How antifungal drugs kill fungi and cure disease

Snake-oil Salesmen

New Product Devours Candida-Yeast Without Major Dietary Change

Do you suffer from **depression**, **anxiety**, **irritability**, **heartburn**, **indigestion** and **bloating**, **constipation**, **foul breath**, rashes, **lethargy**, **some food and environmental allergies**, **acne**, dry flaky skin, jock itch, or vaginal infections?

If you do, there is a good chance you could have an overgrowth of Candida and other unfriendly bacteria flourishing in your intestinal tract.

A groundbreaking product was released in Japan that actually eats Candida-yeast and brings your inner ecology back to normal, all without having to go on special diets that are impossible to follow.

The secret behind this product's effectiveness is the micro-encapsulation process that gets live lactic acid producing bacteria safely past the acidic environment in the stomach.

These oxygen-loving bacteria go to work creating an environment that is unfriendly to anaerobic problem organisms such as Candida. Many people who have suffered for years and tried everything on the market with little to no success report amazing results in the first few days. Reference reveals source to buy wholesale. $5.00

Types of fungal disease

- Skin infections: e.g. foot fungus (usually smelly but not life threatening, sometimes becomes serious), ring worm
- Mucosal infections: oral or vaginal (range from annoying to painful to very difficult; uncomfortable but rarely life threatening)
- Systemic infections: fungus in the blood and tissues (immunocompromised population, usually life threatening)

Onychomycosis: foot fungus

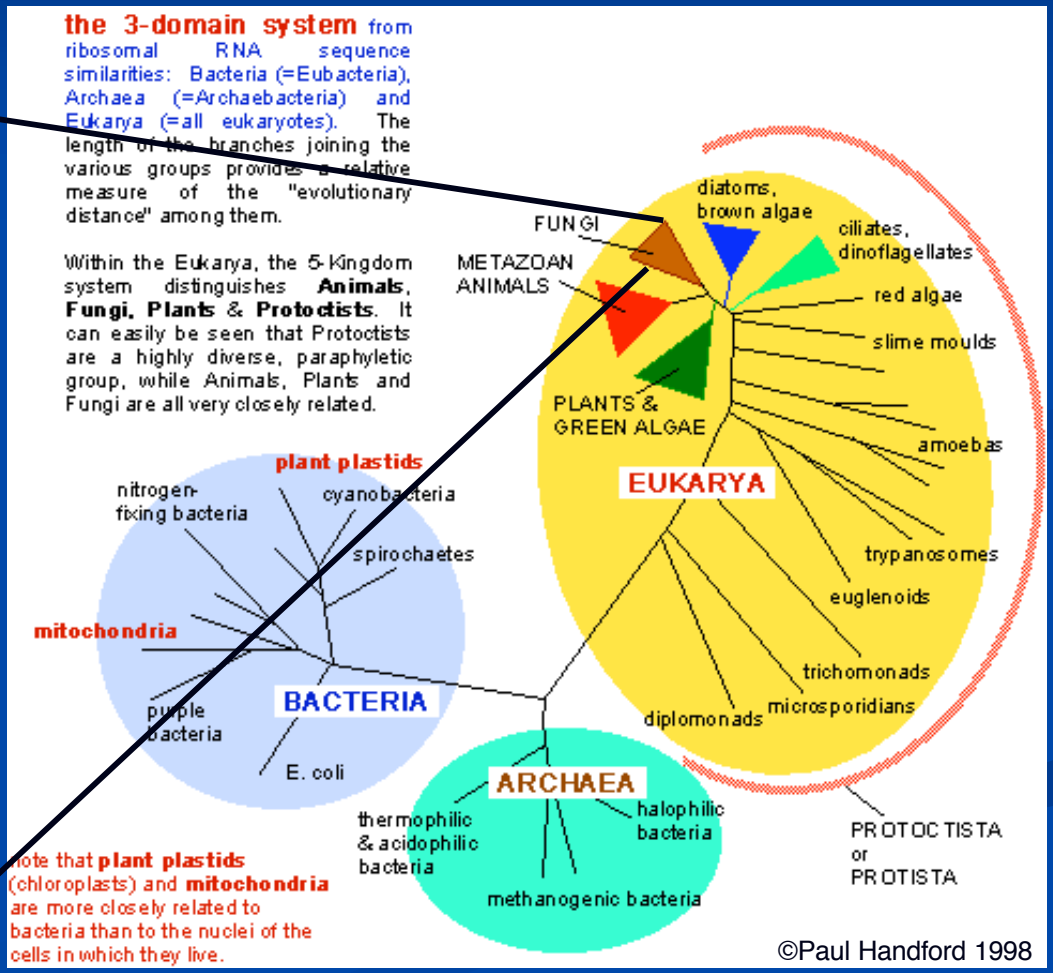
www.medscape.com/viewprogram/2963_pn

Oral Candidiasis

Systemic Infection

- Susceptible population: abdominal surgery, cancer chemotherapy, bone marrow transplant, organ transplants, other immunotherapy, other immune-compromising disease
- High mortality: those people that get systemic infection are already sick; current drugs are not effective

Fungi are relatively closely related to humans



Anti-microbial drugs

- Specificity (no side effects)
- Activity throughout the body
- Broad spectrum
- Kill microbes, not just prevent growth
- No drug-drug interactions
- Low cost

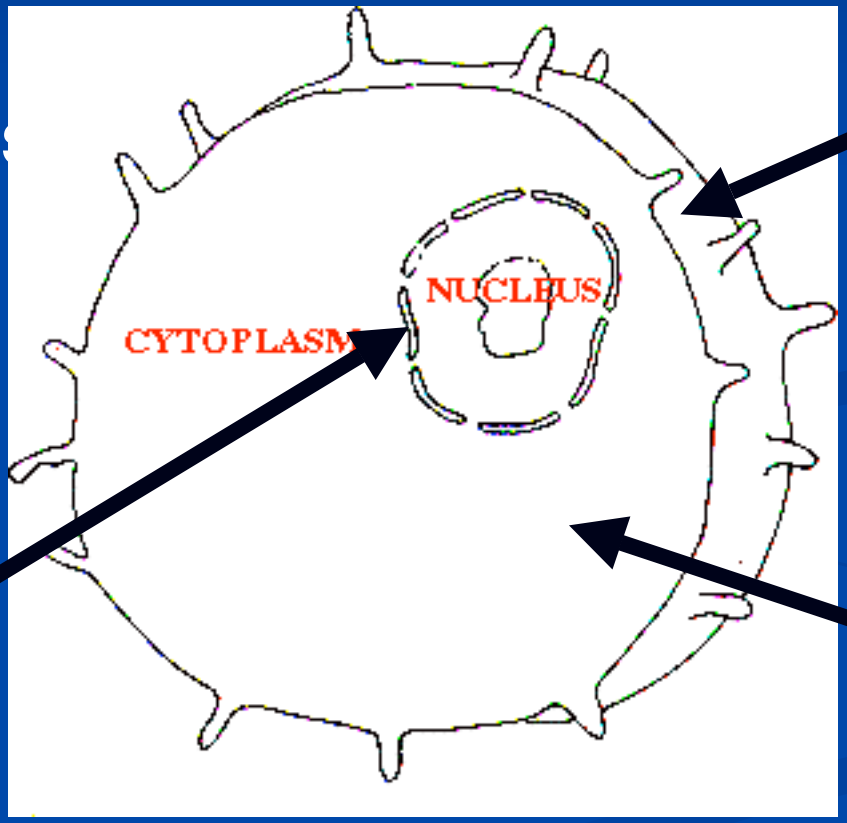
Current anti-fungal drugs

- Different classes of drugs target the plasma membrane, sterol biosynthesis, DNA biosynthesis, and β-glucan biosynthesis
- Fungal membranes and sterol biosynthetic enzymes are different enough from ours that these agents can kill fungi but not us
- Fungi make β-glucan, we don't, so drugs that target β-glucan biosynthesis have low side-effects

Mechanism of action (I)

Cell wall biosynthesis

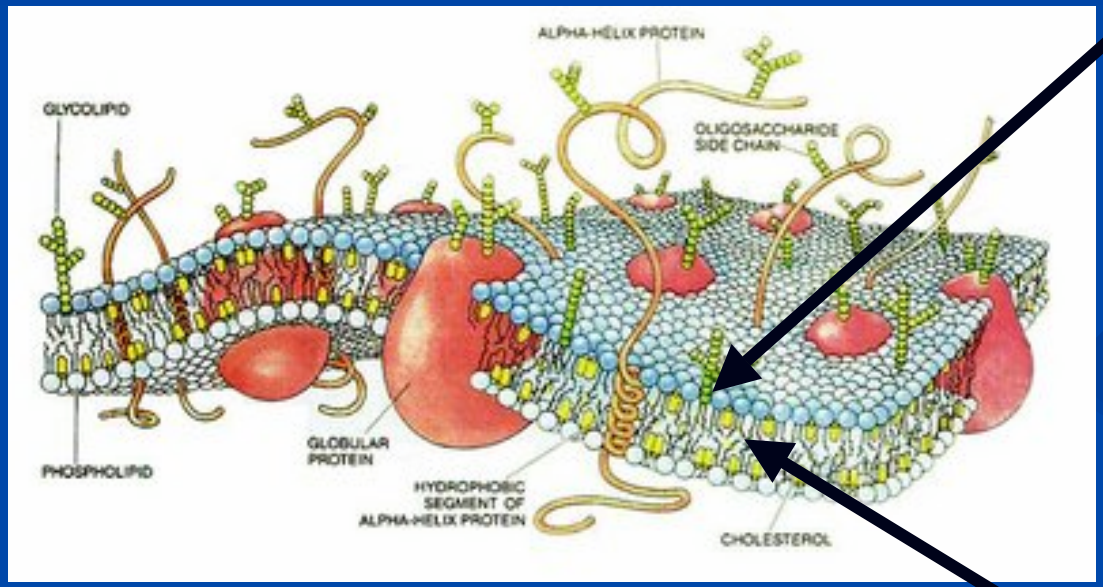
Cell Membranes



DNA Synthesis

Sterol biosynthesis

Mechanism of action (II)

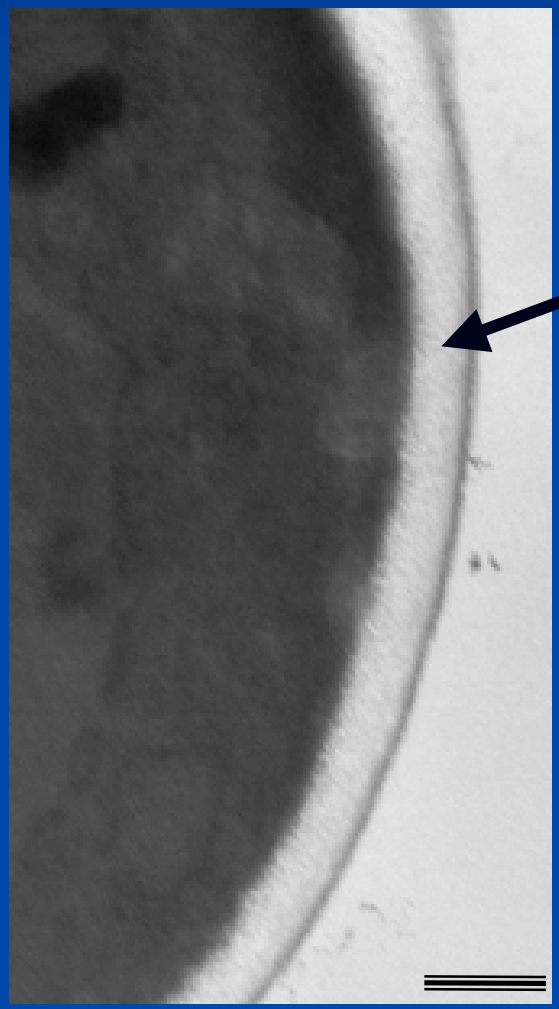


Azole drugs target the fungal-specific synthesis of membrane lipids

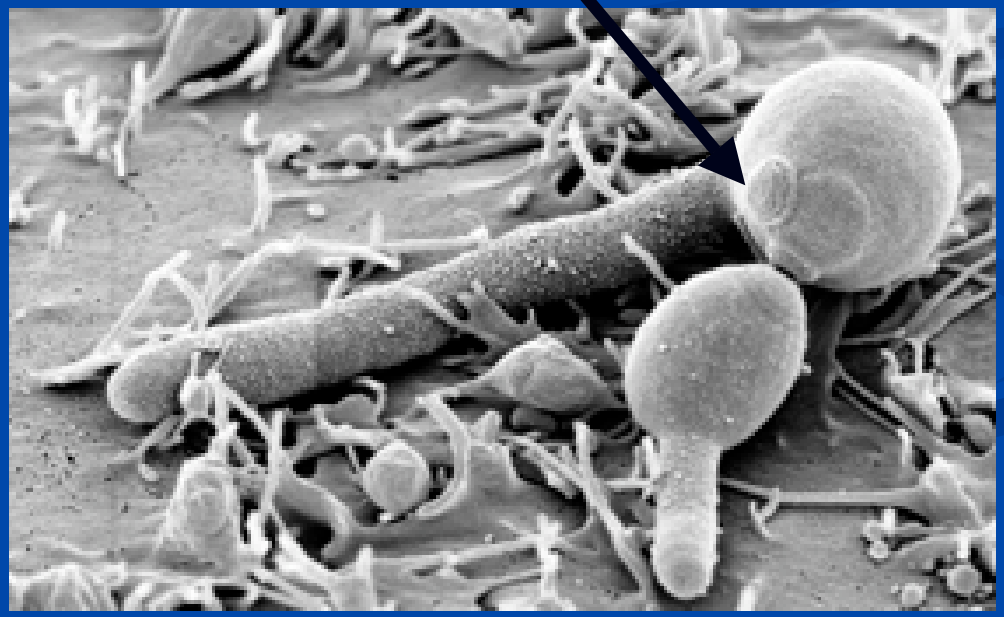
Amphotericin inserts preferentially into fungal membranes and disrupts their function

Mechanisms of action (III)

Echinocandins target synthesis of β-glucan, a fungal-specific cell wall molecule

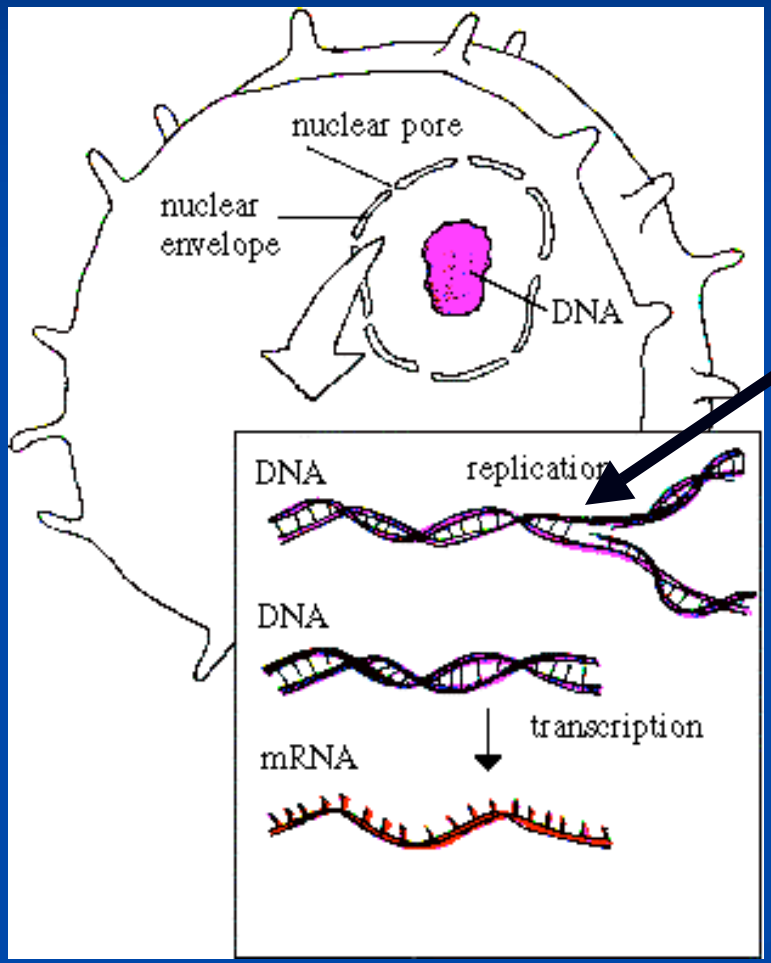


300 nM



Candida albicans on human epithelium Source: Holland/Özel, Robert Koch-Institut Ber

Mechanism of action (III)



5-fluorocytosine targets fungal-specific DNA replication

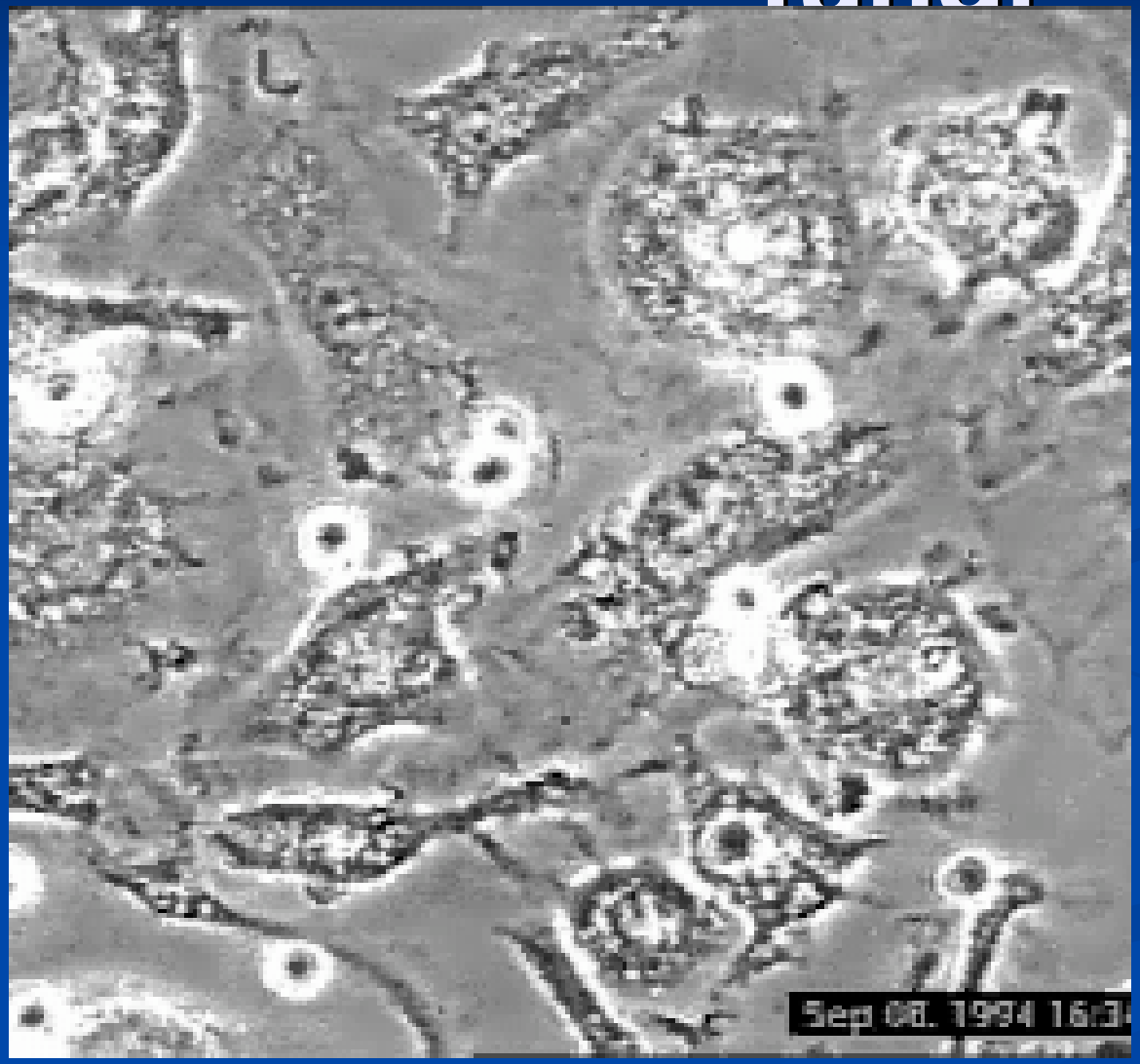
What's missing in antifungal therapy?

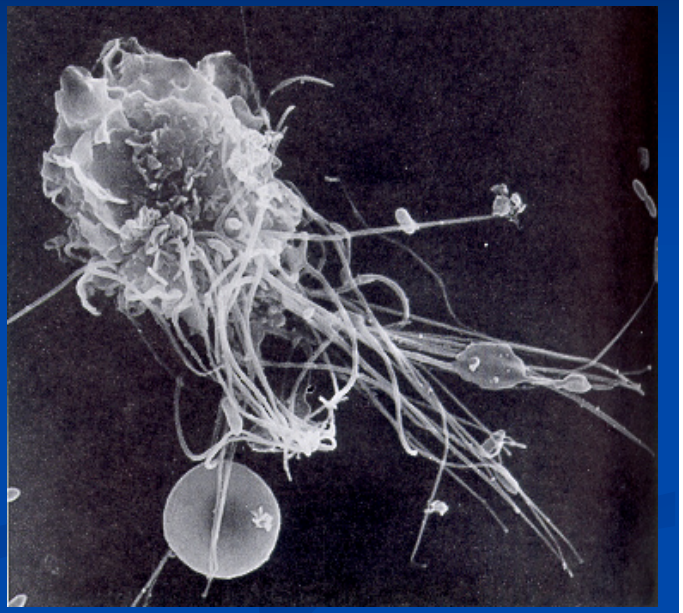
- Specificity (no toxicity)
  - Activity throughout the body
- Broad spectrum
  - Kill microbes, not just prevent growth
- No drug-drug interactions
  - Low cost

Molecular dissection of fungal infections

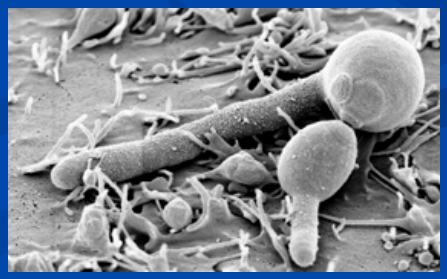
How can we identify new targets for broad-spectrum, safe, effective drugs?

When macrophages meet fungi



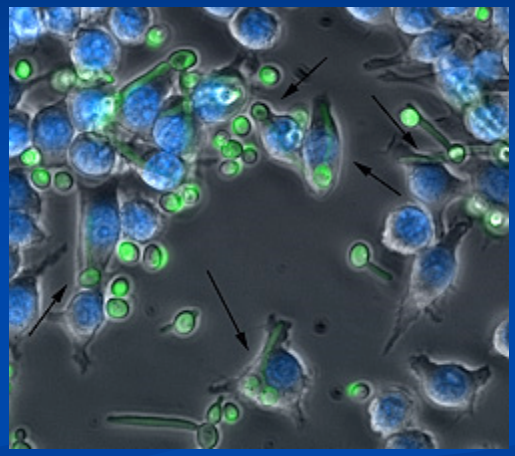


VS.



Immune cells recognize and respond to fungal surface molecules

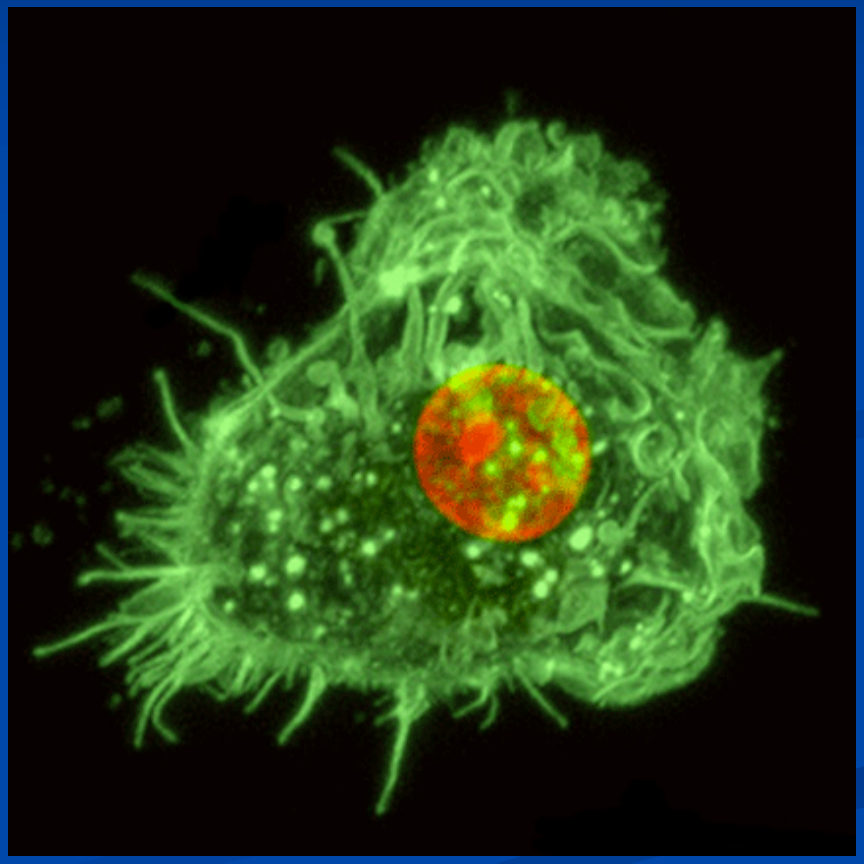
- Two main fungal-specific molecules are β-glucan and mannan, chains of sugars linked in particular order
- Immune receptors bind to these molecules and begin a choreographed immune response
- A productive immune response is tiered: first immune cells signal an invasion and recruit more immune cells to the site of infection, then these cells kill the fungus and stimulate a long-lived response that protects against future infection



The Macrophage
Body's Radar

Recognition of β-glucan stimulates the anti-fungal immune response

- Phagocytosis of the fungus (leads to killing)
- Activation of killing functions
- Production of attractive and activating signaling molecules
- Priming of the adaptive (memory) arm of the immune system to develop fungal-specific antibodies and T-cells



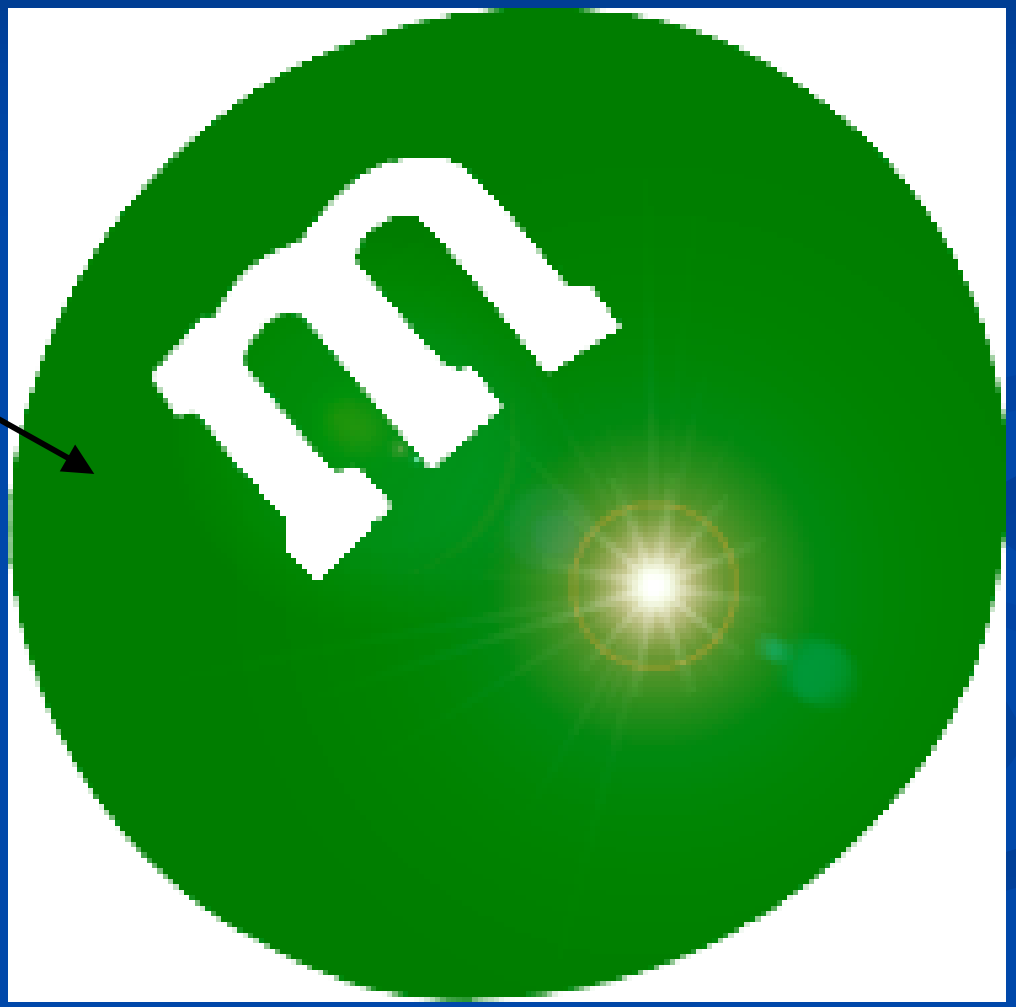
β-glucan, it cures what ails you

DO YOU EAT RIGHT, HAVE NO STRESS, EXERCISE REGULARLY AND SLEEP 8 HOURS A NIGHT TO KEEP YOUR IMMUNE RESPONSE IN PEAK CONDITION?

FOR WHEN YOU CAN'T – MG BETA GLUCAN!

Fungi are just like M&Ms!

1st Layer:
Colored Candy Paint



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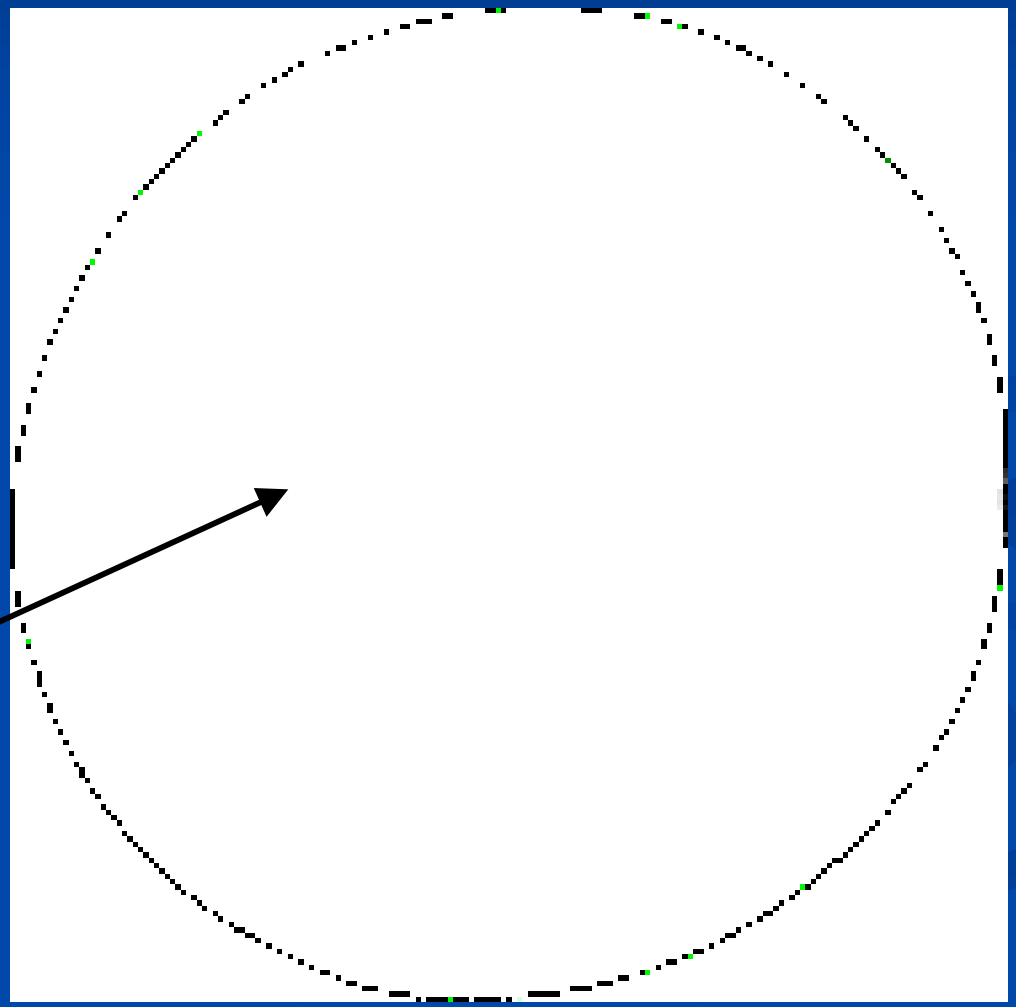

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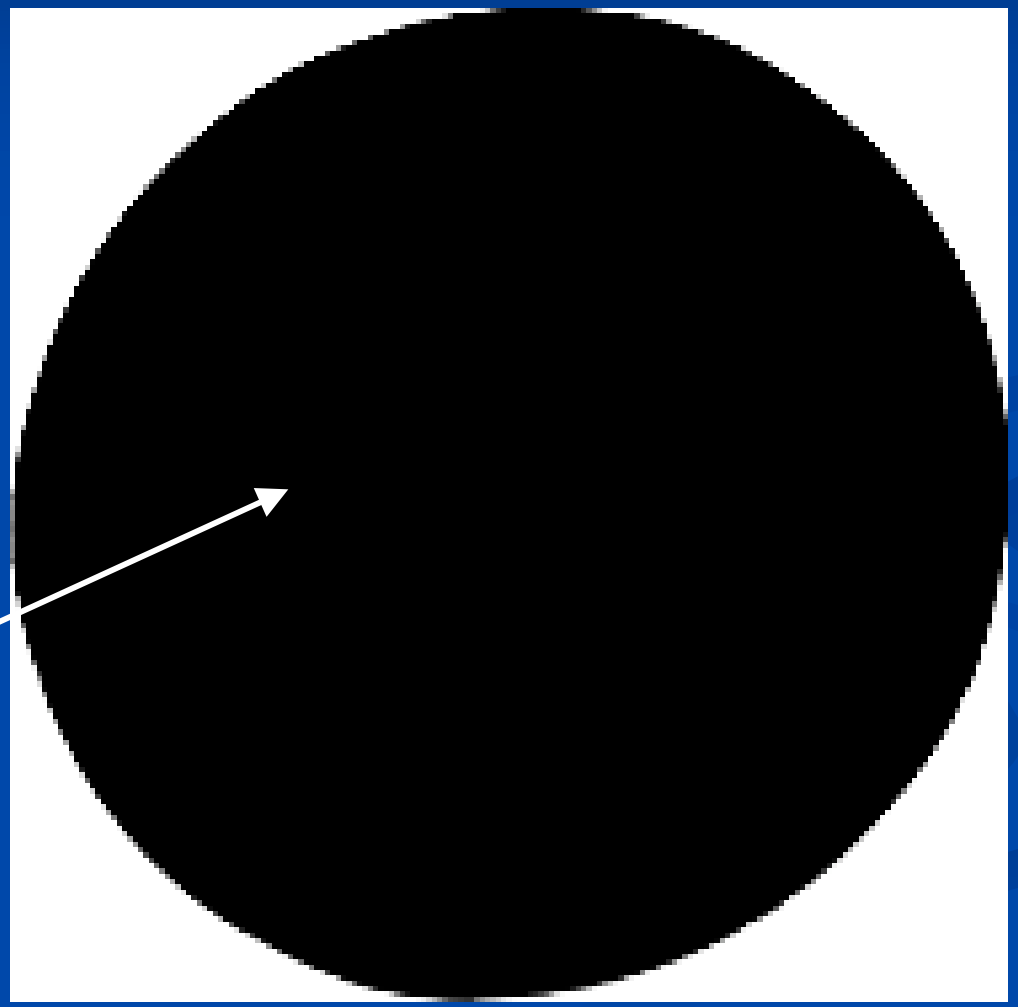
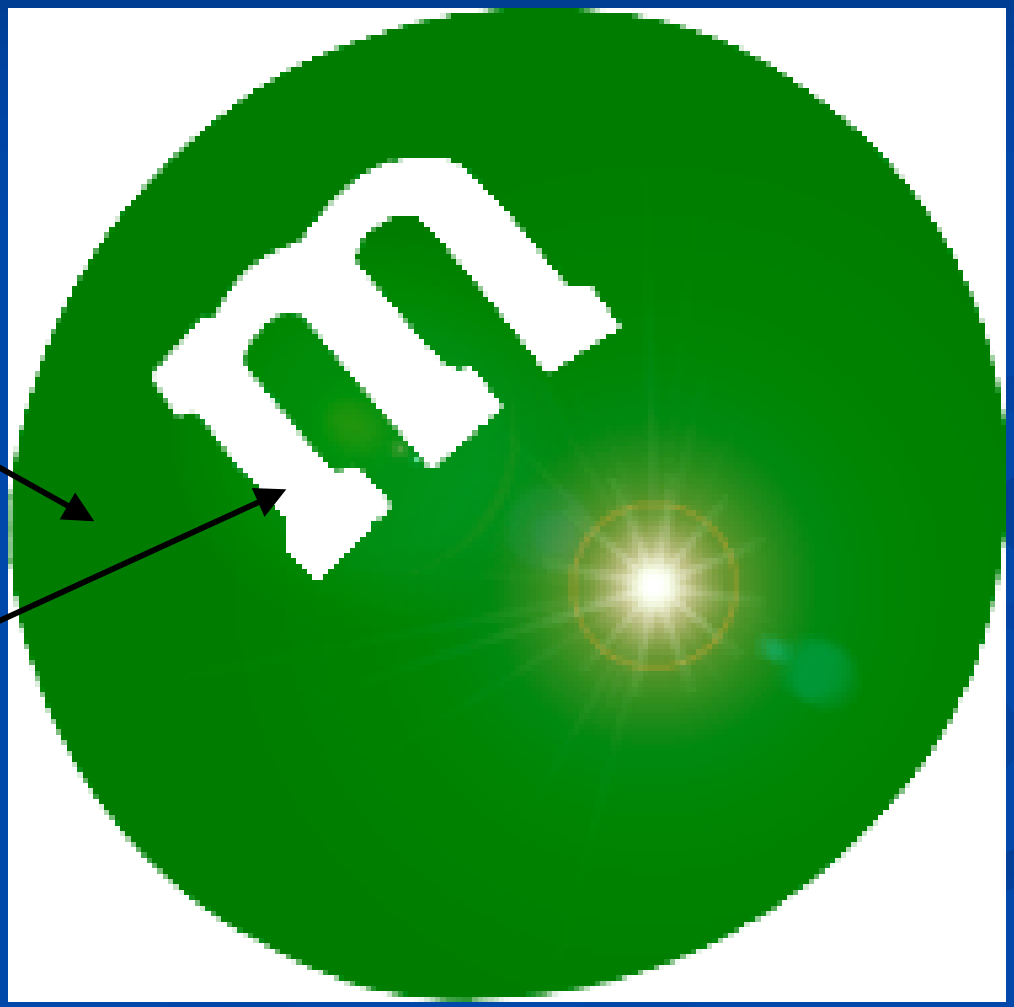


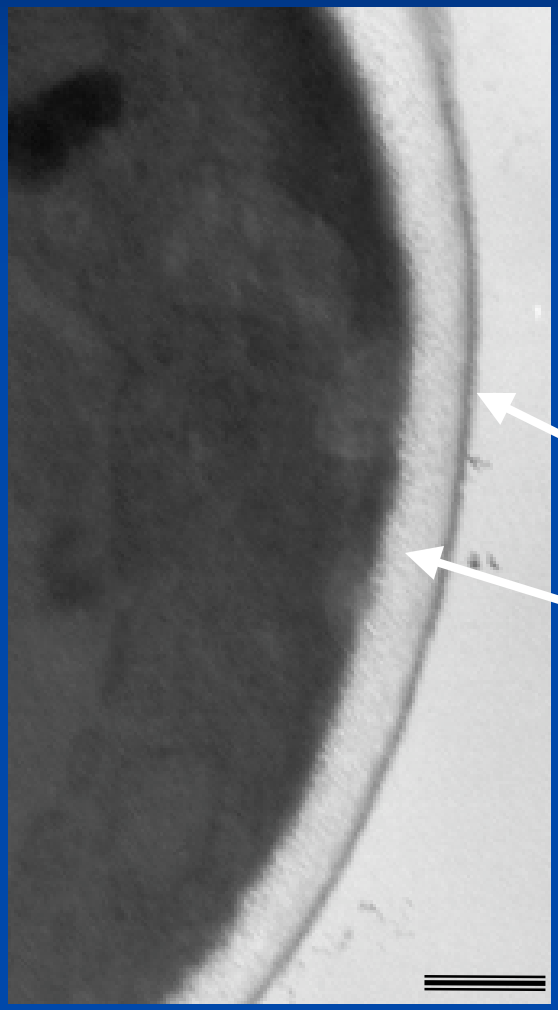
Fungi are just like M&Ms!

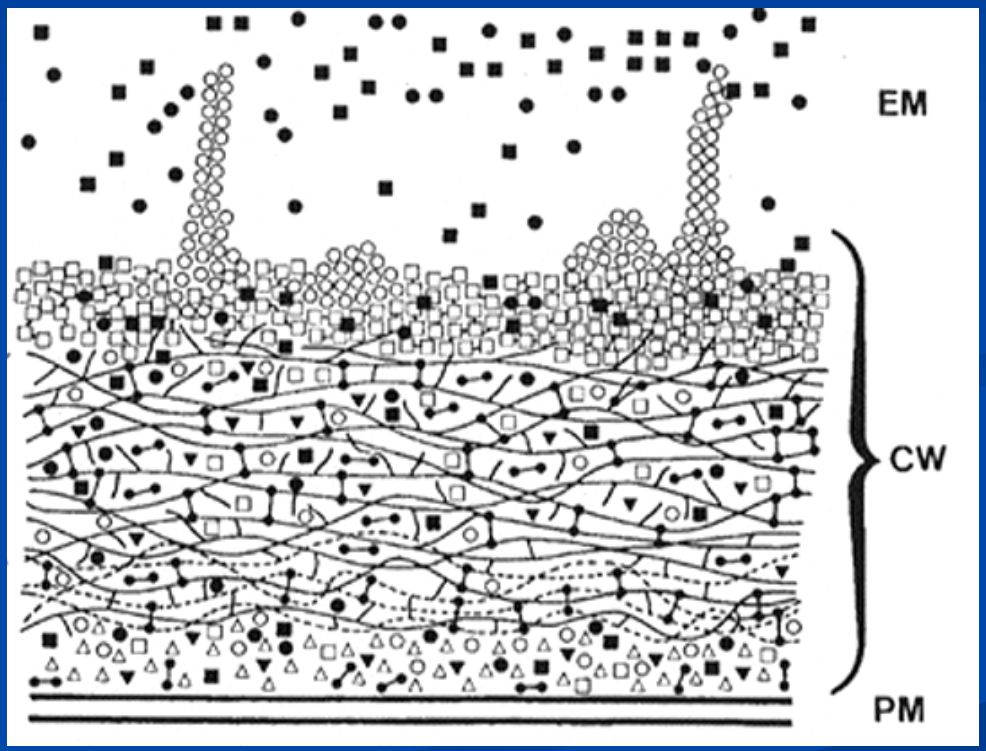
Colored Candy Paint
(Mannan)

Exposed White
Candy Layer
(β-glucan)

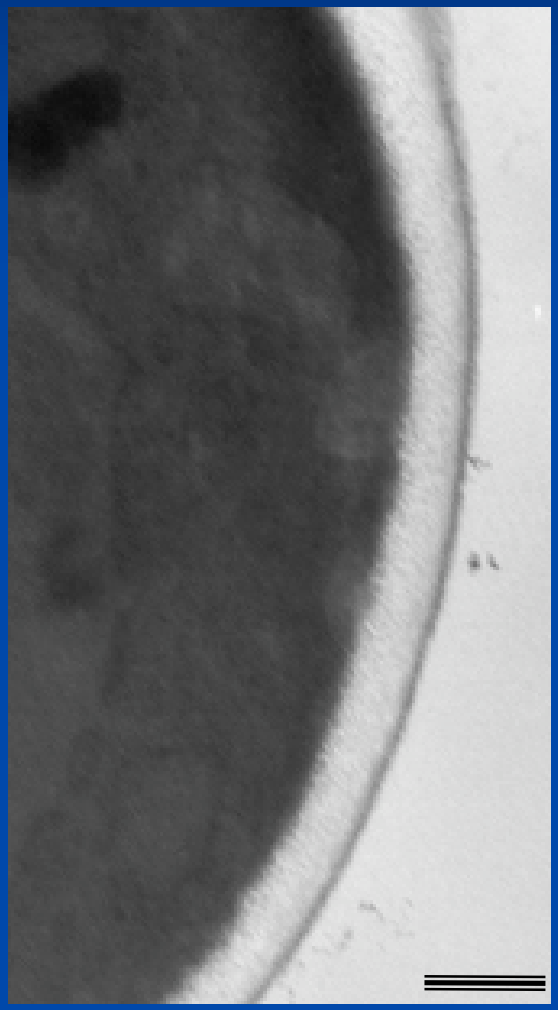


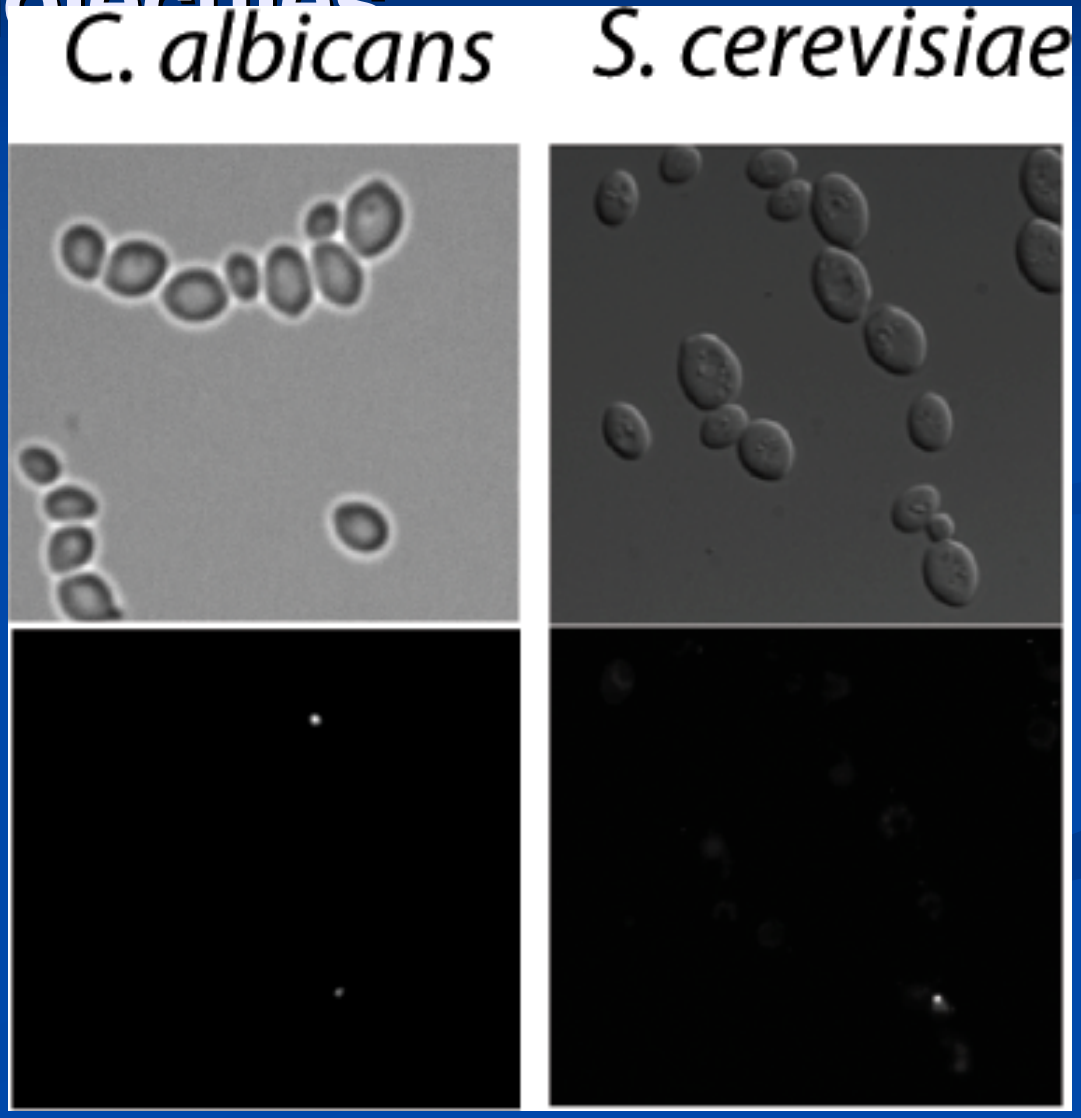
Layered architecture masks most β-glucan from the immune system





β-glucan is present everywhere but is mostly invisible to immune molecules

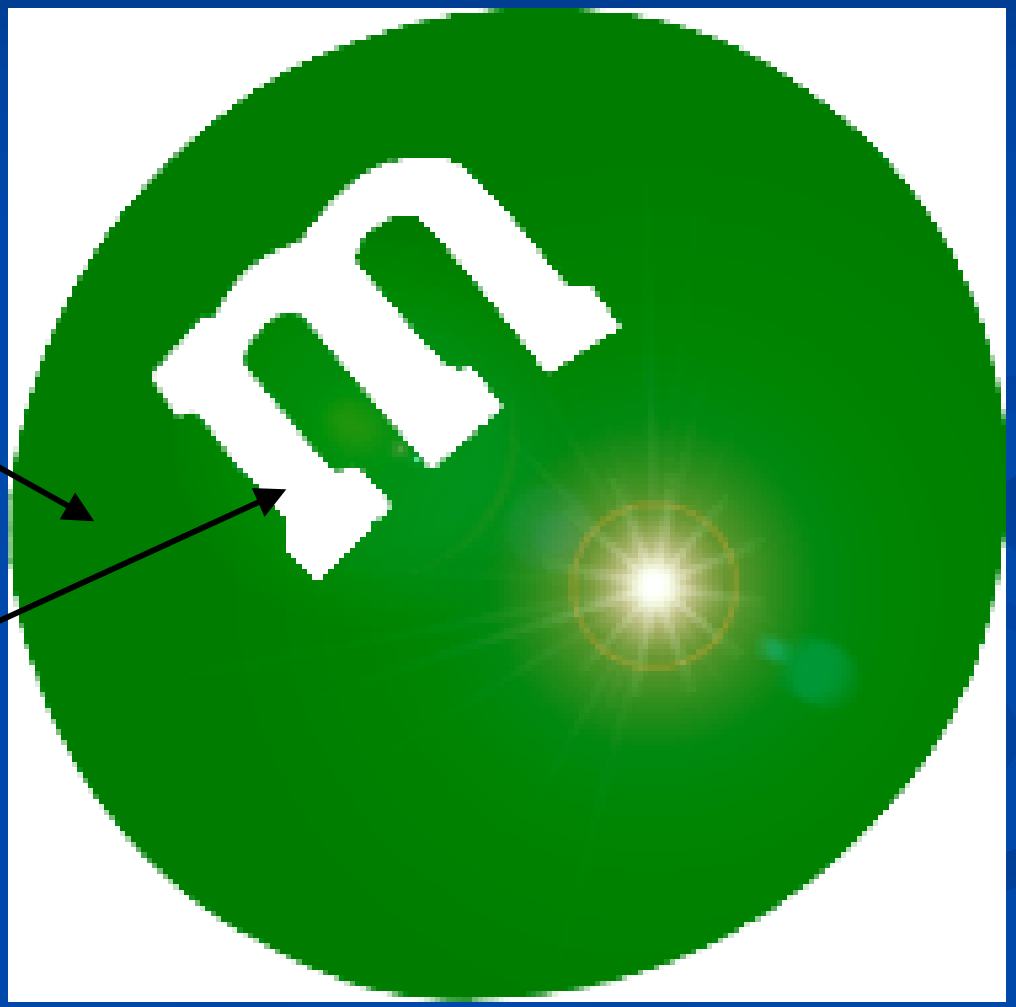




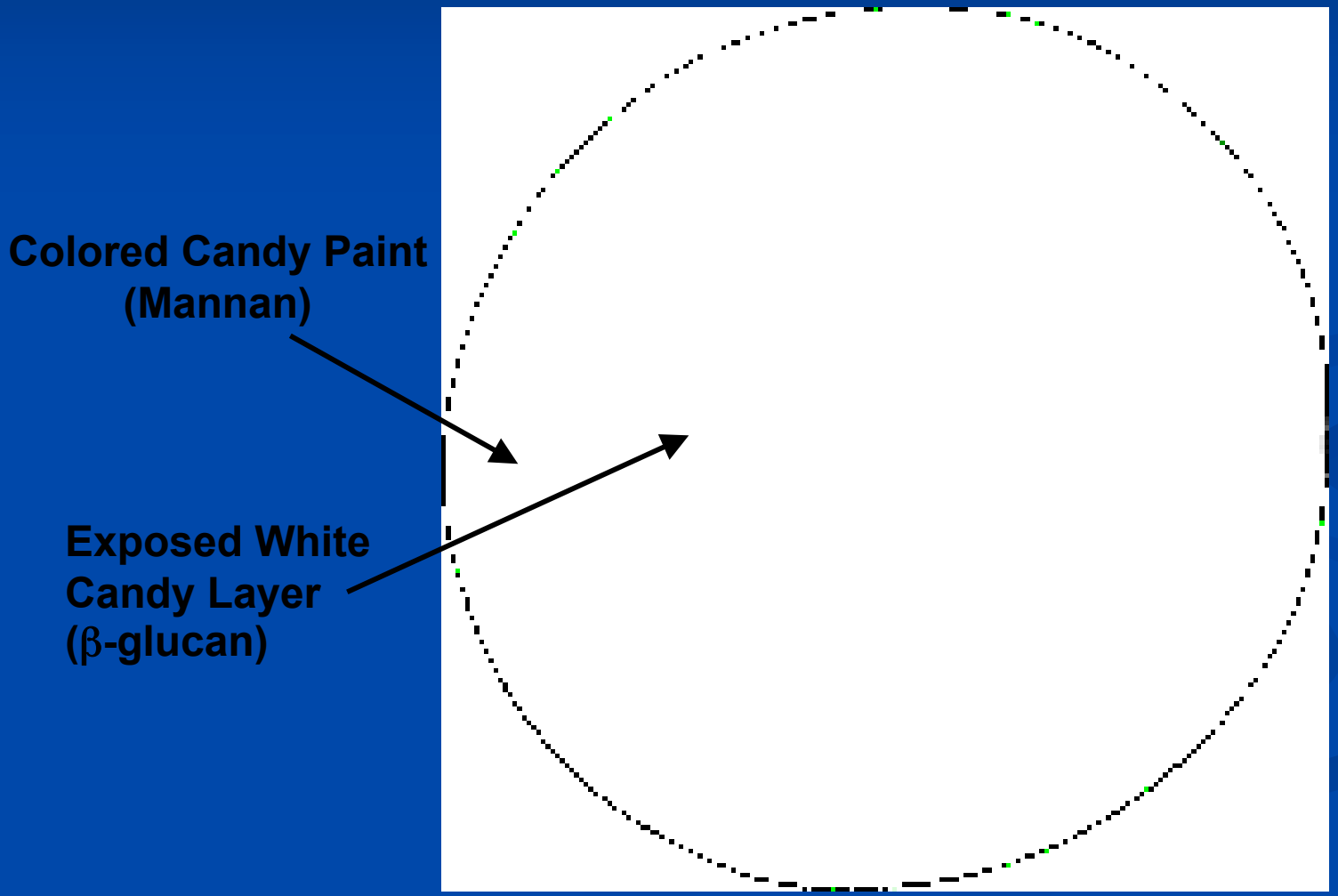
Wildtype yeast have very little exposed β-glucan

Colored Candy Paint (Mannan)

Exposed White Candy Layer (β-glucan)



Disruption of the cell wall exposes β-glucan and fungi are recognized better



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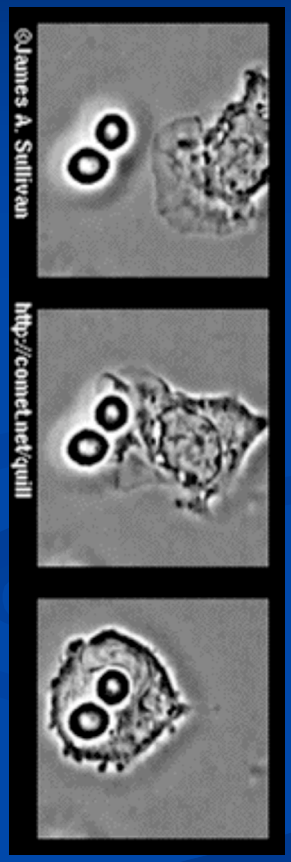
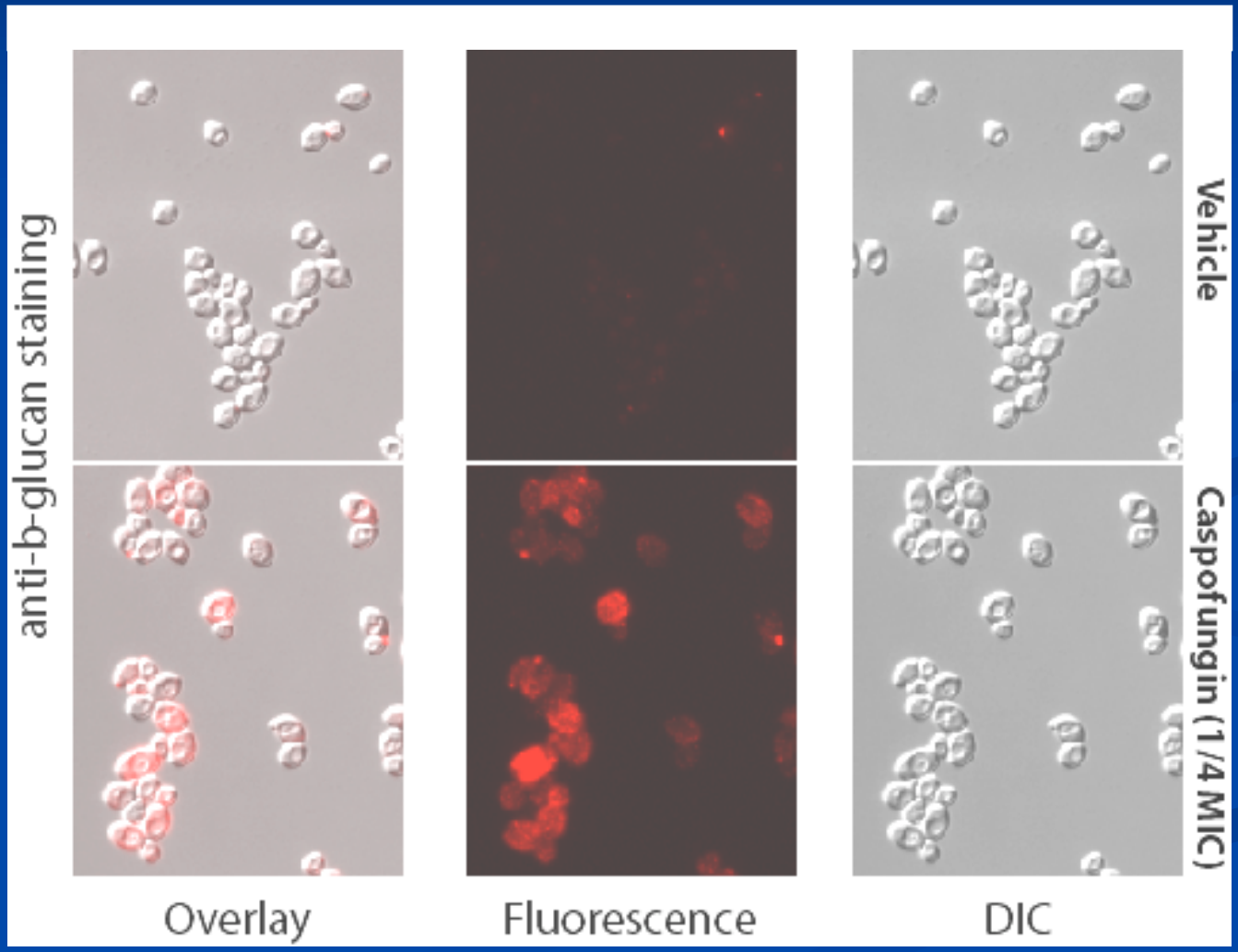


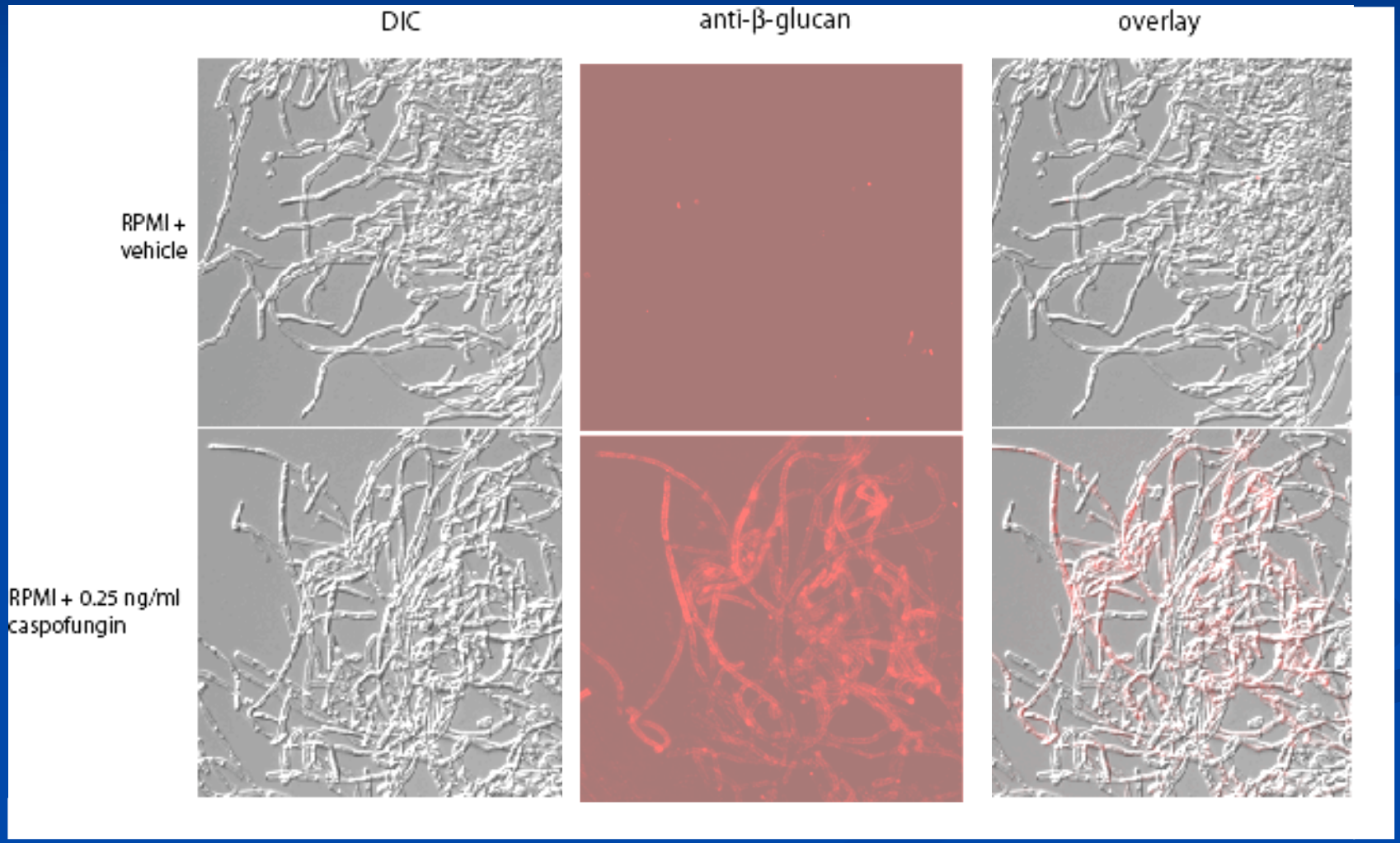
BUT: The fungi masks its β-glucan under a candy coat to block these responses

Is there a drug that can unmask fungi?

Caspofungin causes exposure of β-glucan at sub-MIC concentrations



Caspofungin also causes β-glucan exposure in filaments



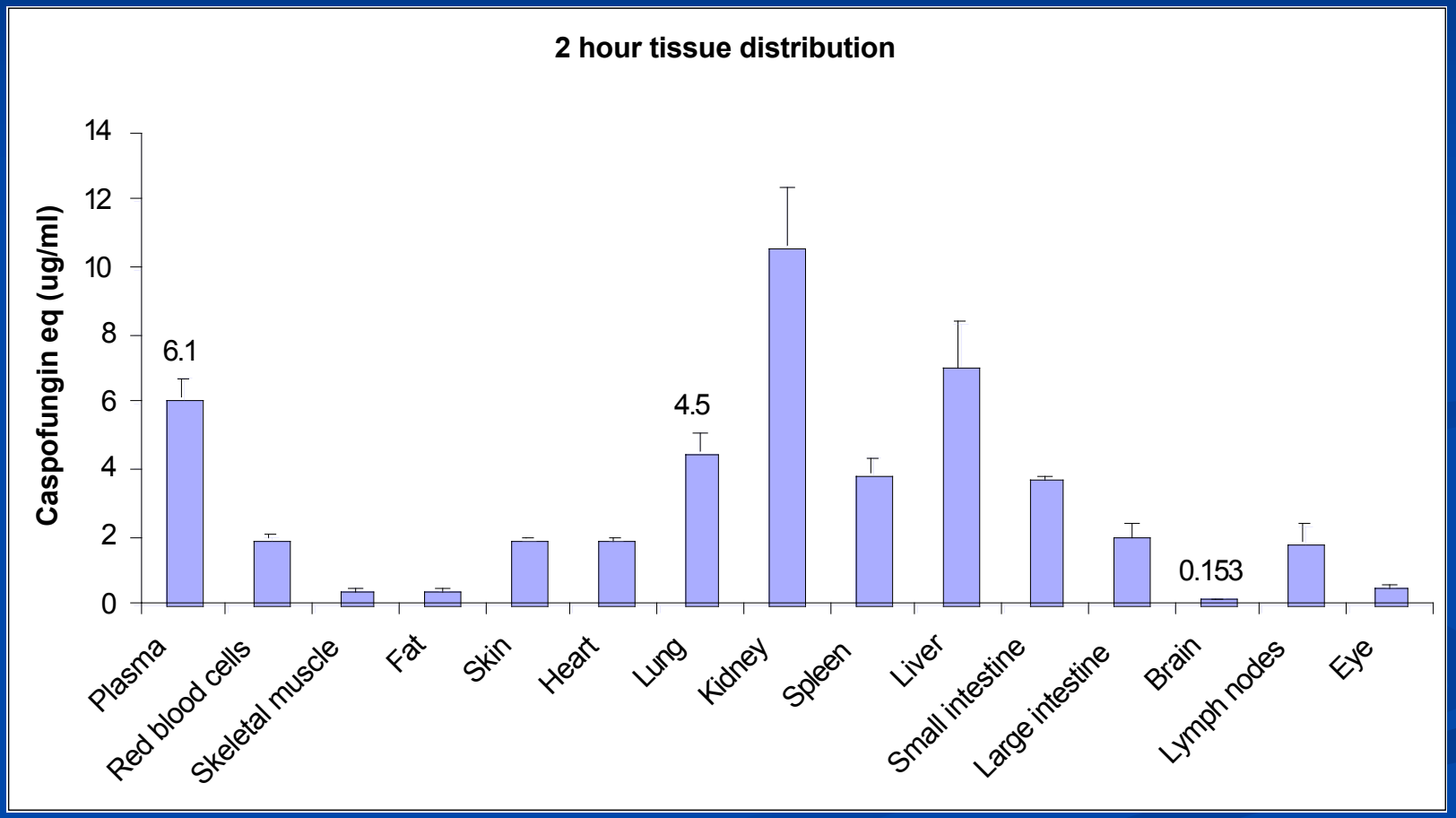
Is there a clinical relevance?

- We still have not tested this in a mouse model of fungal infection but we hope that drugs that can “unmask” fungi will lead to better immune responses against the fungi

Is there a clinical relevance?

- Many “targeted” drugs have more than one activity which contribute to their effectiveness (e.g. Gleevec, fluconazole) or toxicity (Vioxx)
- Most drugs, including caspofungin, do not have homogeneous tissue distribution

Variability in tissue distribution of caspofungin



The take-home message

- There is a clear need for new anti-fungal drugs (and identification of new targets) to treat systemic infection
- The immune system recognizes fungi based on conserved fungal molecules which can induce protective (anti-fungal) responses
- *Candida* may mask these molecules to prevent a full-blown immune response
- Masking may be a drug-targetable mechanism useful in combatting fungal infection

Acknowledgements

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