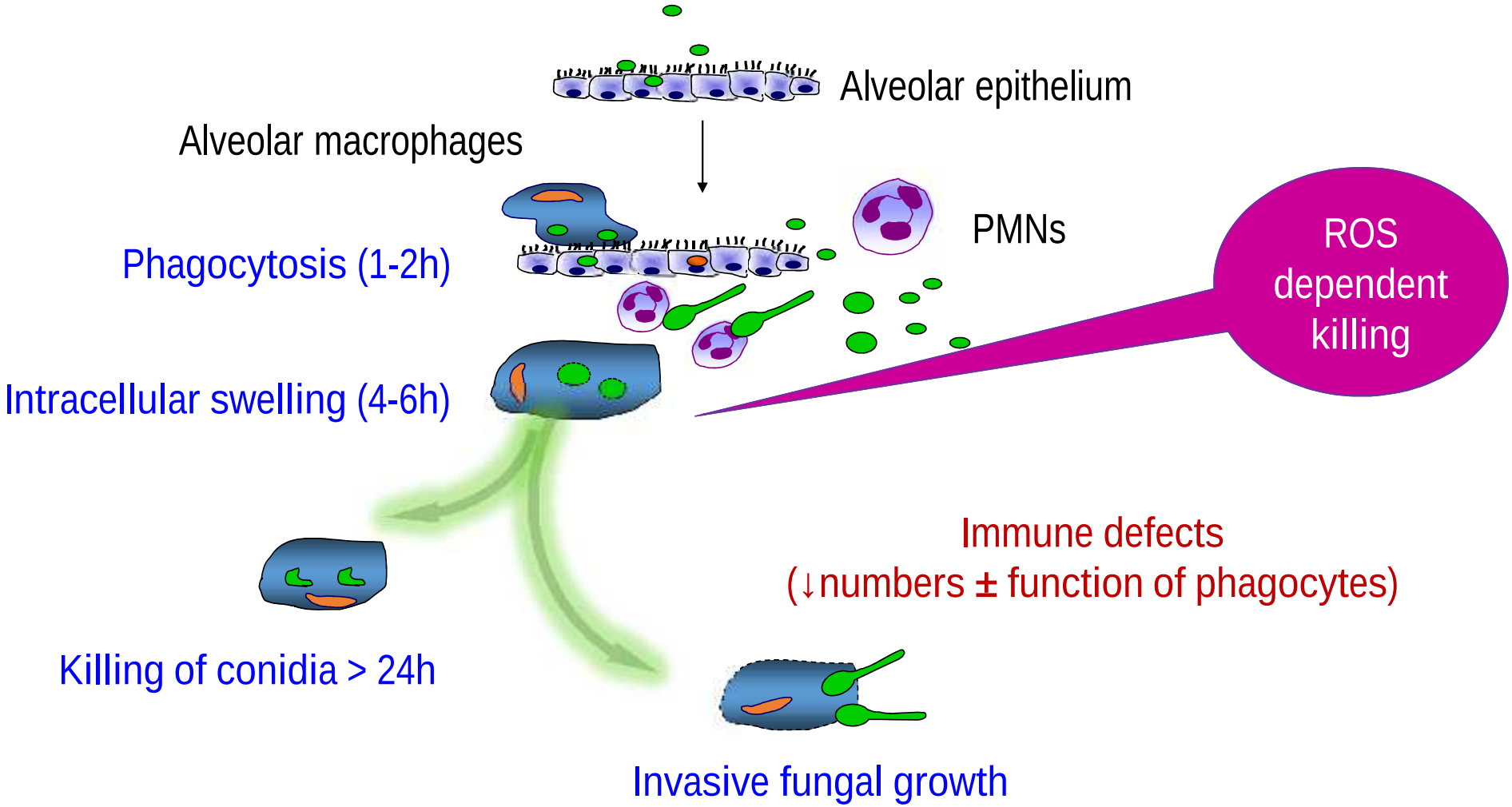
Invasive mold infections (IMIs): lessons from primary immunodeficiencies

Defects in myeloid cell numbers, chemotaxis and function mediate susceptibility to invasive diseases by Candida and airborne filamentous fungi (molds)

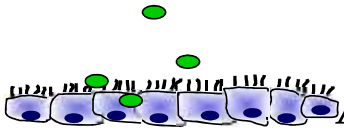
- Functional defects in myeloid cells
  - ➢CGD (NADPH oxidase)
  - ➢Pulmonary alveolar proteinosis (GM-CSF signaling)
- Defects in myeloid cell numbers or chemotaxis
  - ➢MonoMAC syndrome (GATA2)-numbers
  - ➢Severe congenital neutropenia (ELA2, HAX1)-numbers
  - ➢Leucocyte adhesion deficiency (CD18)-trafficking
  - ➢CARD9 deficiency-chemotaxis

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

Physiological Immune Response against Extracellular fungi



Physiological Immune Response against Molds

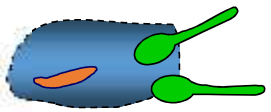


Alveolar epithelium

Alveolar macrophages

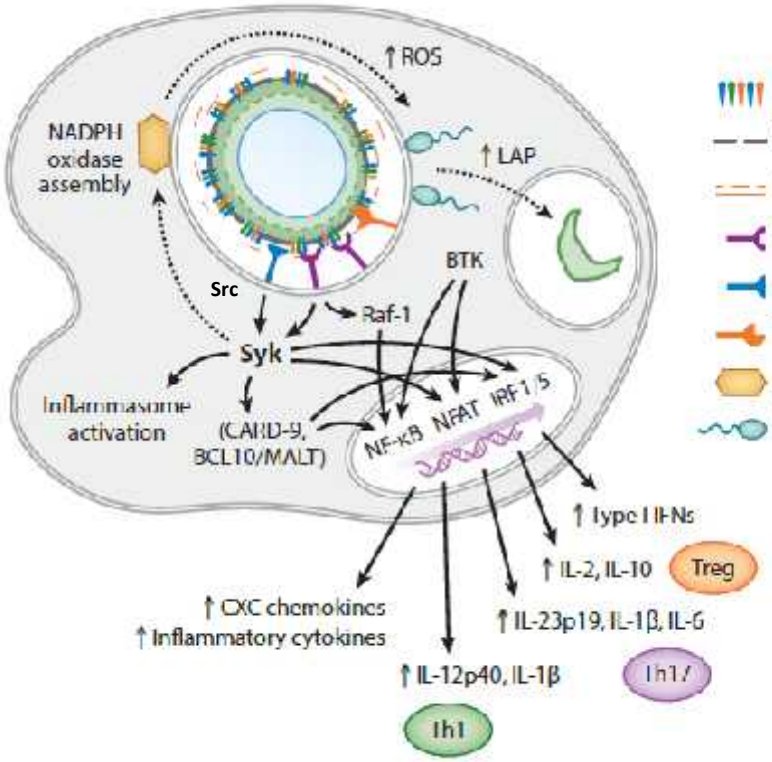
- Cells of lymphoid origin (T cells, B cells) are dispensable for Immunity against extracellular fungi
- Defects in phagocytes account for development of systemic infections caused by Candida and molds

Killing of conidia > 24h

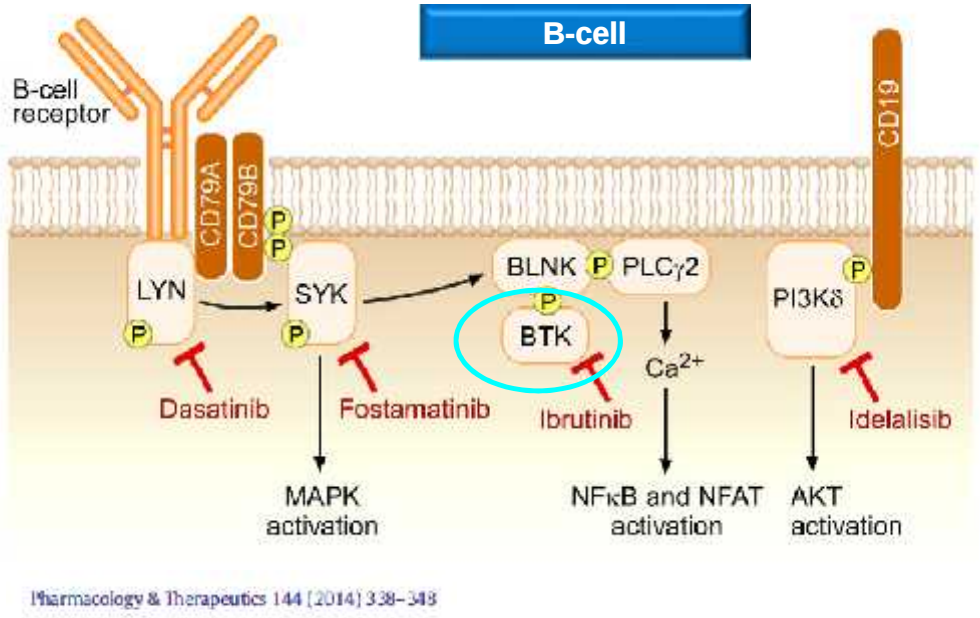


Invasive fungal growth

The other side of SMKIs…..

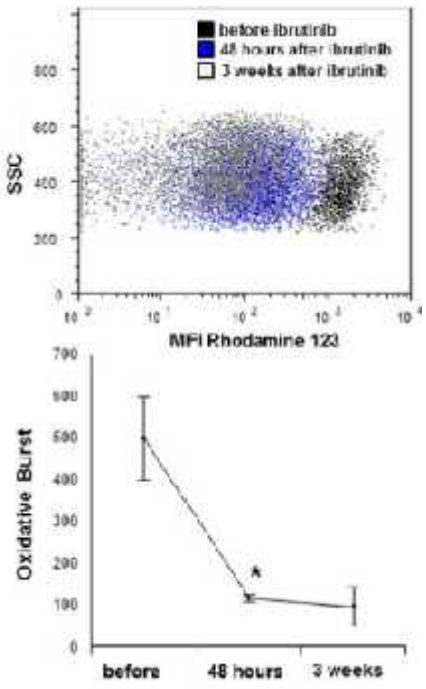


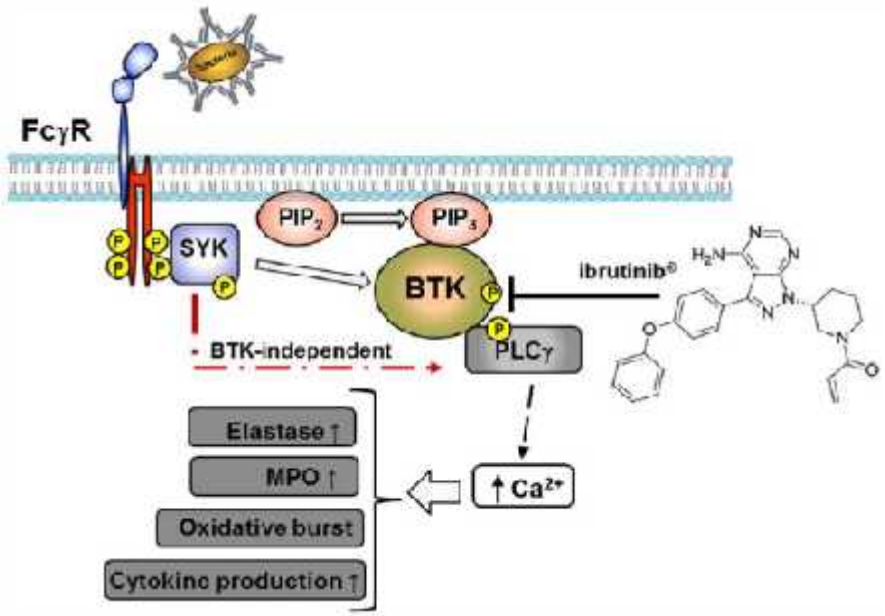
Clinical Infectious Diseases
VIEWPOINTS



Latge JP and Chami., Ann Rev Microbiol 2017;71:99-116

BTK inhibitors inhibit activation of NADPH oxidase in neutrophils





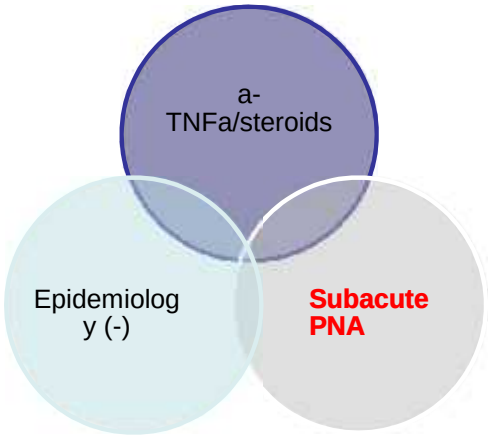
Prezzo A, et al Leuk Res. 2019 Oct 3;87:106233

Biological therapies are associated with increased risk for ***OIs caused by intracellular pathogens***

Κλινικό παράδειγμα 2

•61 y/o M/RA,
•MTX/prednisone/**Infliximab**
•Anemia/SOB/RLL infiltrate
•No response to Levofloxacin

CHEST 2003; 124:2395–2397)



Clinical manifestations

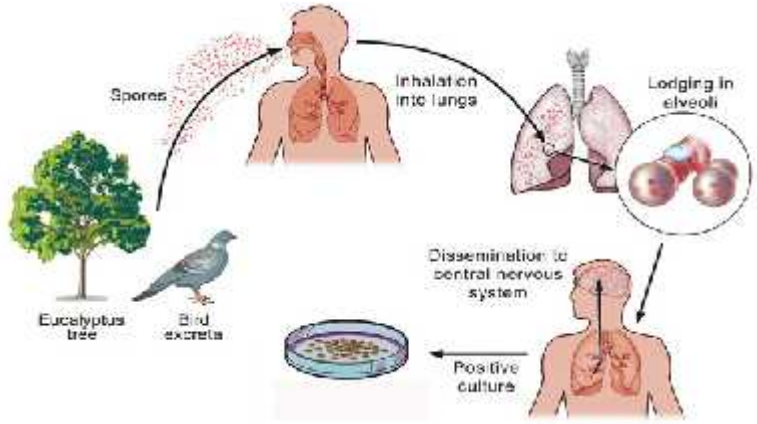
Λοιμώξεις από *Cryptococcus*

Variable	AIDS	Cancer	Transplantation	Other
Incidence	1,7%-6,6%	0.5 per 100,000	Liver transplant: 0.3%-2%	1/100,000 DM/CS/Cirrhosis
Clinical Presentation	Meningitis, fungemia	Meningitis, fungemia	Skin, OA, lungs, meningitis	NA
Survival	70%-78%	43%-70%	50% mortality in pneumonitis	NA

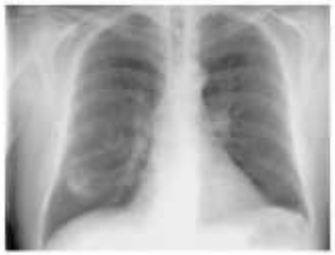
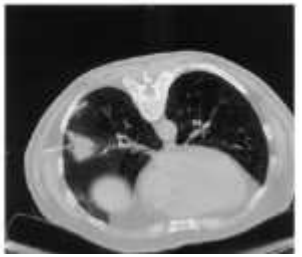
Sepkowitz KA, Clin Infect Dis 2002; 34:1098-107

Cryptococcosis

Κύκλος Ζωής

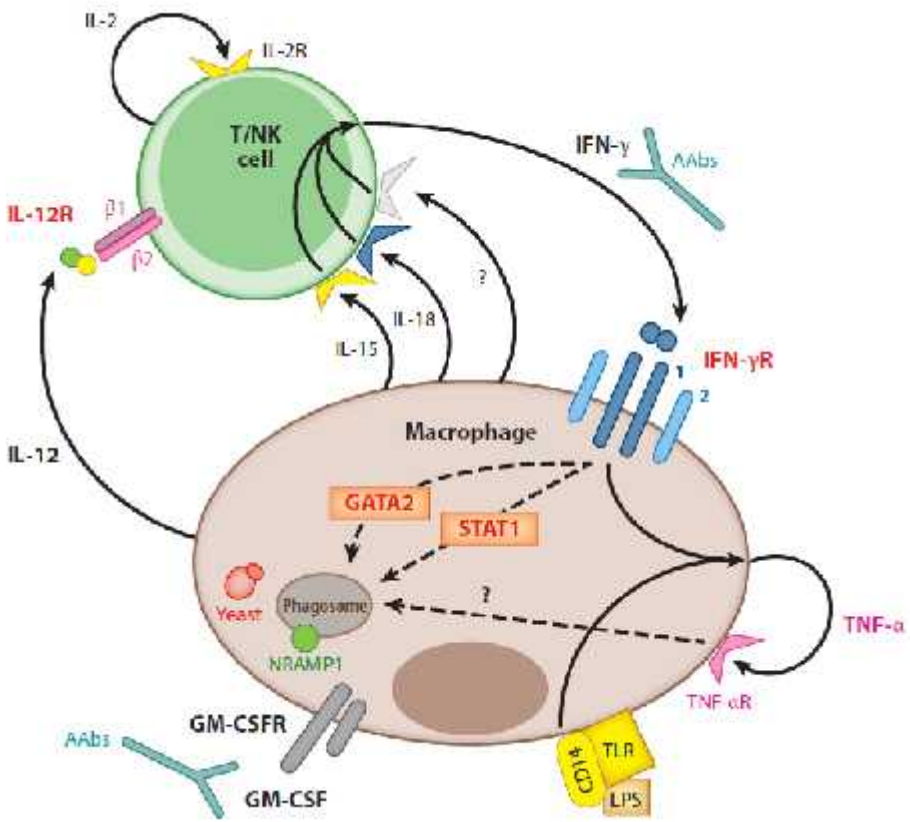


Κλινικές εκδηλώσεις


Διάγνωση

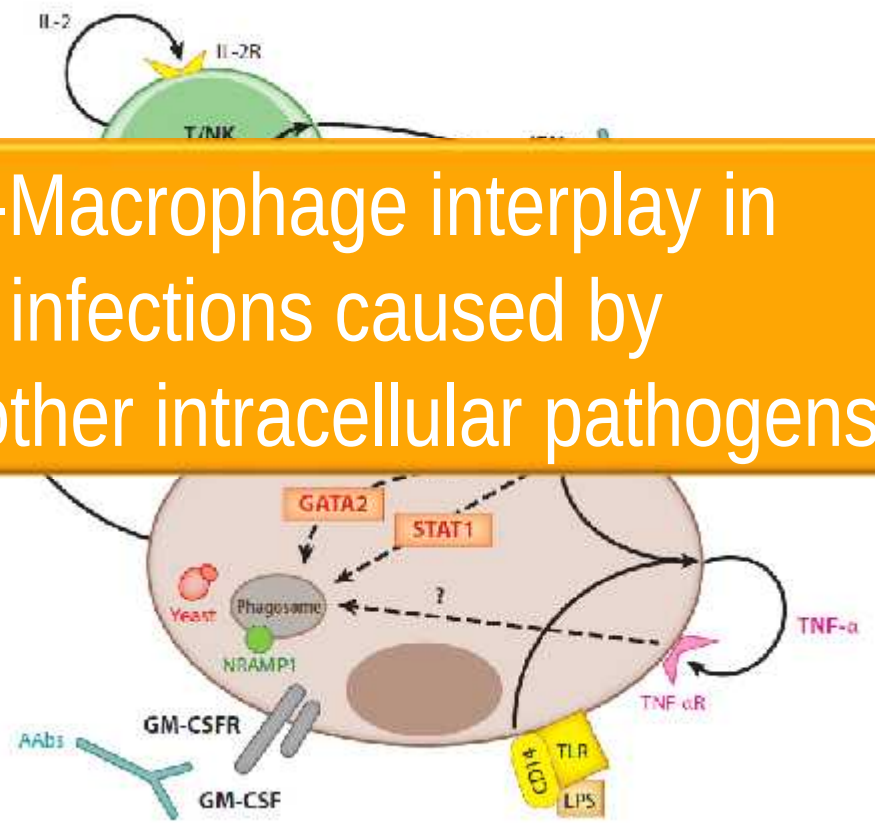
T cell-Macrophage cross talk via JAK/STAT signaling and the IL-12/IFNγ axis are critical for control of Intracellular pathogens (Cryptococcus) and PJP



Lionakis MS& Levitz SM. Annu Rev Immunol. 2018 Apr 26;36:157-191.

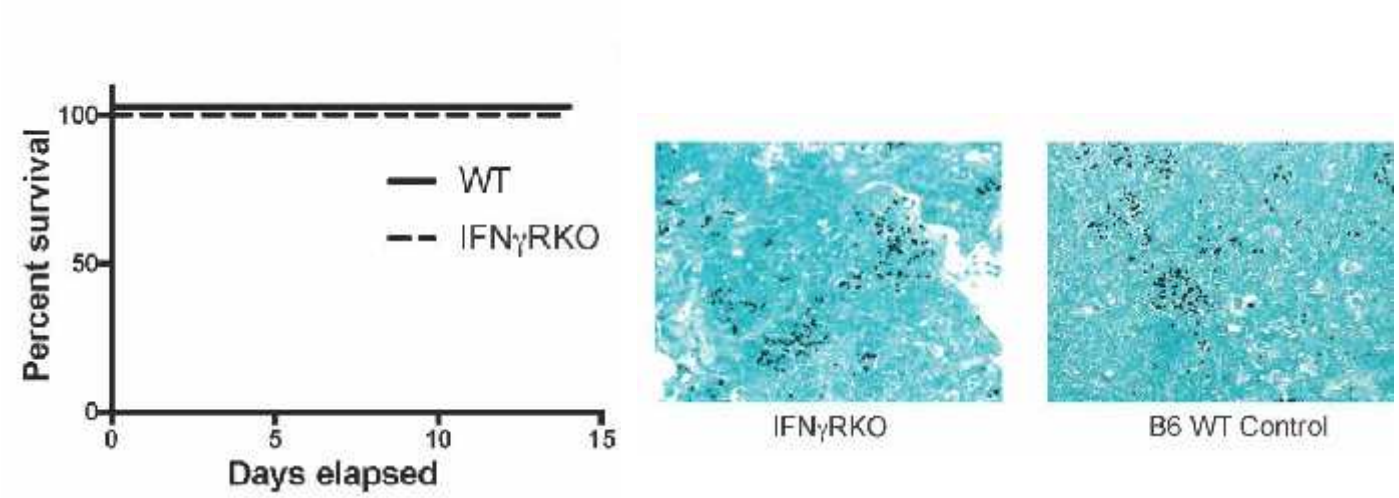
T cell-
talk via
and the
critical for control of
Intracellular fungal
pathogens

- Defects in T cell-Macrophage interplay in patients with infections caused by Cryptococcus and other intracellular pathogens



Lionakis MS& Levitz SM. Annu Rev Immunol. 2018 Apr 26;36:157-191.

IFNγ signaling is redundant in immunity against extracellular fungi (*Aspergillus*)



Espinosa V et al., Sci Immunol. 2017 Oct 6;2(16). pii: eaan5357

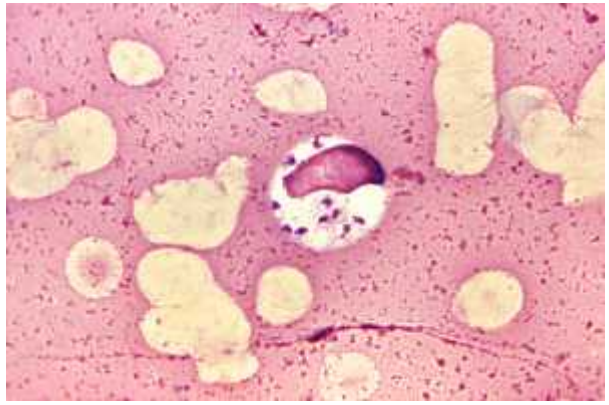
SMKIs associated with development of OIs

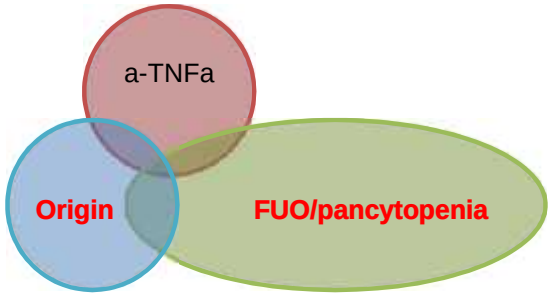
Compound (Year of approval)	Targets	Indications	Comments on type of IFIs
Dasatinib (2006)	BCR-Abl, **Src**, **Lck**, **Fyn**, Kit, EphA2, PDGFRβ	Ph+ CML, ALL	**Several cases of PJP, possible fungal pneumonia, candidemia**, and CMV reactivation
Ruxolitinib (2011)	**JAK 1/2**	Myelofibrosis, PV	Mycobacterial**, fungal (*Cryptococcus*> PJP> Molds> *Candida* esophagitis)**, viral (VZV, PML)
Tofacitinib (2012)	**JAK 1/3**	Rheumatoid arthritis	Disseminated tuberculosis, ***Cryptococcus*, PJP, Candida esophagitis**; disseminated VZV, CMV
Idelalisib (2014)	**PI3Kδ**	Small lymphocytic lymphoma, NHL, CLL	CMV reactivation, **PJP**

Clin Infect Dis. 2018 Jan 6;66(1):140-148; Polvereli et al; AM J Hem 2017; Dioverti et al; Infect Dis 2017; Sylvine P et al., Ann Hematol 2018

Κλινικό παράδειγμα 3

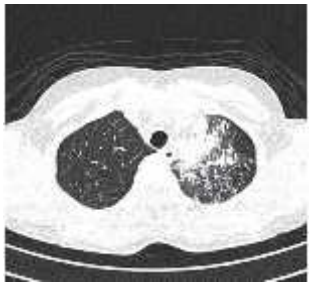
- 70 y/o F from Crete, hx of RA
- On **Infliximab** 18 months and prednisone
- FUO/negative workup
- Persistent fever, worsening pancytopenia
- Bone Marrow Biopsy (+++)

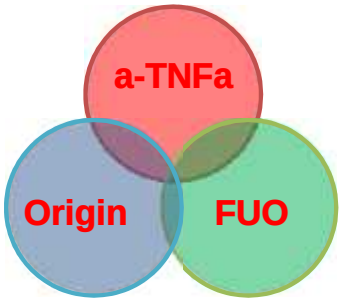




Κλινικό παράδειγμα 4

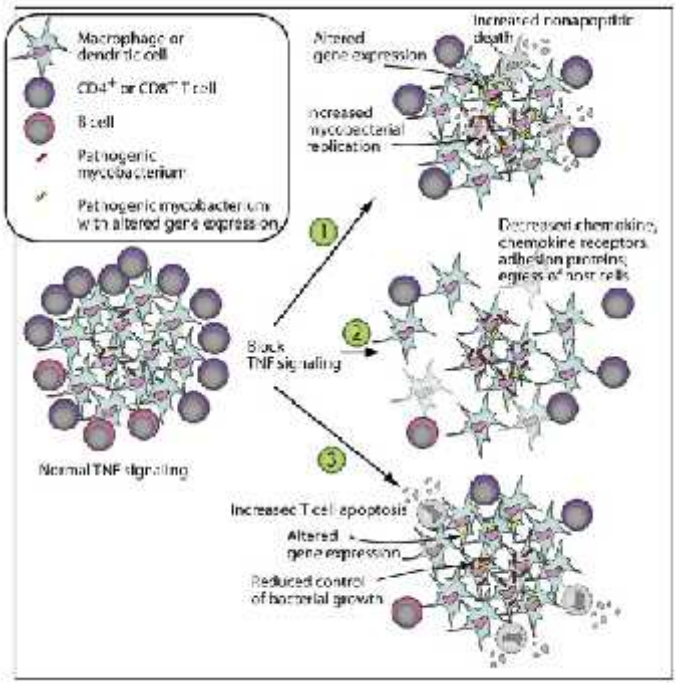
- 41 y/o Indian M, psoriatic arthropathy on **infliximab**
- FUO, severe weight loss
- Extensive workup : CTs, Bcx, sputum Cx, endoscopy (-)
- 5 months later: persistent fever, (+) cough
- CT chest : cavitary RUL mass, numerous bilateral nodules
- mediastinal and supraclavicular LAD
- multiple splenic, liver, kidneys lesions





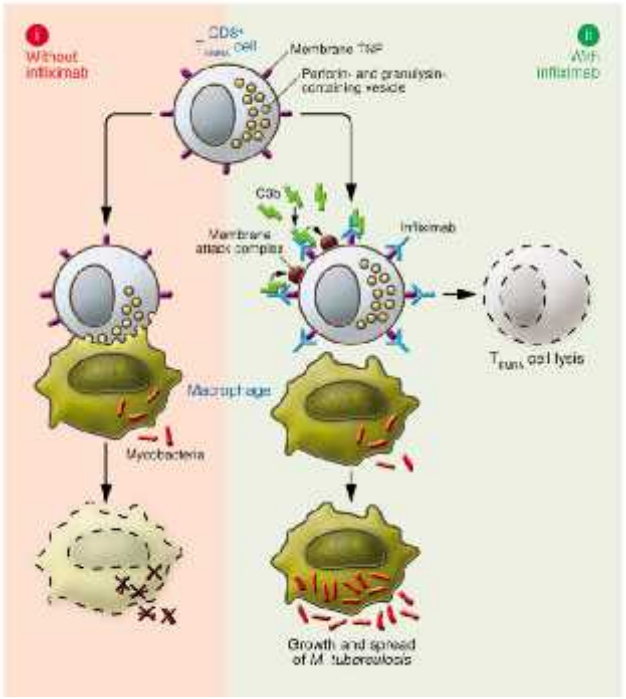
Παθογένεση λοιμώξεων: αναστολείς TNF και φυματίωση

Αναστολή σχηματισμού κοκκιώματος



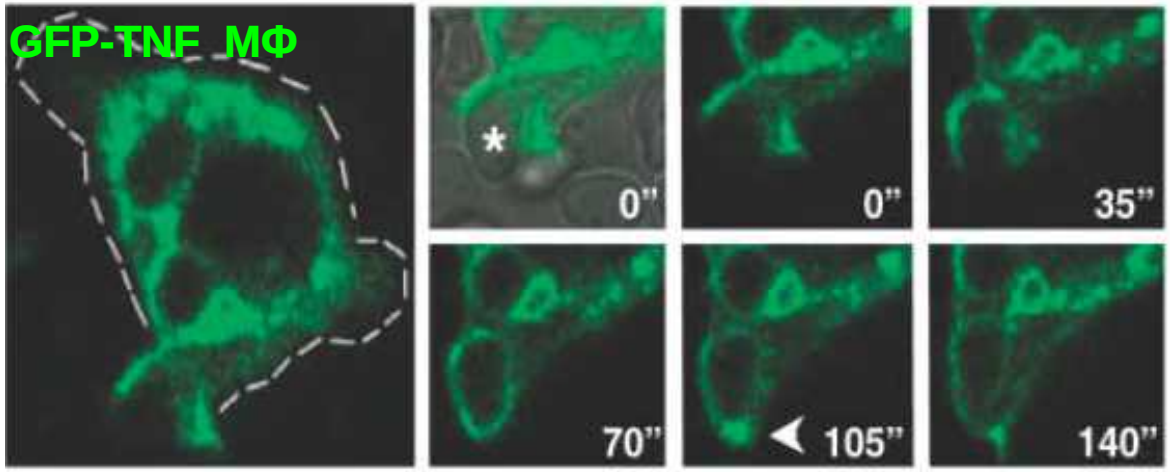
Immunity 2008; 29:175-177

CD8+ T-λεμφοκύτταρα (Granulysin)



J Clin Invest 2009; 119:1079-1082

TNF rapidly accumulates in the phagocytic cup



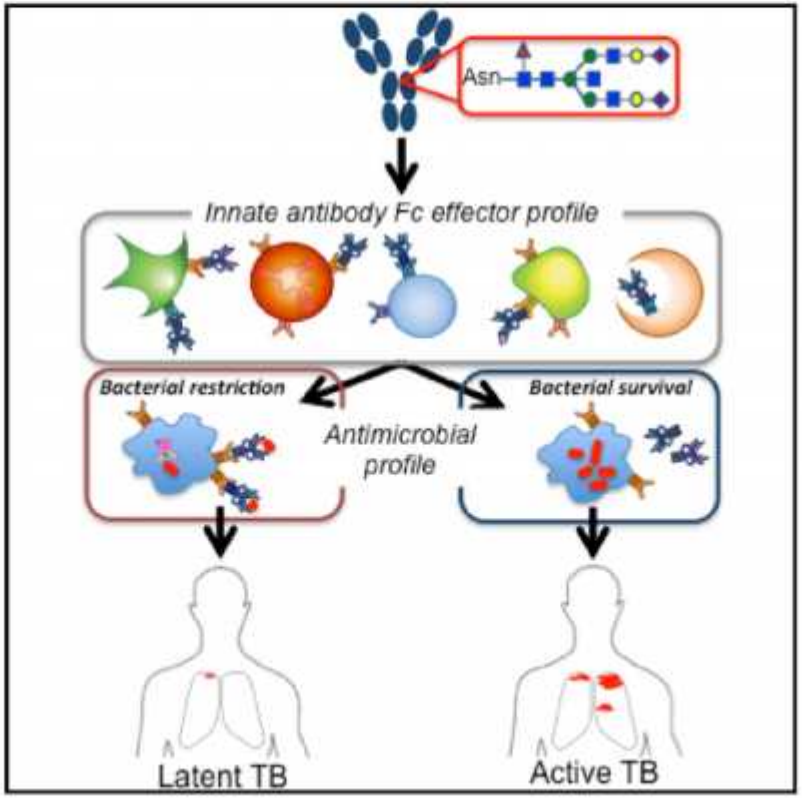
TNF function in the phagosome?

Science. ***2005*** *Dec 2;310(5753):1492-5*

A Functional Role for Antibodies in Tuberculosis

Cell

Lenette L. Lu,[1,2,11] Amy W. Chung,[1,3,11] Tracy R. Rosebrock,[2,11] Musie Ghebremichael,[1] Wen Han Yu,[1,4] Patricia S. Grace,[1] Matthew K. Schoen,[1] Fikadu Tafesse,[1] Constance Martin,[2] Vivian Leung,[2] Alison E. Mahan,[1] Magdalena Sips,[1,6] Manu P. Kumar,[4] Jacquelynne Tedesco,[1] Hannah Robinson,[1] Elizabeth Tkachenko,[1] Monia Draghi,[1] Katherine J. Freedberg,[1] Hendrik Streeck,[5] Todd J. Suscovich,[1] Douglas A. Lauffenburger,[4] Blanca I. Restrepo,[7] Cheryl Day,[8,9,10] Sarah M. Fortune,[2,*] and Galit Alter[1,12,*]



nature medicine

ARTICLES

https://doi.org/10.1038/s41591-019-0441-3

OPEN

IFN-γ-independent immune markers of *Mycobacterium tuberculosis* exposure

Lenette L. Lu[1,2], Malisa T. Smith[3], Krystle K. Q. Yu[3], Corinne Luedemann[2], Todd J. Suscovich[2], Patricia S. Grace[2], Adam Cain[2], Wen Han Yu[2,4], Tanya R. McKitrick[5], Douglas Lauffenburger[4], Richard D. Cummings[5], Harriet Mayanja-Kizza[6], Thomas R. Hawn[3], W. Henry Boom[7], Catherine M. Stein[7,8], Sarah M. Fortune[1,2], Chetan Seshadri[3,9*] and Galit Alter[2,9*]

Exposure to *Mycobacterium tuberculosis* (*Mtb*) results in heterogeneous clinical outcomes including primary progressive tuberculosis and latent *Mtb* infection (LTBI). *Mtb* infection is identified using the tuberculin skin test and interferon-γ (IFN-γ) release assay IGRA, and a positive result may prompt chemoprophylaxis to prevent progression to tuberculosis. In the present study, we report on a cohort of Ugandan individuals who were household contacts of patients with TB. These individuals were highly exposed to *Mtb* but tested negative disease by IFN-γ release assay and tuberculin skin test, 'resisting' development of classic LTBI. We show that 'resisters' possess IgM, class-switched IgG antibody responses and non-IFN-γ T cell responses to the *Mtb*-specific proteins ESAT6 and CFP10, immunologic evidence of exposure to *Mtb*. Compared to subjects with classic LTBI, 'resisters' display enhanced antibody avidity and distinct *Mtb*-specific IgG Fc profiles. These data reveal a distinctive adaptive immune profile among *Mtb*-exposed subjects, supporting an expanded definition of the host response to *Mtb* exposure, with implications for public health and the design of clinical trials.

Conclusions

- Preclinical studies-Basic research on OI pathogenesis
- Basic research on understanding molecular mechanisms of immunodeficiency
- Urgent need for development of novel biomarkers of immunodeficiency

Need for development of functional assays of immune deactivation

nature COMMUNICATIONS

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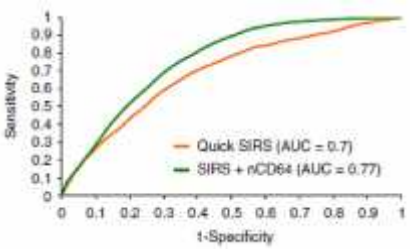
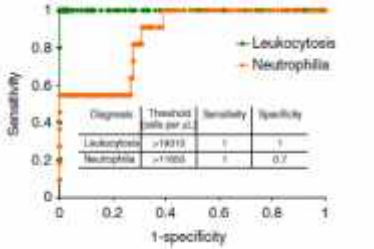
A point-of-care microfluidic biochip for quantification of CD64 expression from whole blood for sepsis stratification

U. Hassan[1,2,3], T. Ghonge[1,3], B. Reddy Jr.[2,3,†], M. Patel[1,3], M. Rappleye[1,3], I. Taneja[1,3,†], A. Tanna[1,3,†], R. Healey[1,3], N. Manusry[1,3], Z. Price[1,3], T. Jensen[3], J. Berger[1,3], A. Hasnain[1,3], E. Flaugher[1,3], S. Liu[1,3], B. Davis[3], J. Kumar[3], K. White[3] & R. Bashir[1,2,3,4]





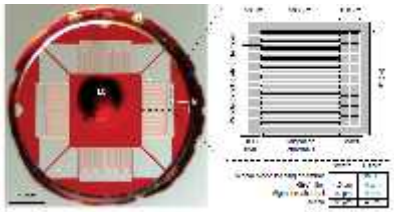
nature biomedical engineering

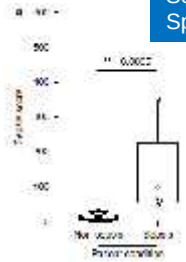
ARTICLES

Diagnosis of sepsis from a drop of blood by measurement of spontaneous neutrophil motility in a microfluidic assay

Felix Ellett[1,2,3,4], Julianne Jorgensen[3,4], Anika L. Marand[1,4], Yuk Ming Liu[2,3,4], Myriam M. Martinez[4], Vicki Sein[3,4], Kathryn L. Butler[3,4], Jarone Lee[3,4,5] and Daniel Irimia[1,2,3,4]*

Sens: 97%
Spec: 98%





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