

PACCARB Presentation

# Fungi, Climate Change, Drug Resistance

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# The Fungal Kingdom

- > 6 million species
- Includes major pathogens of plants, insects, invertebrates and ectothermic vertebrates
- Fungi currently devastating major ecosystems
  - Bats devastated by 'white nose syndrome'
  - Catastrophic amphibian declines from *Batrachochytrium dendrobatidis*
  - Salamanders declines in Europe from *Batrachochytrium salamandrivorans*
  - Snakes in North America
- Mammals are remarkably resistant!

# Relatively few fungal species are pathogenic for humans

## Host Associated



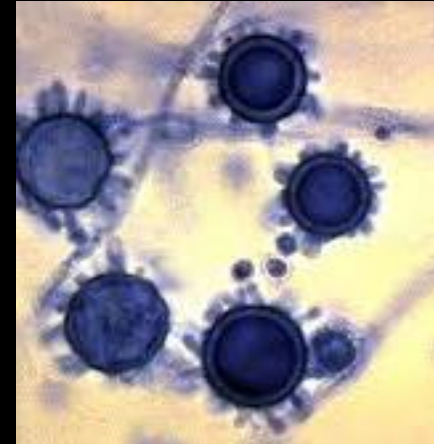
*Candida* spp.



Dermatophytes



*Pneumocystis* spp.



*Histoplasma* spp.

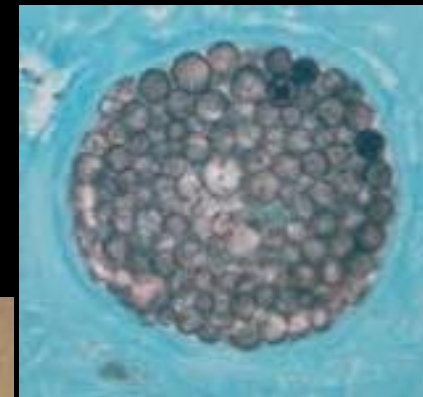


*Aspergillus* spp.

## Environment



*Cryptococcus* spp.



*Coccidioides* spp.



*Blastomyces* spp.

# Requirements for Fungal Human Pathogenicity

## Thermotolerance

- Host associated such as *Candida* spp. already thermotolerant
- Only 6% of species in environment can tolerate > 37 °C (Robert & Casadevall JID 2009)
- Only a few 'major' pathogenic fungi (*Aspergillus*, *Cryptococcus*, *Histoplasma*, *Sporothrix*, *Coccidioides* spp.)

## Survival in host and replication

- "Virulence factors"
- Survive, replicate and evade immune mechanisms
- Highly varied...

Capsules

Toxins

Antioxidant systems

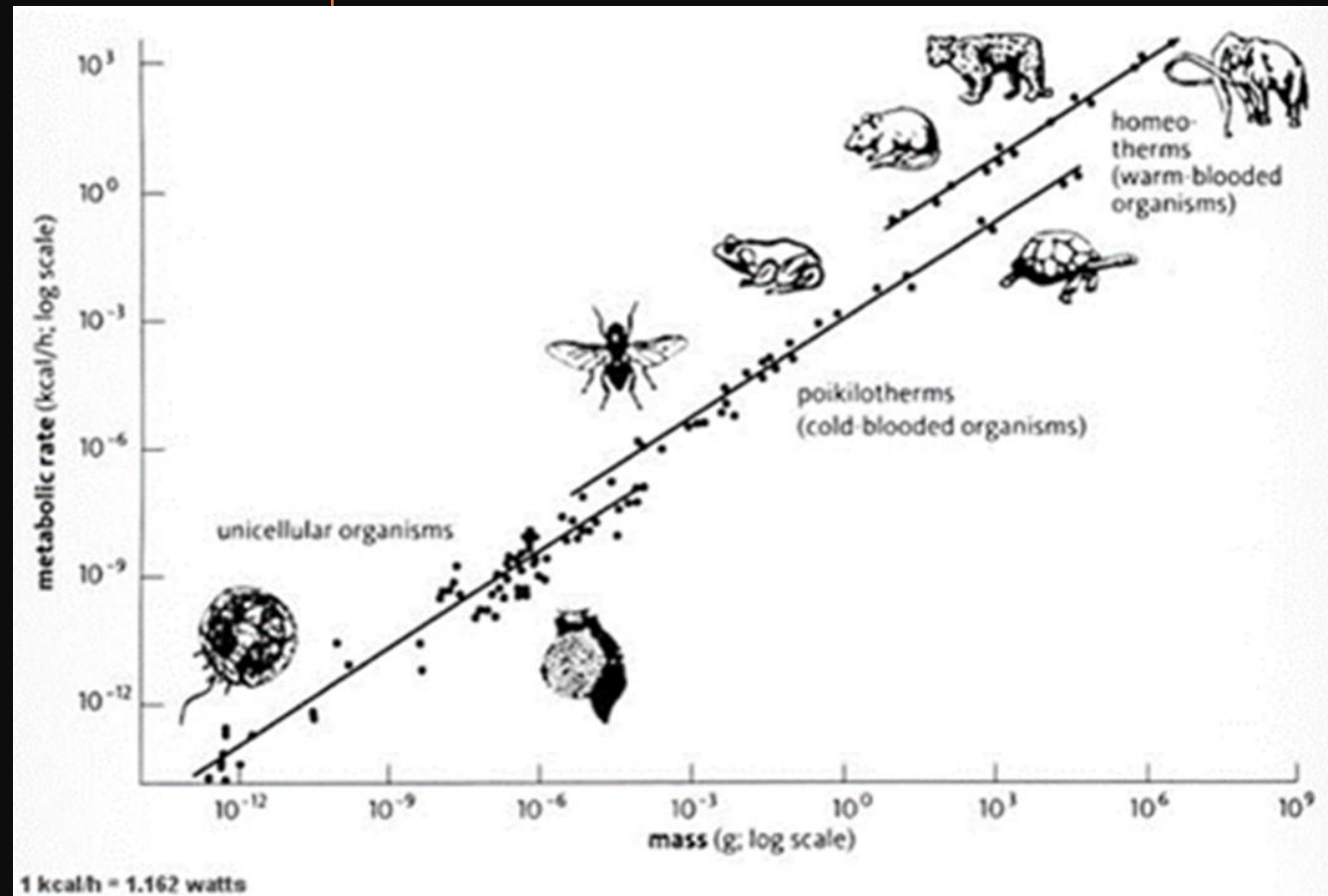
Intracellular replication

Stress resistance

etc., etc., etc.

# Mammalian Lifestyle

- Mammalian lifestyle is very expensive
- Mammals very minor class until 65 mY ago
- Great mammalian radiation after K/T event
- How did this unfavorable lifestyle become dominant?



# THE POST-IMPACT WORLD

## Indication of Global Deforestation at the Cretaceous-Tertiary Boundary by New Zealand Fern Spike

Vivi Vajda,<sup>1\*</sup> J. Ian Raine,<sup>2</sup> Christopher J. Hollis<sup>2</sup>

The devastating effect on terrestrial plant communities of a bolide impact at the Cretaceous-Tertiary boundary is shown in fossil pollen and spore assemblages by a diverse flora being abruptly replaced by one dominated by a few species of fern. Well documented in North America, this fern spike signals widespread deforestation due to an impact winter or massive wildfires. A Southern Hemisphere record of a fern spike, together with a large iridium anomaly, indicates that the devastation was truly global. Recovery of New Zealand plant communities followed a pattern consistent with major climatic perturbations occurring after an impact winter that was possibly preceded by global wildfires.

Science 2002



- FIRES, SMOKE, DUST OBSCURES SUN
- PHOTOSYNTHESIS SHUT DOWN FOR > 6 MONTHS
- GLOBAL TEMPERATURES DROP

## Fungal Proliferation at the Cretaceous-Tertiary Boundary

Vivi Vajda<sup>1</sup> and Stephen McLoughlin<sup>2</sup>

The evolution of life on Earth has been interrupted by several mass extinction events. The Cretaceous-Tertiary (K-T) extinction (65 million years ago (Ma)) is associated with the impact of a large bolide (1). On the basis of extensive

undescribed species of fungi (7) (Fig. 1A). Overlying laminae contain low-diversity, fern-dominated assemblages. No significant macroscopic changes or clastic partings occur within the coal to suggest a change in sedimentation rate or depositional setting across the

This fungi-rich interval implies a dieback of photosynthetic vegetation at the K-T boundary in this region. The peak is interpreted to represent an increase in the available substrate for saprophytic organisms (which are dependent on photosynthesis) provided forest dieback after the Chicxulub impact (5). Post-impact conditions of high and reduced solar insolation due to atmospheric sulfur aerosols and would have favored saprophyte as this interval would have been short-lived.

Science 2003



VEGETATION DIEOFF = FUNGAL PROLIFERATION  
FUNGAL PROLIFERATION = SPORE PROLIFERATION  
SPORE PROLIFERATION = LARGE INOCULA  
ENDOTHERMY = RESISTANCE TO FUNGAL DISEASE

# THE POST-IMPACT WORLD

Fungal virulence, vertebrate endothermy, and dinosaur extinction:  
is there a connection?

Arturo Casadevall\*

**FUNGAL GEN BIOL 2005**

# THE POST IMPACT WORLD ADVANTAGE: MAMMALS



REPTILIAN MEGAFAUNA KILLED BY:

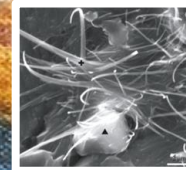
- IMPACT BLAST
- DISRUPTION IN FOOD SOURCES
- CHILLING OF THE PLANET
- FUNGAL DISEASES?



REPTILES FIGHT OFF FUNGAL INFECTIONS WITH INDUCED FEVERS BUT THERE WAS NO SUN



REPTILIAN EGGS SUSCEPTIBLE TO FUNGAL DISEASES



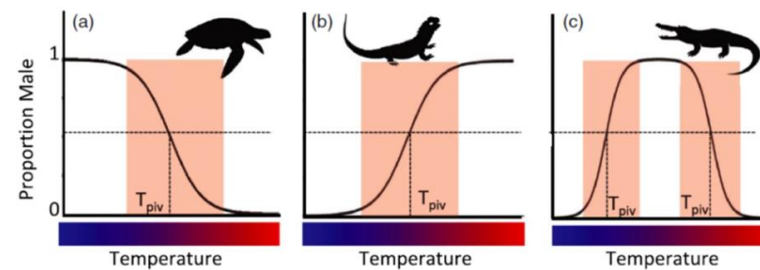
Endolithic fungi: A possible killer for the mass extinction of Cretaceous dinosaurs

GONG YIMing<sup>1,2\*</sup>, XU Ran<sup>1</sup> & HU B<sup>1</sup>

CHINESE EARTH SCIENCES 2008



As temperatures drop  
Ectotherms cannot move  
Or digest their food



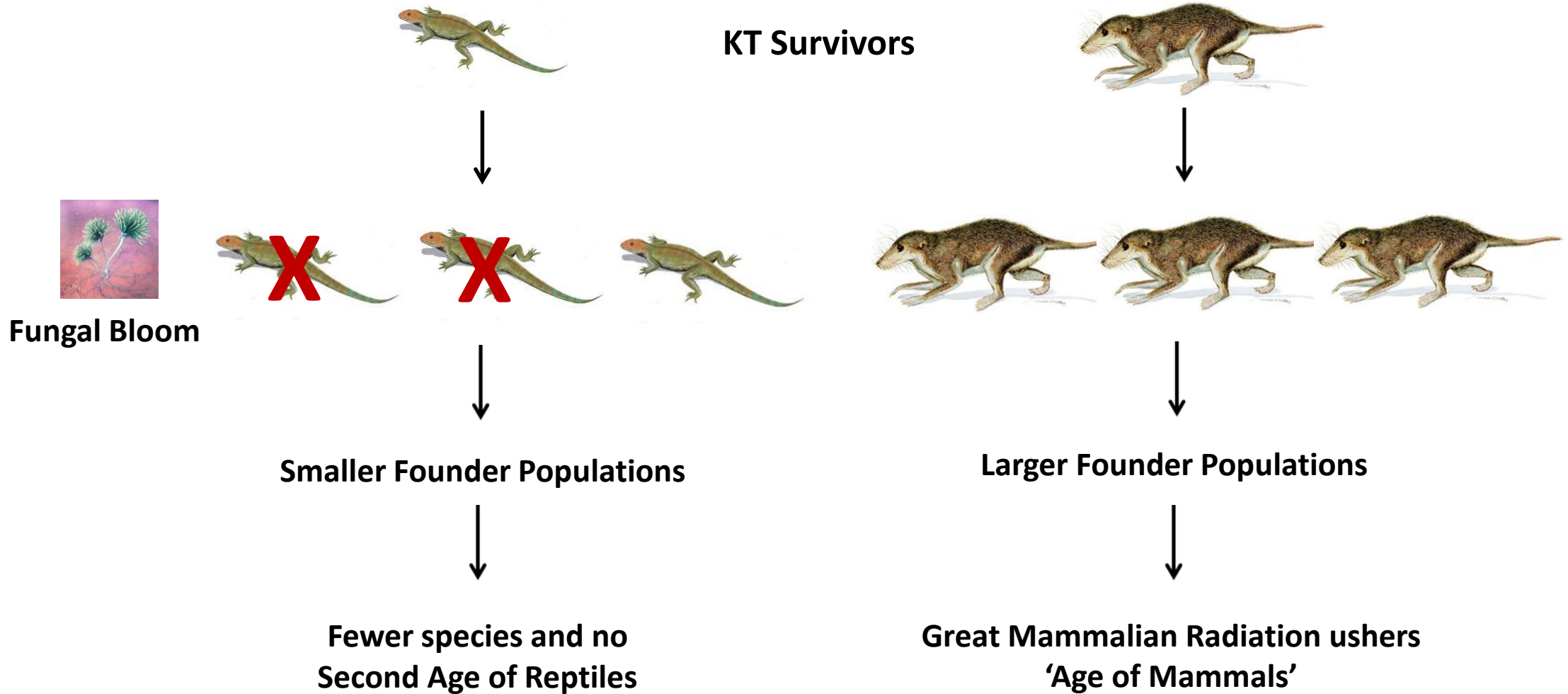
Temperature changes have profound effect on reptilian sex Ratios (Evolutionary Applications 2021)



Small mammals would have  
Been able to move and forage  
Due to their endothermy



# Fungal Infection Mammalian Selection (FIMS)



PEARLS

## Updating the fungal infection-mammalian selection hypothesis at the end of the Cretaceous Period

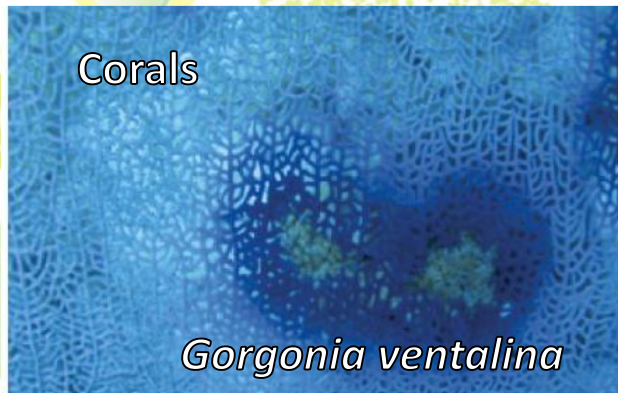
Arturo Casadevall <sup>1\*</sup>, Chris Damman <sup>2,3</sup>

1 Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, United States of America, 2 The Bill & Melinda Gates Foundation, Seattle, Washington, United States of America, 3 University of Washington, Seattle, Washington, United States of America

\* [acasade1@jhu.edu](mailto:acasade1@jhu.edu)

What is the evidence that  
endothermy protects  
against fungal disease?

# Ectothermic organisms vulnerable to fungal diseases



**Emerging fungal threats to animal, plant and ecosystem health**

Matthew C. Fisher<sup>1</sup>, Daniel A. Henk<sup>1</sup>, Cheryl J. Briggs<sup>2</sup>, John S. Brownstein<sup>3</sup>, Lawrence C. Madoff<sup>4</sup>, Sarah L. McCraw<sup>5</sup> & Sarah J. Gurr<sup>5</sup>

# Human fungal diseases are far more common in cooler parts than systemic infections



**Nail fungus**



**Athlete's Foot**

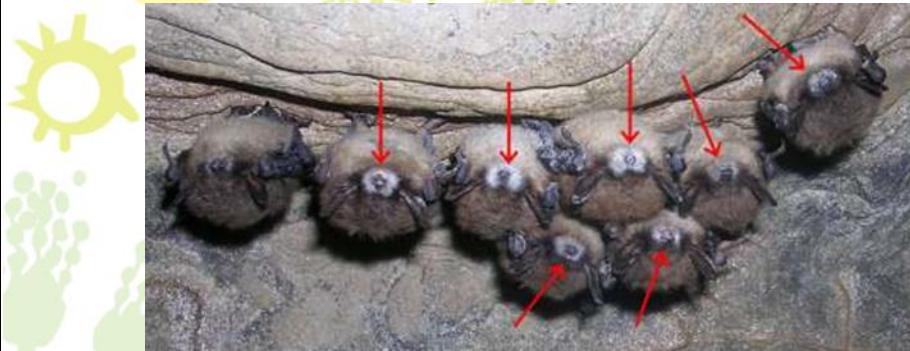


**Dandruff**



**Fungal Diaper Rash**

# White Nose Syndrome in Bats



04/07/09  
**Bat White Nose Syndrome (WNS)**  
**Occurrence by County\***

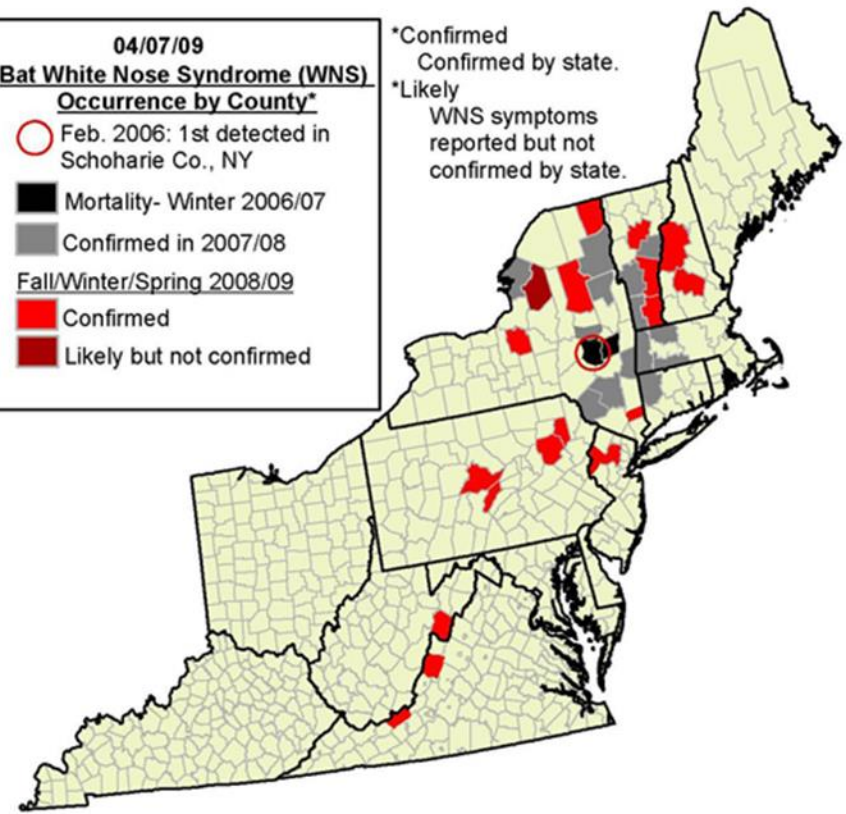
- Feb. 2006: 1st detected in Schoharie Co., NY
- Mortality- Winter 2006/07
- Confirmed in 2007/08

Fall/Winter/Spring 2008/09

- Confirmed
- Likely but not confirmed

\*Confirmed  
Confirmed by state.

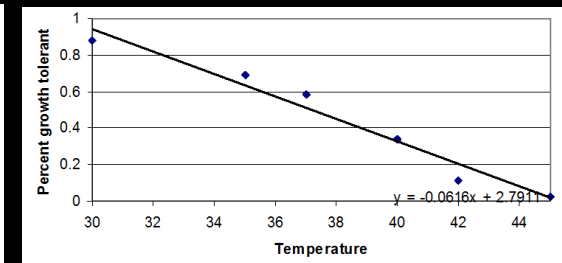
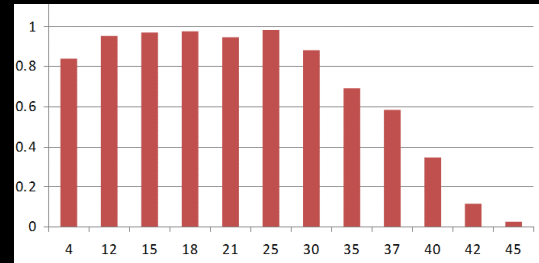
\*Likely  
WNS symptoms reported but not confirmed by state.



**AS BATS HIBERNATE TEMPERATURE DROPS TO 10-12 C AND THEY BECOME SUSCEPTIBLE TO GEOMYCES spp.**

# Mammalian temperatures reflect optima in the tradeoff of food consumption vs. protection against fungi

- Being 'hot' is a tradeoff
- Birds are resistant to fungi
- Primitive mammals (e.g. platypus) susceptible



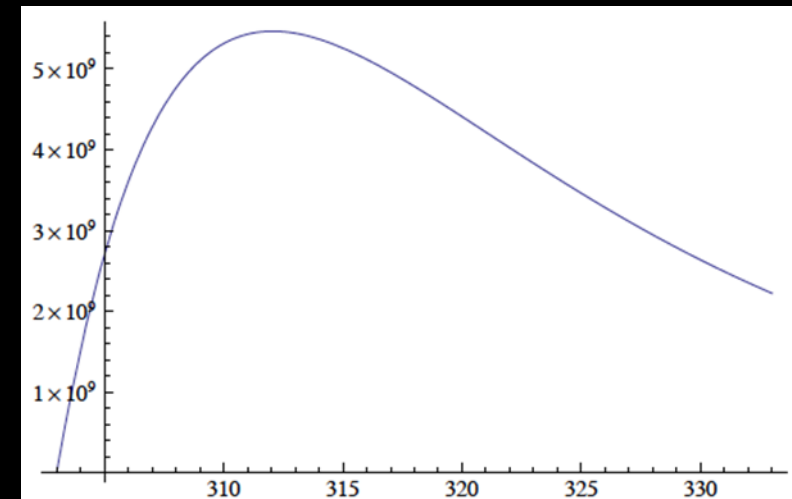
Vicent Robert

Robert & Casadevall, JID 2009

Cost  $B(T) \propto M^{3/4} e^{-E_i/kT}$

Benefit  $F(T) \propto F_0 [1 - (1 - s)^T]$

Maxima: 36.7 C



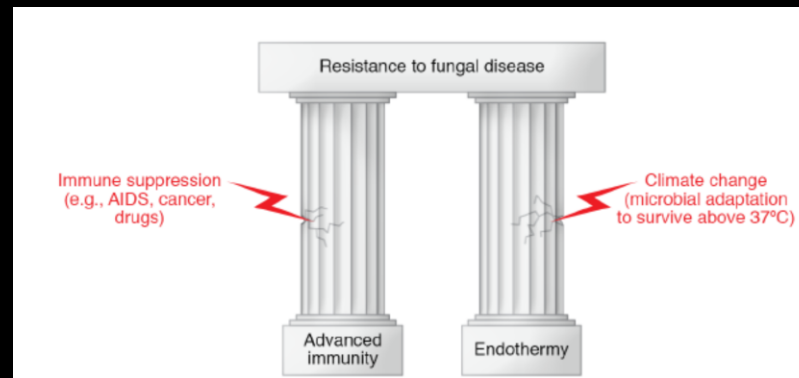
Bergman & Casadevall, mBio 2010



Aviv Bergman

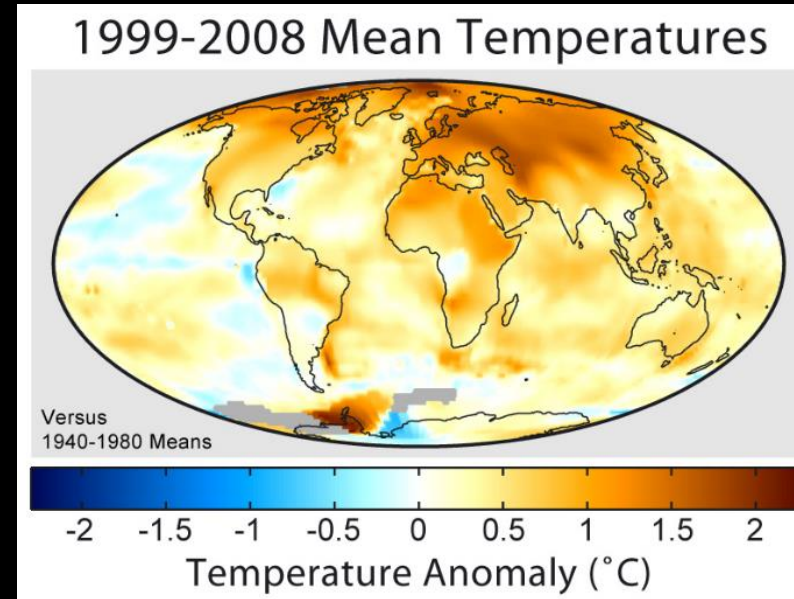
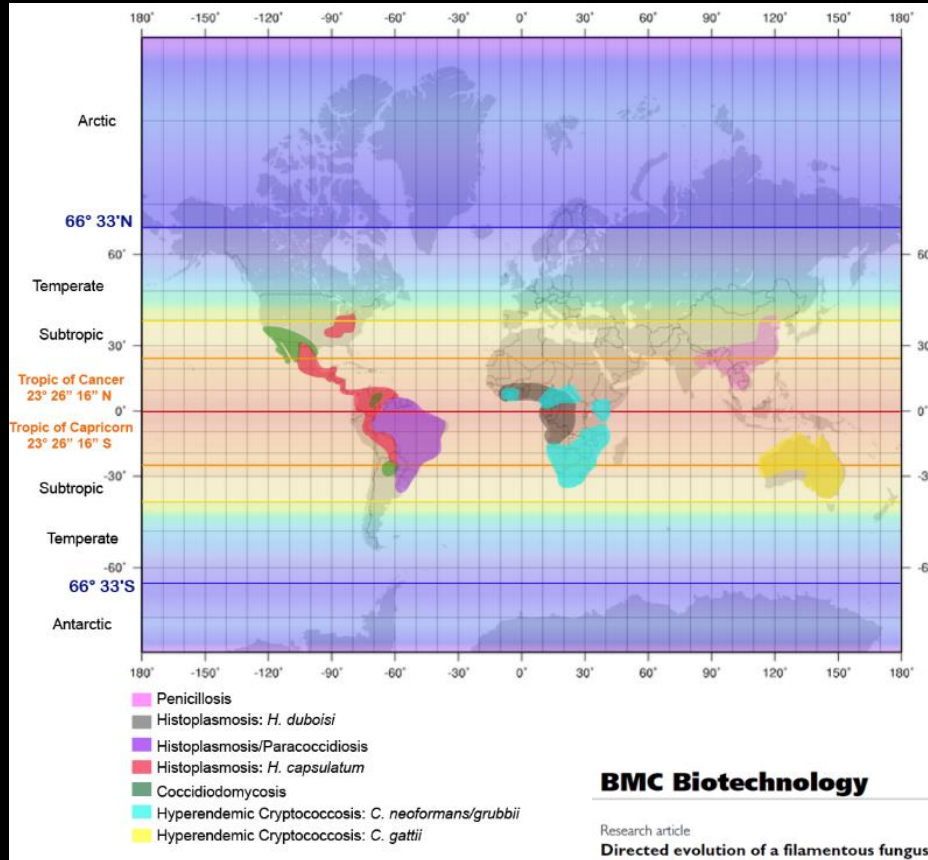
# Fungal Infection Mammalian Selection (FIMS) Theory has Explanatory Power

- Internally consistent – no obvious contradictions or pushback
- Provides a selection mechanism of energetically costly lifestyle
- Explains why most mammalian temperatures in high 30's C
- Explains the tremendous resistance of mammals to fungal disease
- Posits endothermy as major host defense mechanism
- Explains minor role for fever as protective mechanisms in modernity





# GEOGRAPHIC FACTS: MOST ENDEMIC MYCOSES OCCUR IN TROPICAL AND SUB-TROPICAL REGIONS



## BMC Biotechnology

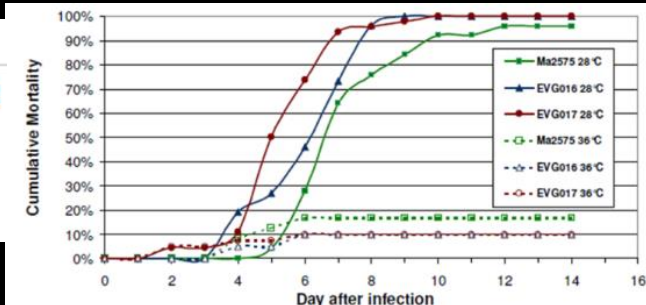
Research article  
**Directed evolution of a filamentous fungus for thermotolerance**  
Eudes de Crecy<sup>1</sup>, Stefan Jaronski<sup>2</sup>, Benjamin Lyons<sup>1</sup>, Thomas J Lyons<sup>1</sup> and Nemat O Keyhani<sup>1\*3</sup>

Address: <sup>1</sup>Evolvegate LLC, 2153 SE Hawthorne Road, 15 Gainesville, FL 32641, USA; <sup>2</sup>USDA ARS NPARRL, 1500 N. Central Ave., Sidney MT 59270, USA and <sup>3</sup>Department of Microbiology and Cell Science, University of Florida, Gainesville, FL 32611, USA  
Email: Eudes de Crecy - ead@evolvegate.com; Stefan Jaronski - stefan.jaronski@ars.usda.gov; Benjamin Lyons - blyons@evolvegate.com; Thomas J Lyons - tomlyons@evolvegate.com; Nemat O Keyhani<sup>1</sup> - keyhani@ufl.edu

\* Corresponding author



Open Access



## Global Warming Will Bring New Fungal Diseases for Mammals

Monica A. Garcia-Solache and Arturo Casadevall

Albert Einstein College of Medicine of Yeshiva University, Department of Microbiology and Immunology, Bronx, New York, USA

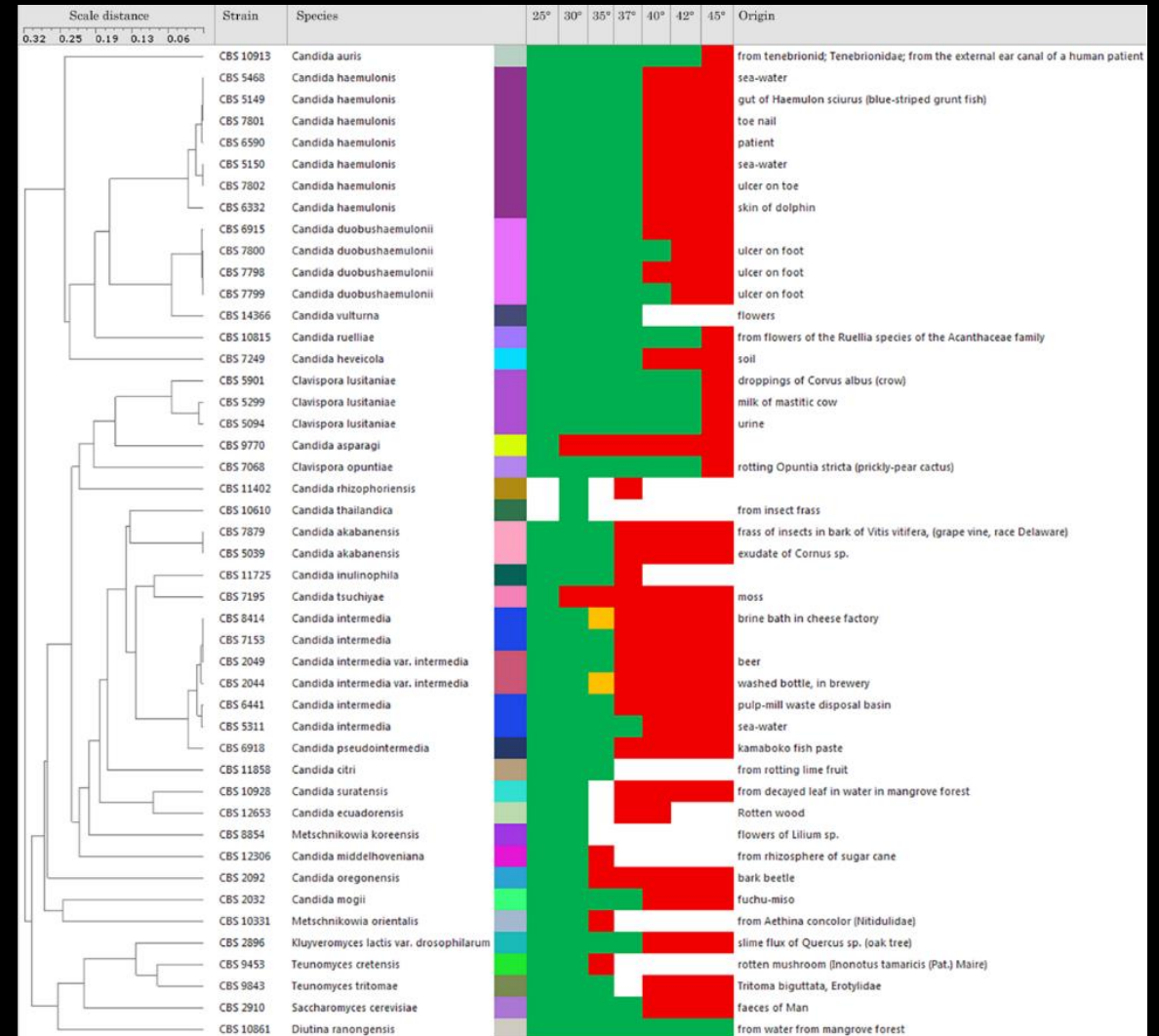
DEADLY GERMS, LOST CURES

### *A Mysterious Infection, Spanning the Globe in a Climate of Secrecy*

The rise of *Candida auris* embodies a serious and growing public health threat: drug-resistant germs.

# *Candida auris*: first example of fungal species becoming pathogenic for humans by breaking through the mammalian thermal barrier?

- Resistant to most commonly used antifungal drugs
- Not known to medicine prior to 2007
- Emerged simultaneously in three continents (Venezuela, South Africa, India)
- Isolates from the three locations are genetically very distant





# Some *Candida auris* environmental isolates are less thermotolerant than clinical isolates

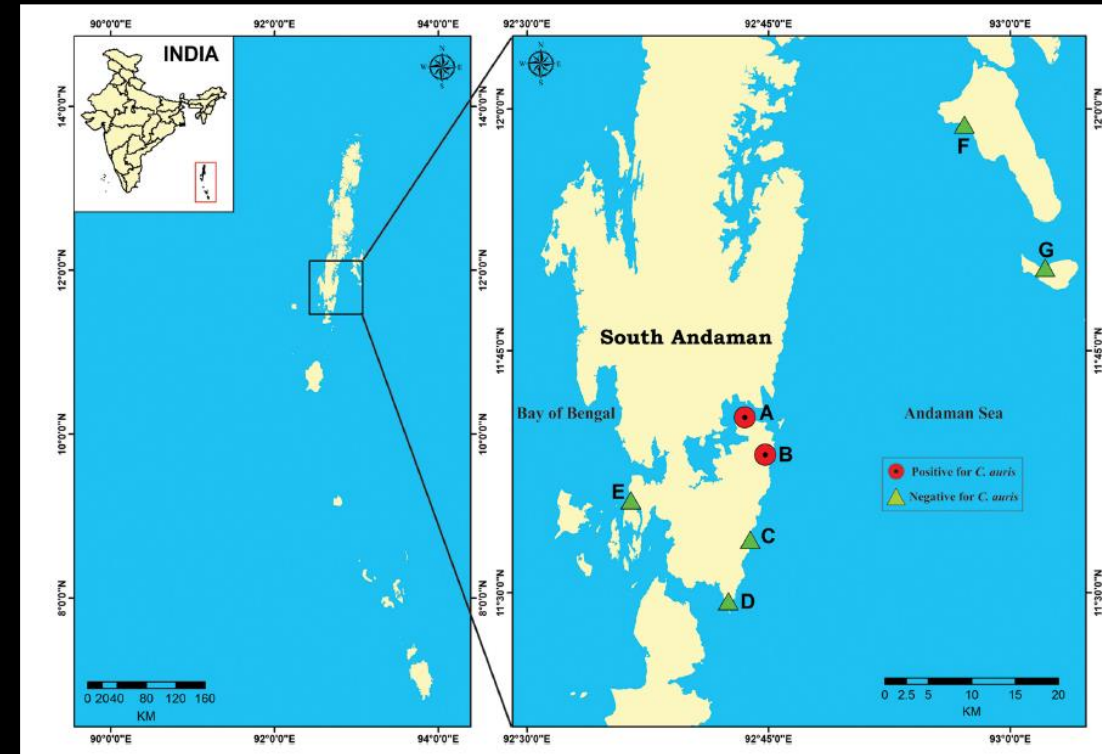
## Environmental Isolation of *Candida auris* from the Coastal Wetlands of Andaman Islands, India

Parth Arora,<sup>a,b</sup> Prerna Singh,<sup>a</sup> Yue Wang,<sup>c</sup> Anamika Yadav,<sup>a</sup> Kalpana Pawar,<sup>a</sup> Ashutosh Singh,<sup>a</sup> Gadi Padmavati,<sup>b</sup>  Jianping Xu,<sup>c</sup>  Anuradha Chowdhary<sup>a</sup>

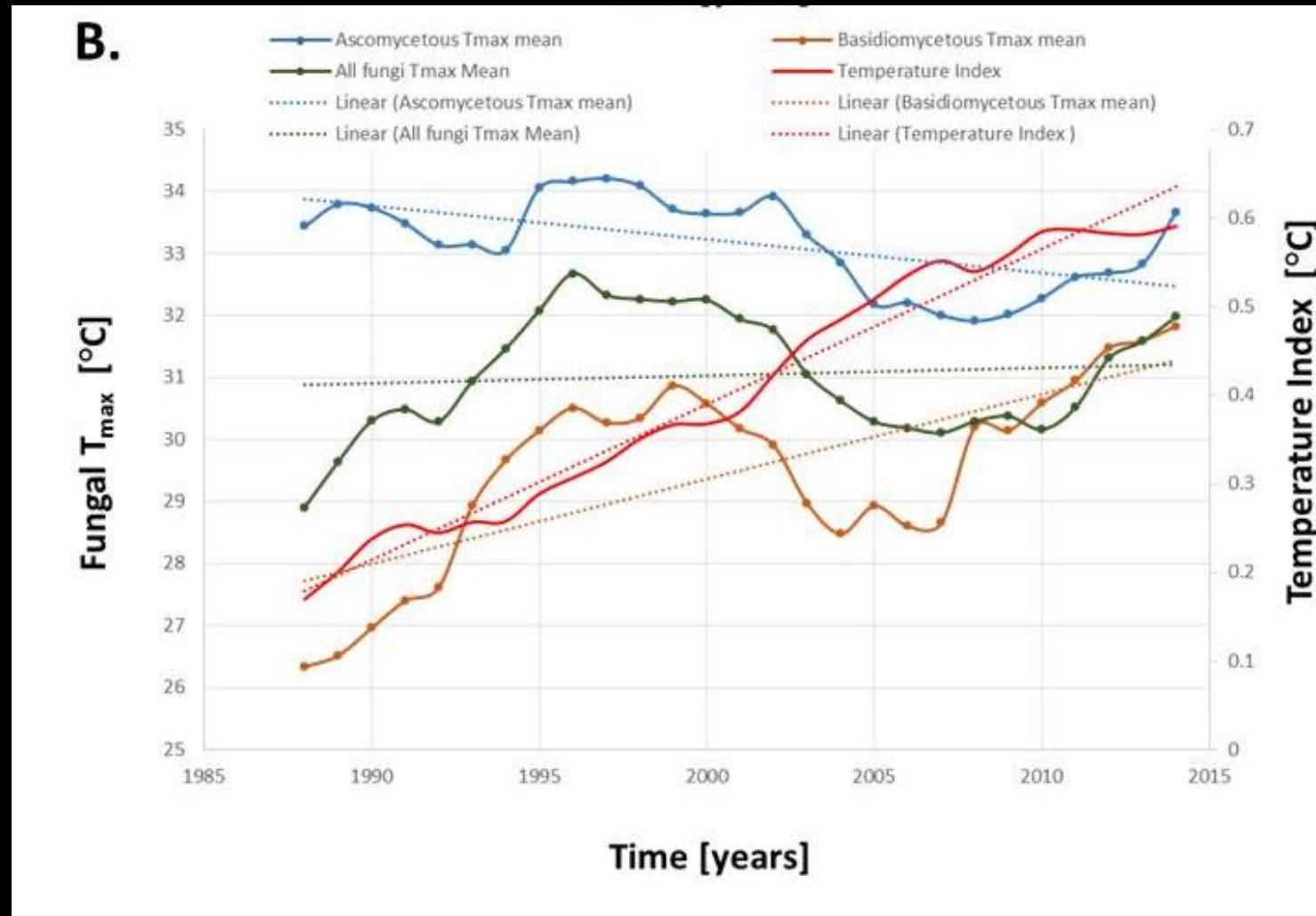
mBio 2021

## Environmental *Candida auris* and the Global Warming Emergence Hypothesis

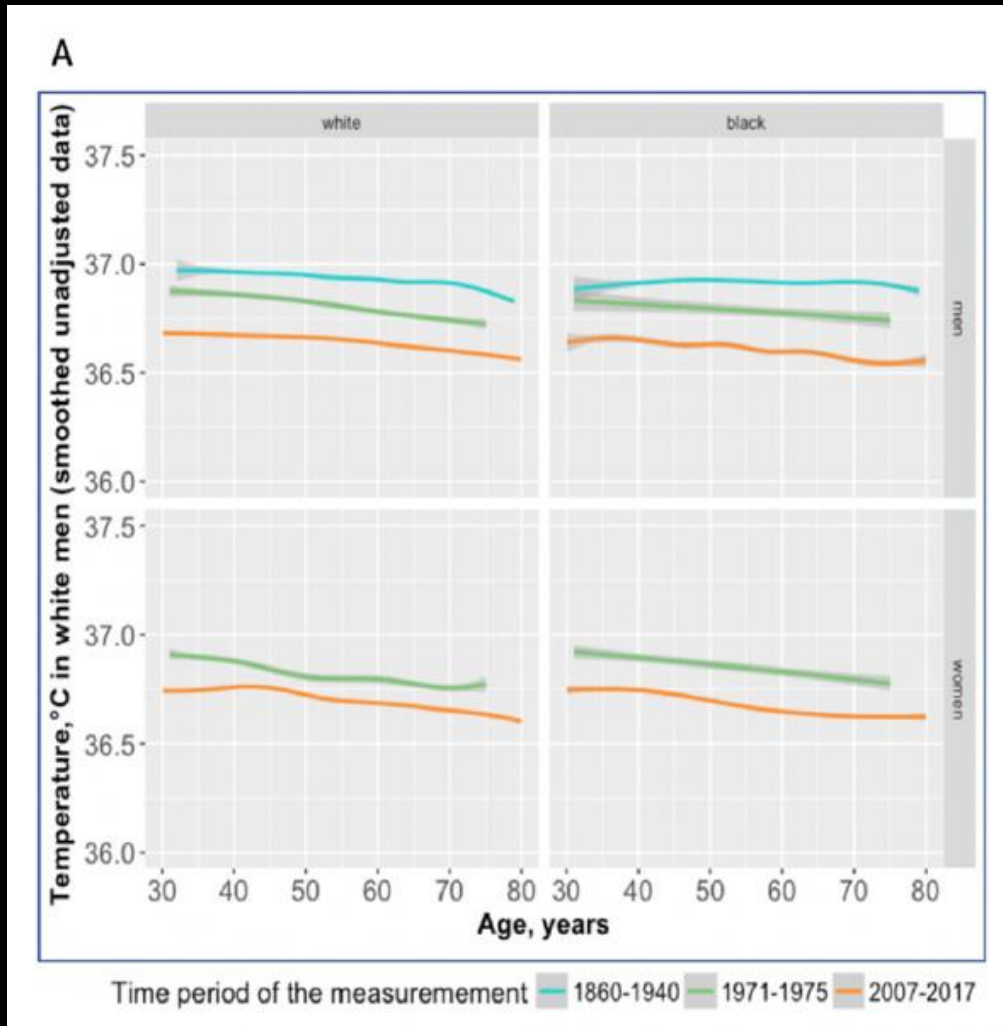
 Arturo Casadevall,<sup>a</sup>  Dimitrios P. Kontoyiannis,<sup>b</sup> Vincent Robert<sup>c</sup>



# AVERAGE FUNGAL THERMAL TOLERANCES OVER PAST 30 YEARS



# Human Core Temperatures have Dropped in past century



## Decreasing human body temperature in the United States since the Industrial Revolution

Myroslava Protsiv<sup>1</sup>, Catherine Ley<sup>1</sup>, Joanna Lankester<sup>2</sup>, Trevor Hastie<sup>3,4</sup>, Julie Parsonnet<sup>1,5\*</sup>

# Closing Thoughts

- The thermal barrier that protects mammals is narrowing as world is getting warmer, the fungi are adapting to higher temperatures, human are getting colder...I think this means **TROUBLE** ahead
- When you think of global warming, focus on the number of very hot days, not average temperatures. Each very hot day provides an event for fungal adaptation and selection.
- New fungal diseases are predicted to emerge. *C. auris* may have been the first...the proverbial canary in the coal mine.