Top 3 Basic Science Papers on Aspergillus fumigatus 2011



Nir Osherov, Tel-Aviv University, Israel

Let's start with a quiz...

2.



Q1: Which pathogenic fungus has the most scientific papers?





3,031

Q2: Is the number of Aspergillus papers increasing?



4.

Q3: Basic research or bedside? Who has more A. fumigatus papers?



Basic Research

Bedside (Epidemiology, treatment, clinical resistance etc)

Q4: How many Aspergillus papers made it to Nature, Science or Cell? (last 20 years)

97



Surface hydrophobin prevents immune recognition of airborne fungal spores

Vishukumar Aimanianda¹*, Jagadeesh Bayry^{2,3,4}*, Silvia Bozza⁵, Olaf Kniemeyer⁷, Katia Perryko⁹, Sri Ramulu Elluru^{2,3,4}, Cécile Clavaud¹, Sophie Paris¹, Axel A. Brakhaga², Srini V. Kaveri^{2,3,4} unigram territi & Jean-Paul Latgé¹

Discovery of a sexual cycle in the opportunistic fungal pathogen Aspergillus fumigatus 2009

Céline M. O'Gorman^{1,2}, Hubert T. Fuller¹ & Paul S. Dver²

6.

Genomic sequence of the pathogenic and allergenic filamentous fungus Aspergillus fumigatus 2005 William C. Nierman¹, Arnab Pain², Michael J. Anderson², Jennifer R. Wortman¹, H. Stanley Kun², Jarvier Hrög Matthew Berriman², Keietsu Abe², David B. Archer^e, Clara Bermejo⁴, Joan Bennett⁷, Paul Bowyer², Dan Chen¹

Science AAAS

29?

VelB/VeA/LaeA Complex Coordinates Light Signal with Fungal Development and Secondary Metabolism

Özgür Bayram,¹ Sven Krappmann,¹* Min Ni,² Jin Woo Bok,³ Kerstin Helmstandt,^{1,4} Oliver Valerius,¹ Susanna Braus-Stromeyer,¹ Nak-Jung Kwon,² Nancy P. Kelong Kood Jae-Hyuk Yu,² Gerhard H. Braus¹†

Deconstruction of Iterative Multidomain Polyketide Synthase Function

Jason M. Crawford,¹* Paul M. Thomas,² Jonathan R. Scheerer,¹ Anna L. VagdOO8



Modulation of Polyketide Synthase Activity by Accessory **Proteins During Lovastatin** Biosynthesis 1999 Jonathan Kennedy,¹ Karine Auclair,³ Steven G. Kendrew

Cheonseok Park,¹ John C. Vederas,³[†] C. Richard Hutchinson^{1,2}[†]



Mitotic Histone H3 Phosphorylation
by the NIMA Kinase in Aspergillus nidulans

Colin P. C. De Souza, Aysha H. Osmani, Li-Ping Wu,[†] Jeffrey L. Spotts, and Stephen A. Osmani*

2000

Parallel Activation of the NIMA and p34 ^{cdc2}
Cell Cycle-Regulated Protein Kinases
s Required to Initiate Mitosis in A. nidulans

Aysha H. Osmani, Sarah Lea McGuire, and Stephen A. Osmani

1	9	9	1

γ-Tubulin Is a Component of the Spindle Pole Body That Is Essential for Microtubule Function in Aspergillus nidulans				
Berl R. Oakley, C. Elizabeth Oakley, Yisang Yoon, and M. Katherine Jung	1990			

How did I select the three top papers?

1. Pubmed: Aspergillus fumigatus and 2011

7.

SNCBI Resources) How To 🖸	
Publiced.gov US National Library of Medicine National Institutes of Health	PubMed ((Aspergillus fumigatus) A	ND "2011"[Date - Publication] : "2011"[Date - Publication]) / Search lits Advanced
<u>Display Settings:</u> 🖂 Sumr	nary, 20 per page, Sorted by Recently Added	Send to: 🔍
Results: 1 to 20 of	480	<< First < Prev Page 1 of 24 Next > Last >>
TLR3 essentially pro 1. patients.	omotes protective class I-restricted memory CD8	3+ T-cell responses to Aspergillus fumigatus in hematopoietic transplanted
Carvalho A, De Luca Romani L.	a A, Bozza S, Cunha C, D'Angelo C, Moretti S, P	verruccio K, Iannitti RG, Fallarino F, Pierini A, Latgé JP, Velardi A, Aversa F,
Blood. 2011 Dec 6. [Ep PMID: 22147891 [Publ	ub ahead of print] Aed - as supplied by publisher]	
Related citations	ion ac capping of pasients]	



2. Sort basic science papers into 4 categories



Each of the three papers I have chosen was built on the shoulders of many crucial others



Therefore each paper will be represented as part of a larger story



Disclaimer of Opinion

This lecture contains several possibly <u>controversial opinions</u> that you may find <u>offensive</u>. If you are offended by anything in this lecture, please <u>leave a message</u> and I will gladly elaborate. If you feel the need to trash this lecture, at least <u>make it funny</u>. Thank you! nosherov@post.tau.ac.il

Story 1: What stresses does *A. fumigatus* encounter in the infected lung? Can we use this knowledge to improve treatment?

10.



What conditions does *A. fumigatus* encounter during lung infection?

11



¹²During infection, *A. fumigatus* scavenges iron by secreting siderophores



Schrettl and Haas Curr. Op. Microbiol. 14:400 2011

13.

Can we use this knowledge to diagnose Aspergillosis?

Paper #1

⁶⁸Ga-Siderophores for PET Imaging of Invasive Pulmonary Aspergillosis: Proof of Principle

Milos Petrik¹, Hubertus Haas², Georg Dobrozemsky¹, Cornelia Lass-Flörl³, Anna Helbok¹, Michael Blatzer², Hermann Dietrich⁴, and Clemens Decristoforo¹

Innsbruck Medical University, Innsbruck, Austria,

J Nucl Med 2010; 51:639-645

In vitro and in vivo evaluation of selected ⁶⁸ Ga-siderop	hores
for infection imaging $\stackrel{\text{tr}}{\to}$	NUCLEAR
Milos Petrik ^a , Hubertus Haas ^b , Markus Schrettl ^b , Anna Helbok ^a ,	MEDICINE — AND —
Michael Blatzer ^b , Clemens Decristoforo ^a ,* (2011)	BIOLOGY

The experiment and rationale:

14.

Therefore, we

attempted to use the same siderophores radiolabeled with ⁶⁸Ga as Trojan horses to allow specific imaging of the infection process.



Petrik ey al. J. Nucl. Med. 51:639 2010

15.

The results:



Infection: Severe Mild

Negative Petrik ey al. J. Nucl. Med. 51:639 2010

Story 2: What are the body's main lines of defense against A. fumigatus?



16.

^{17.} What are NK (natural killer) cells?



Mehrad group: Morrison et al. J. Clin Invest. 112:1862 2003; Park et al. J. Imm. 182:4306 2009

18. Paper #2

Human Natural Killer Cells Exhibit Direct Activity Against *Aspergillus fumigatus* Hyphae, But Not Against Resting Conidia

The Journal of Infectious Diseases 2010;203:430-435

Stanislaw Schmidt,¹ Lars Tramsen,¹ Mitra Hanisch,¹ Jean-Paul Latgé,² Sabine Huenecke,¹ Ulrike Koehl,¹ and Thomas Lehrnbecher¹

Goethe University, Frankfurt, Germany

Human NK Cells Display Important Antifungal Activity against Aspergillus fumigatus, Which Is Directly Mediated by IFN- γ Release

J Immunol 2011;187;1369-1376 Maria Bouzani,* Michael Ok,* Allison McCormick,[†] Frank Ebel,[†] Oliver Kurzai,^{‡,§} C. Oliver Morton,[¶] Hermann Einsele,* and Juergen Loeffler*

HKI, Jena, Germany

19.

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20.

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How does IFN-γ Kill AF?

Story 3: Are any completely new classes of antifungals being developed?

Antifungals: Growing needs, few choices



mBiamer

NEXSTAR

21.



- Amphotericin B, Azoles, Candins
- Pharma research down
- •Basic Research up





NOXAF



Novel inhibitors that block incorporation of cell wall proteins into the fungal cell wall

23.



Paper #3

Efficacy of Oral E1210, a New Broad-Spectrum Antifungal with a Novel Mechanism of Action, in Murine Models of Candidiasis, Aspergillosis, and Fusariosis⁷

Katsura Hata,¹* Takaaki Horii,¹ Mamiko Miyazaki,¹ Nao-aki Watanabe,¹ Miyuki Okubo,² Jiro Sonoda,² Kazutaka Nakamoto,³ Keigo Tanaka,¹ Syuji Shirotori,³ Norio Murai,³ Satoshi Inoue,³ Masayuki Matsukura,³ Shinya Abe,⁴ Kentaro Yoshimatsu,⁵ and Makoto Asada⁵

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4543-4551 Vol. 55, No. 10

E1210, a New Broad-Spectrum Antifungal, Suppresses Candida albicans Hyphal

Growth through Inhibition of Glycosylphosphatidylinositol Biosynthesis

Nao-aki Watanabe*, Mamiko Miyazaki, Takaaki Horii, Koji Sagane, Kappei Tsukahara,

and Katsura Hata AAC Accepts, published online ahead of print on 5 December 2011 Antimicrob. Agents Chemother. doi:10.1128/AAC.00731-11



Mode of action (candida)

>Inhibits inositol acylation by Gwt1p in vitro



Reduces: > Switch > Biofilm > Adhesion





In vitro

MIC ~ 10 ng/ml
Azole ^R
Fungistatic
Low toxicity (mammalian cells)



Orally available Non toxic (10X/1 week) T1/2 = 2.2 h

Hata et al., AAC 55:4543 2011

27. Conclusion: Panning for novel antifungals is now attainable at the RESEARCH Lab level





Thank you for your attention!