Linking plants with human: fungicides' role in induction of antifungal resistance

Presented by:

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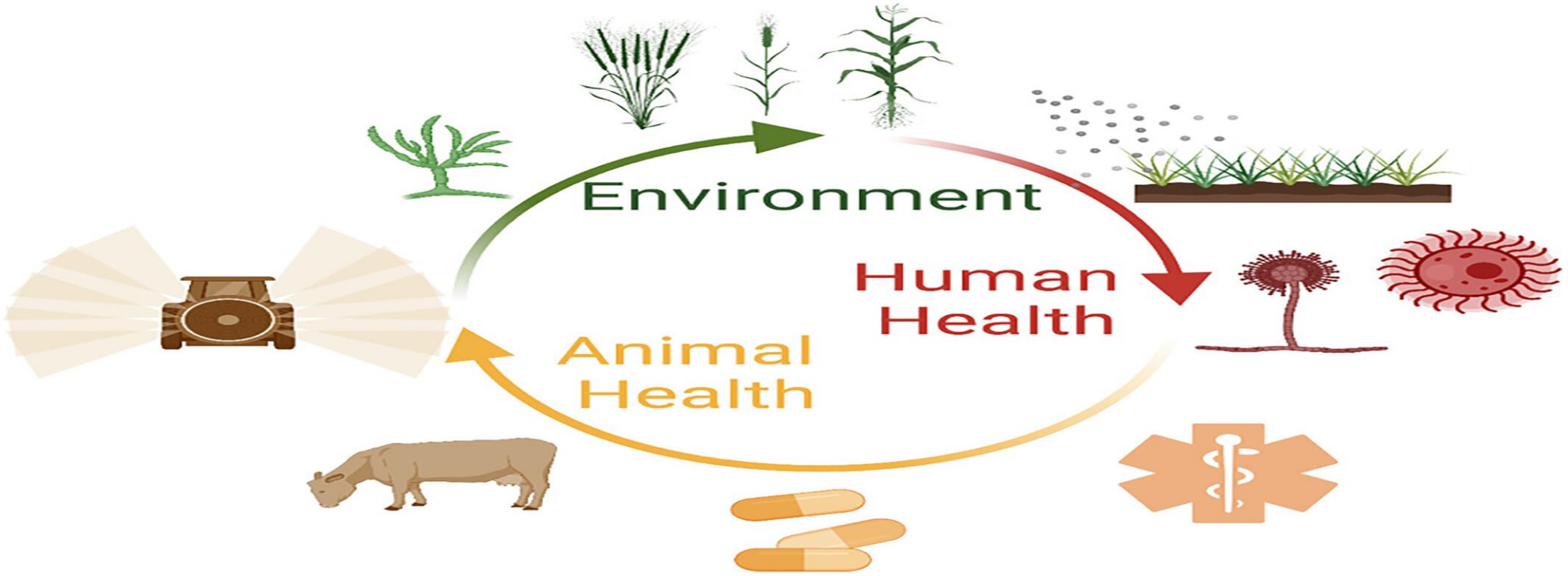
- ✓ **The “One Health” concept** connects the health of plants, humans, animals, and the environment in a unifying approach, aiming to balance and optimize them as only one. Its points of action include food security and safety, the integrity of ecosystems, fungal infections including zoonosis and antimicrobial resistance control, and the promotion of health



Environmental effects:

- Climate change is possibly favoring more thermotolerant, and potentially more aggressive, virulent, and mycotoxigenic fungal species, which represents an increasing concern to human, animal, plants, and environmental health. Therefore, it is important to control carbon emissions and the exacerbation of climate change as well as specific fungal species in certain environments and conditions, without compromising all the other species that are fundamental to the well-functioning of these environments and the surrounding ones.

- **In this way, it's critical to increase the knowledge about fungi and their direct and indirect interaction with human health, different environments, plants, and animals, regarding the "One Health" perspective.**

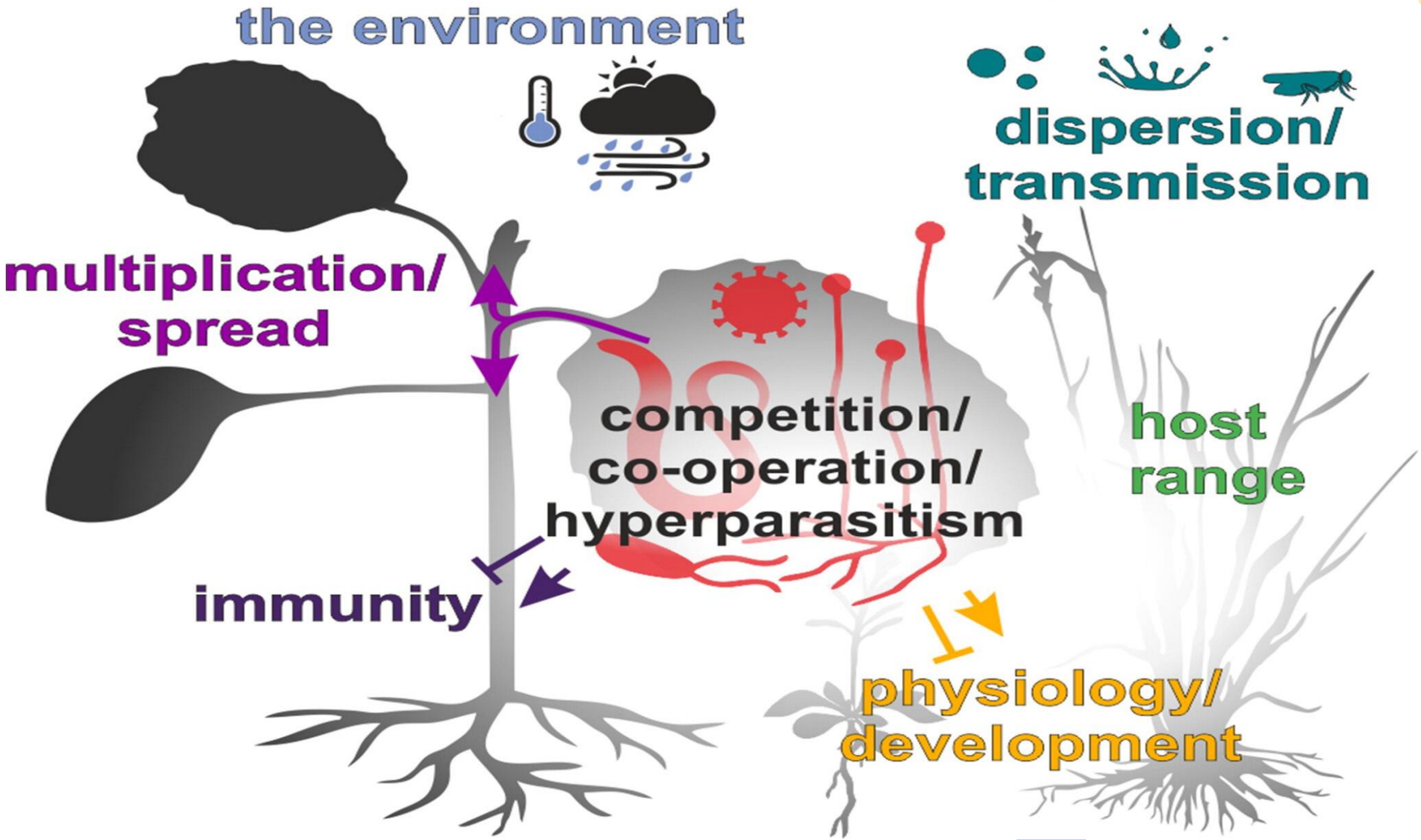
Kingdom Fungi is a complex group with rich biodiversity, having an important role in the environment due to the capability of its species to degrade organic matter and their great potential in biotechnology due their production of metabolites.

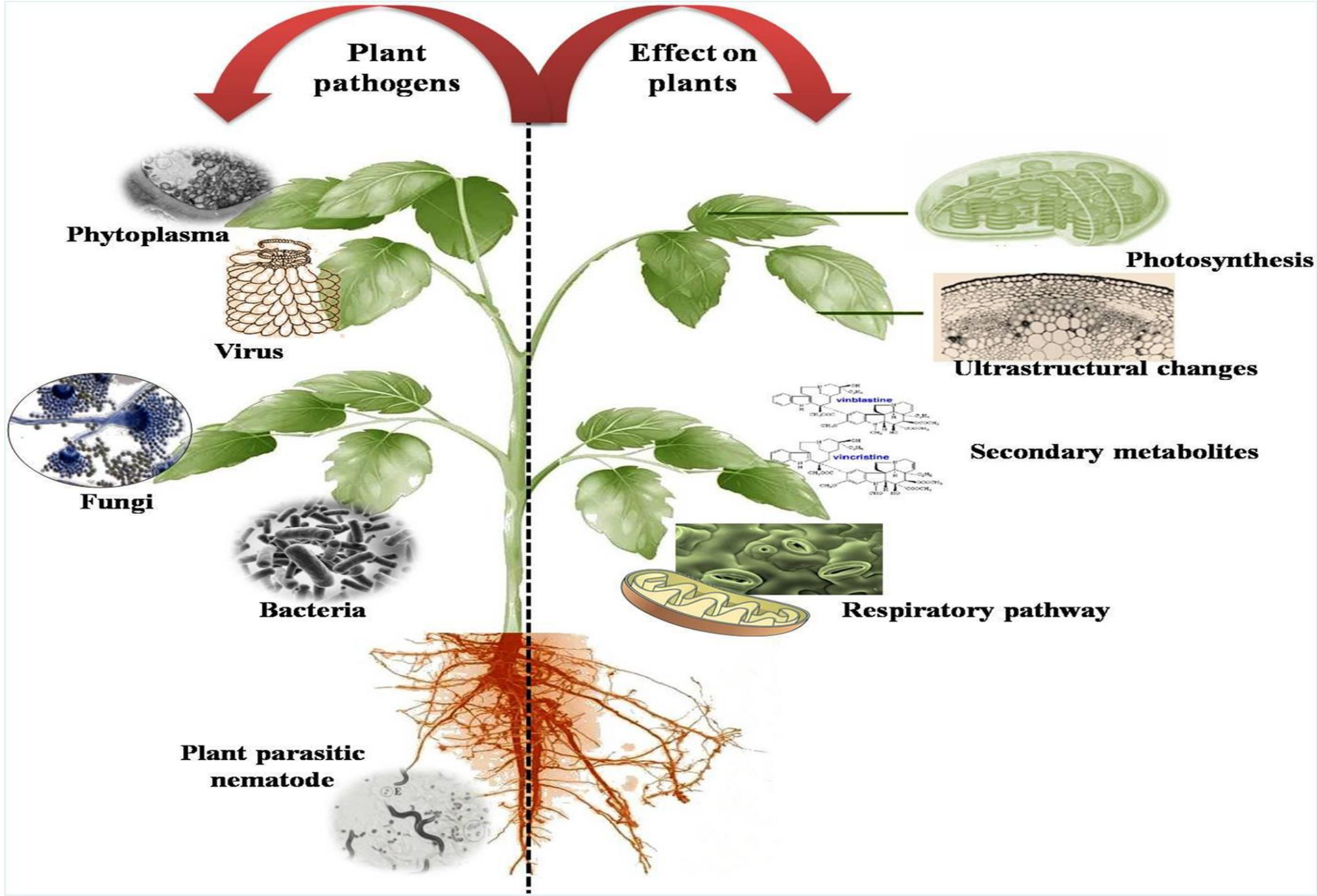
Their presence in the soil is crucial to its fertility, but their presence can also cause diseases in some plants, compromising their production and food security for humans and animals.

The metabolites produced by fungal species can be useful in biotechnological processes, but some of them contaminate food and feed.

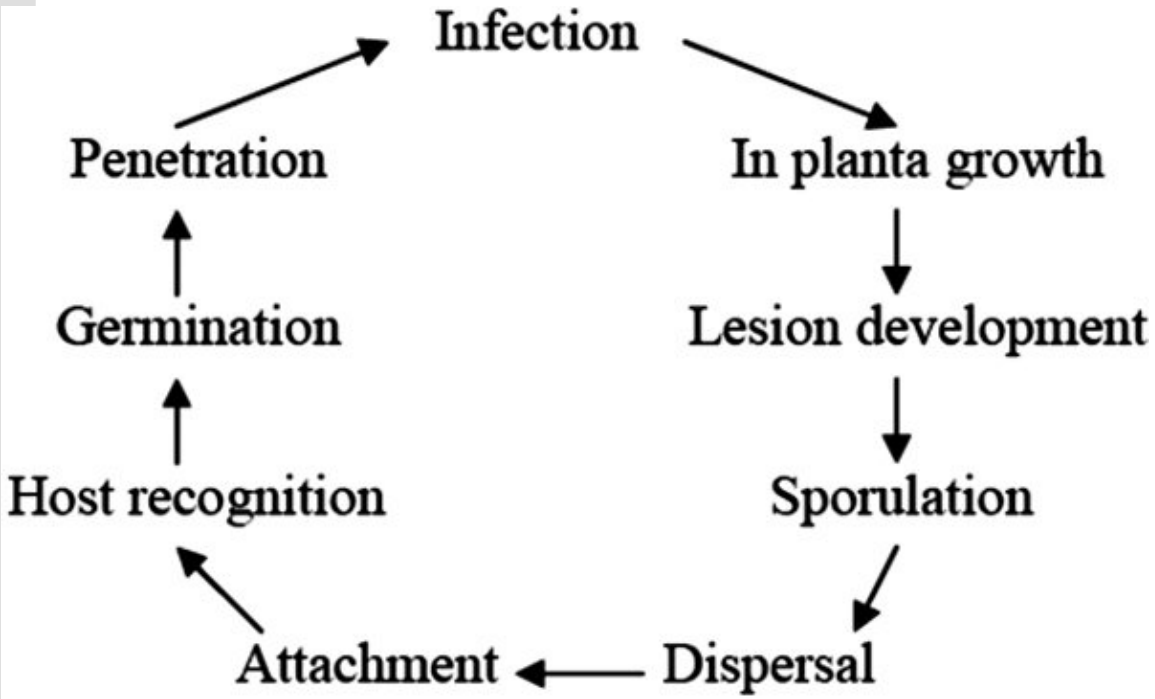
In the same way, some fungal species are important to the well-functioning of the human body including microbiota, others may cause severe, invasive, and deadly infections

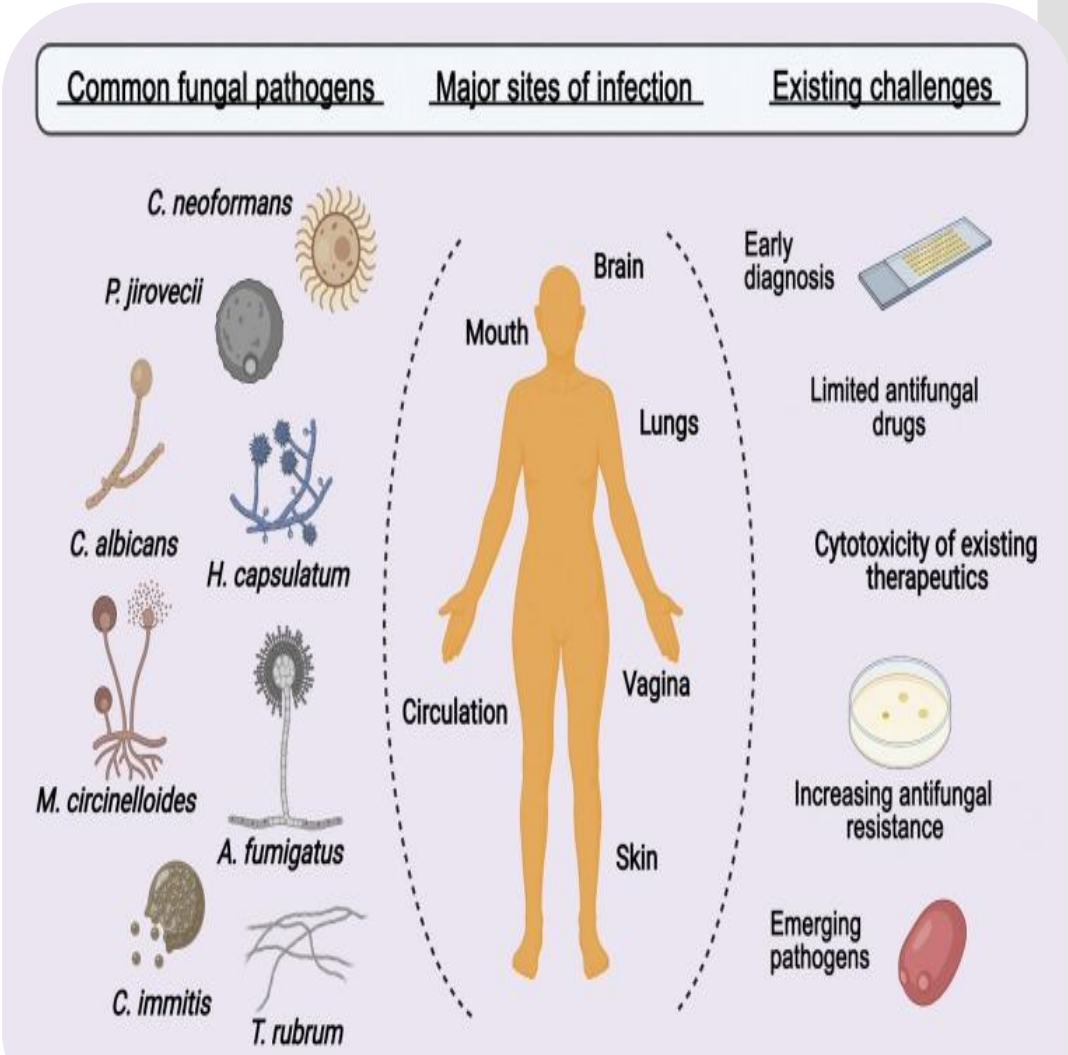
Novel virulence activities can include adaptations involving...

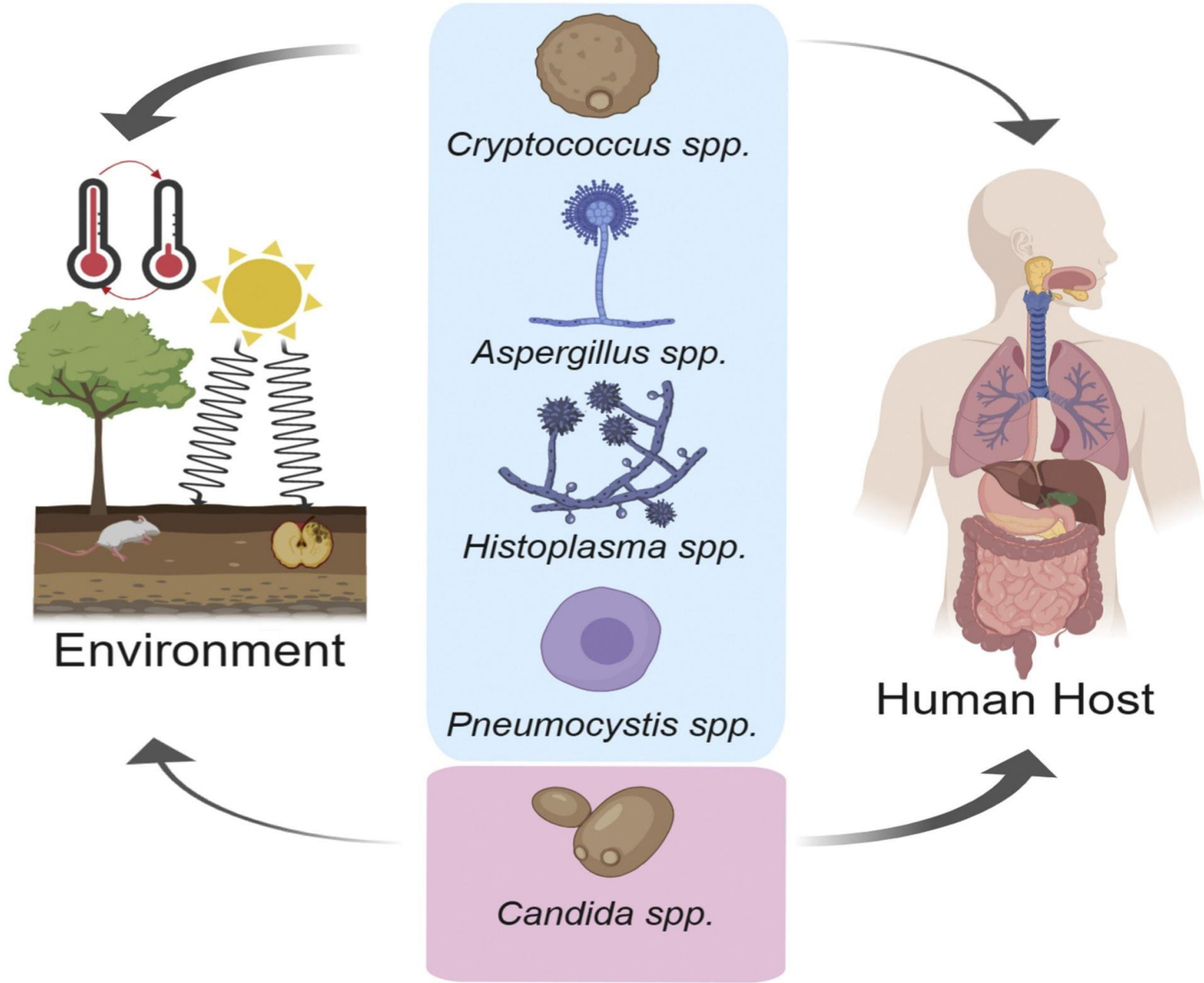


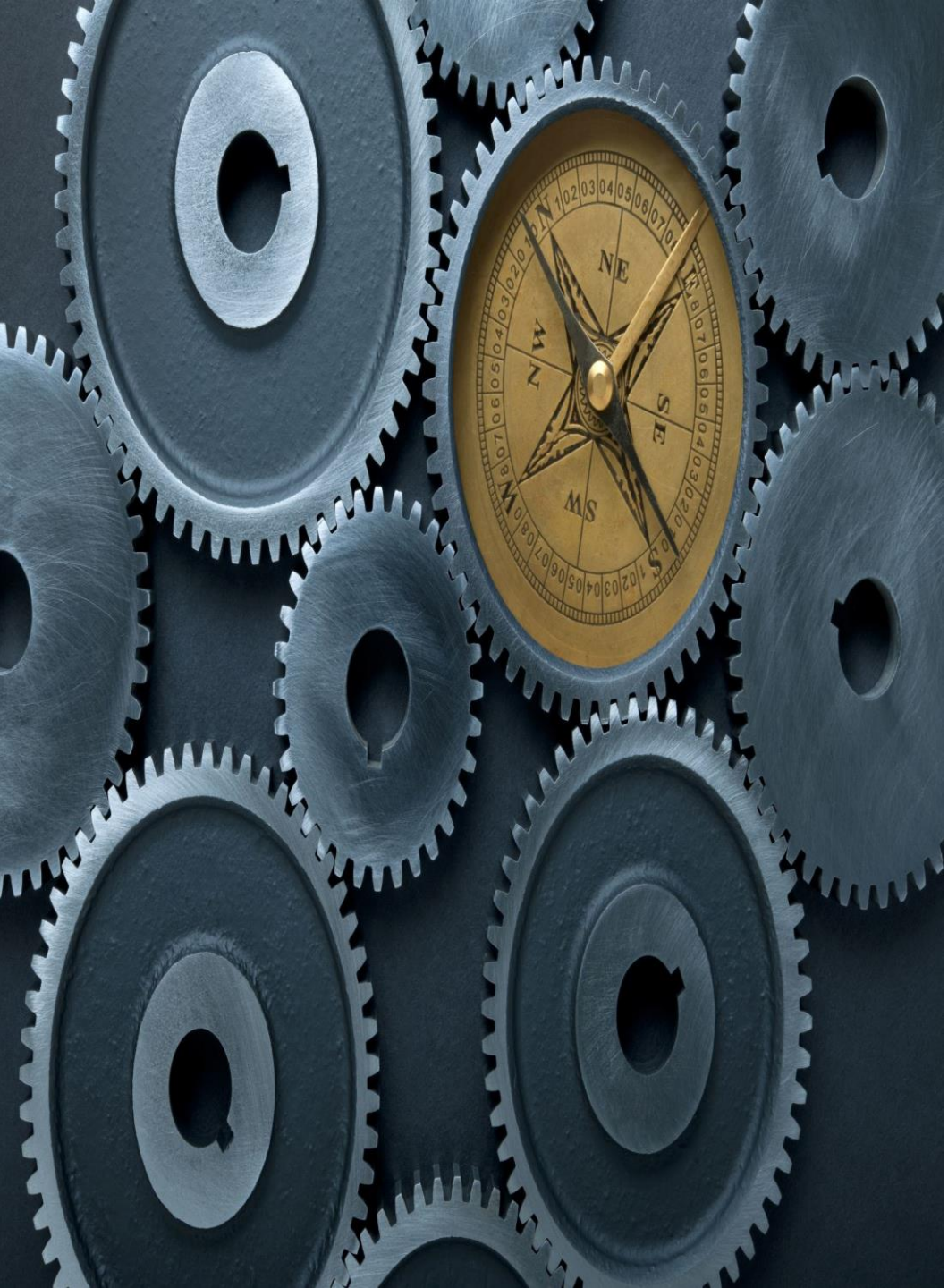

Plant pathogens
Effect on plants
Phytoplasma
Virus
Fungi
Bacteria
Plant parasitic nematode
Photosynthesis
Ultrastructural changes
vinblastine
vincristine
Secondary metabolites
Respiratory pathway

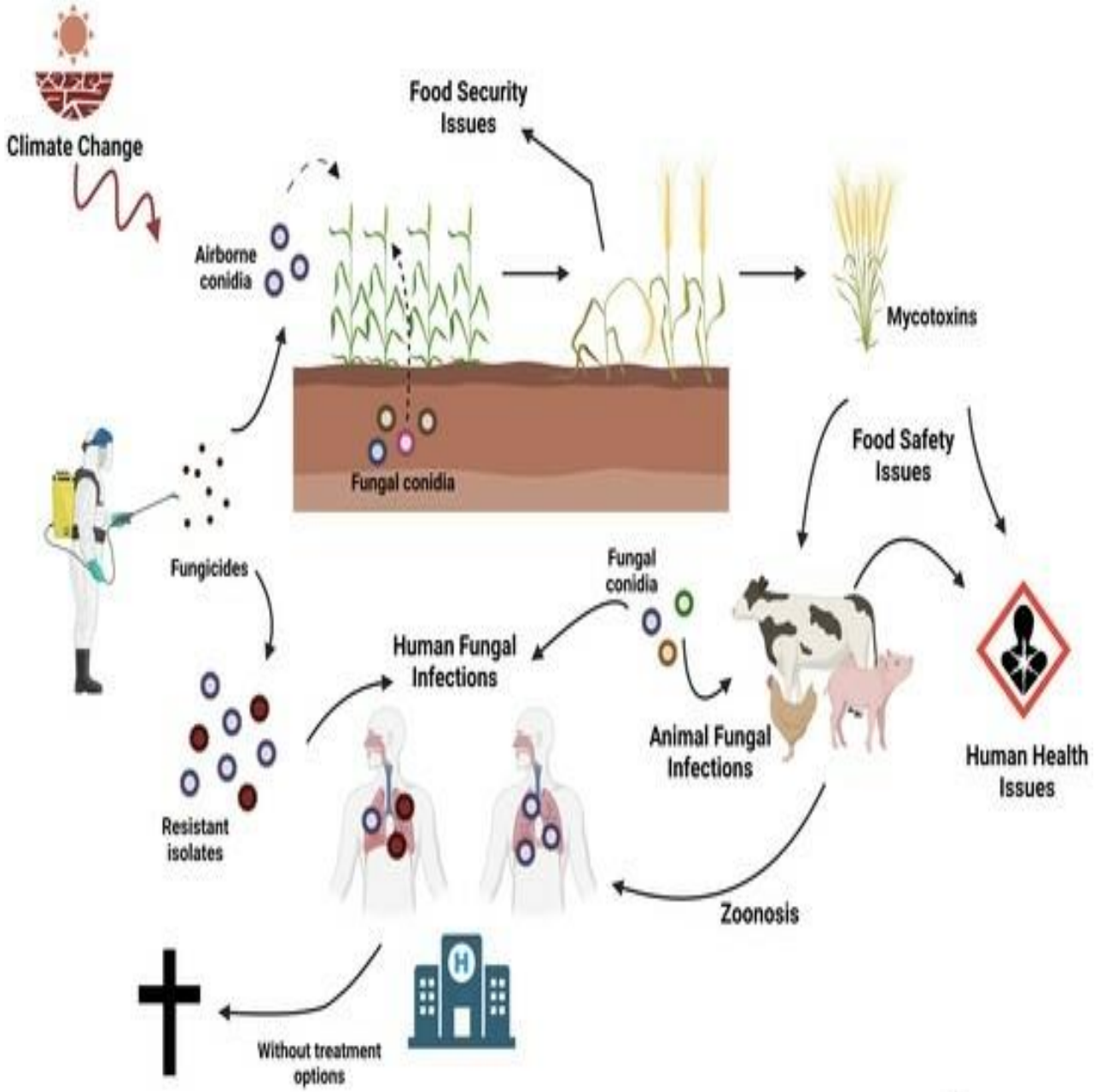
- Fungi are eukaryotes and most are multicellular.
- While once grouped with plants, fungi generally differ from other eukaryotes in nutritional mode, structural organization, growth, and reproduction.
- Molecular studies indicate that animals, not plants, are the closest relatives of fungi.



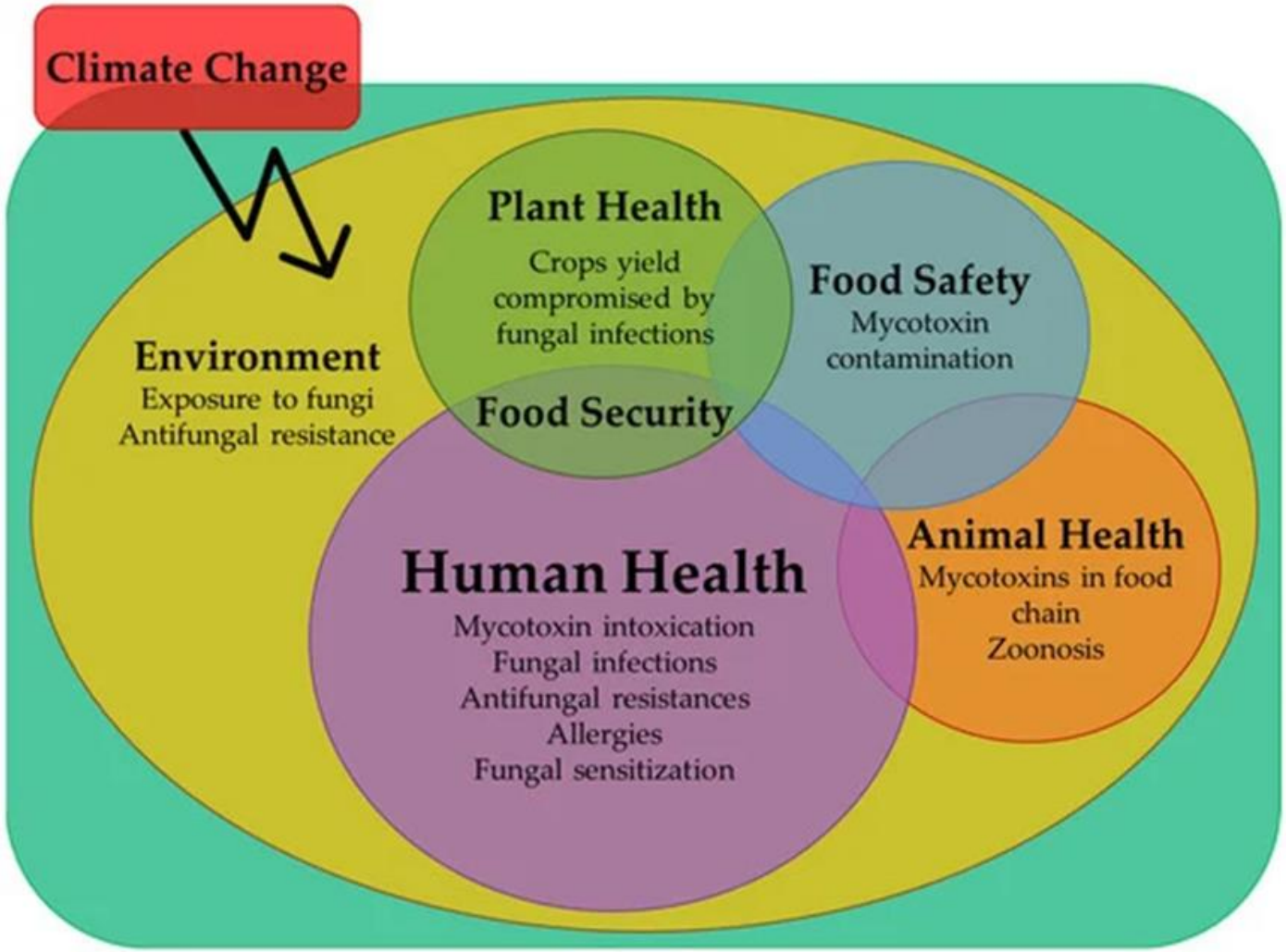



Cryptococcus spp.
Aspergillus spp.
Histoplasma spp.
Pneumocystis spp.
Candida spp.
Environment
Human Host

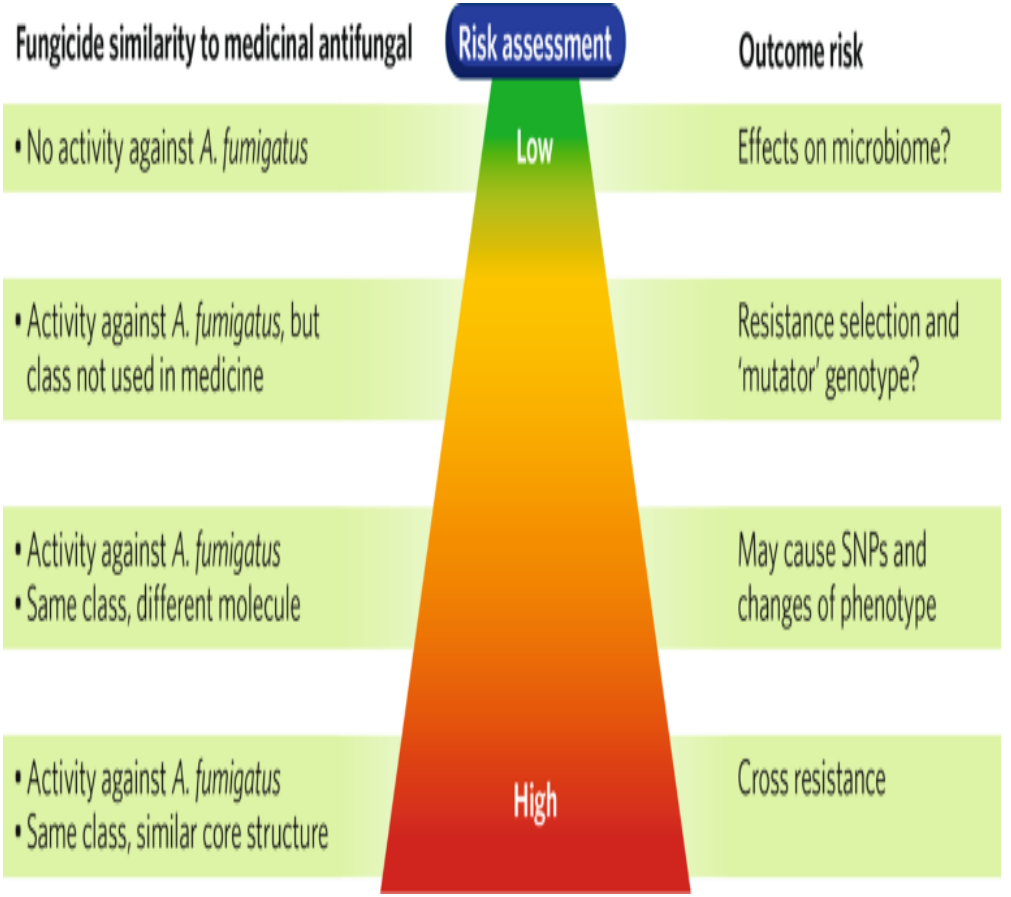



Climate Change
Food Security Issues
Airborne conidia
Mycotoxins
Fungal conidia
Food Safety Issues
Fungicides
Fungal conidia
Human Fungal Infections
Animal Fungal Infections
Human Health Issues
Resistant isolates
Zoonosis
Without treatment options

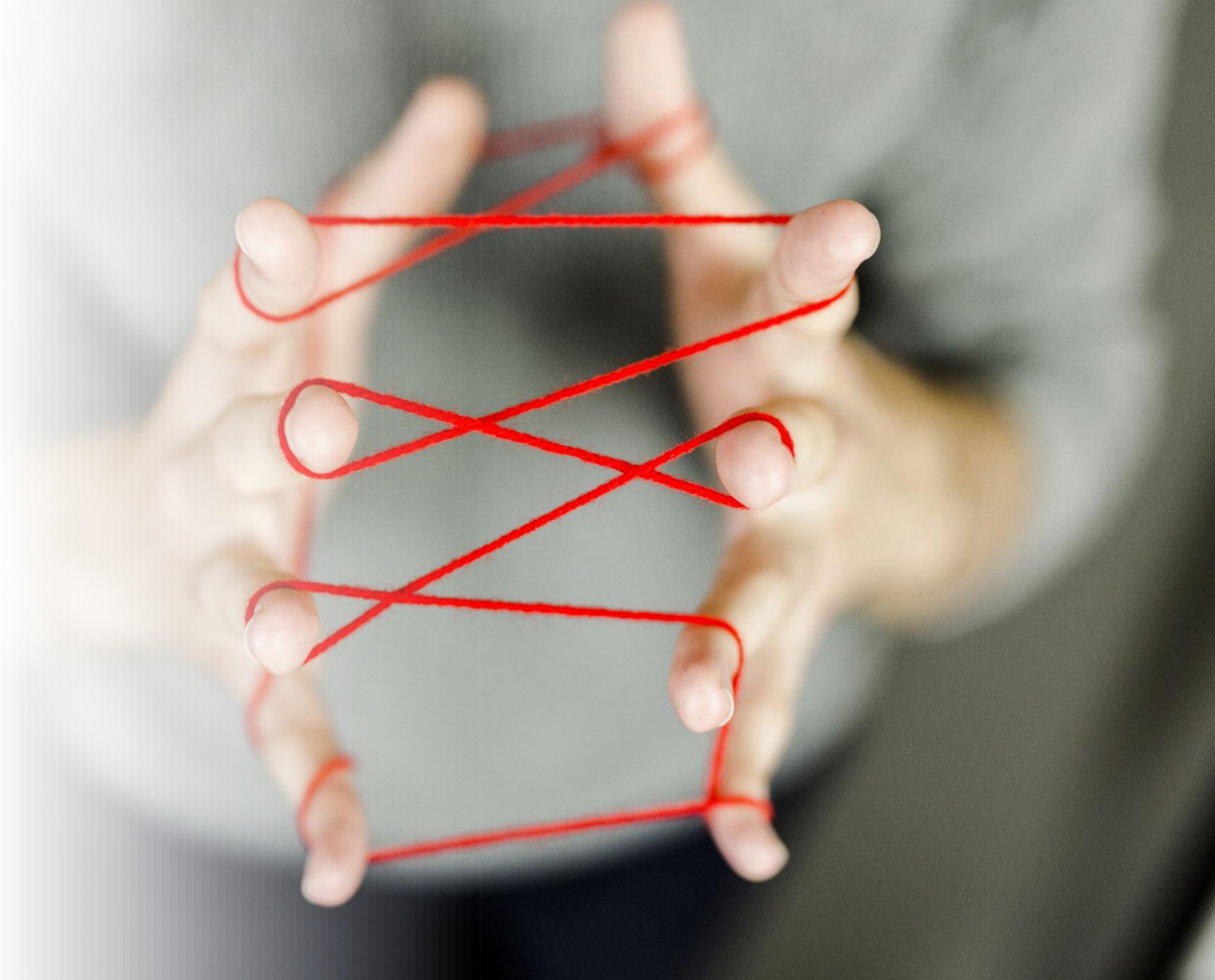
The Role of environmental factors in resistance



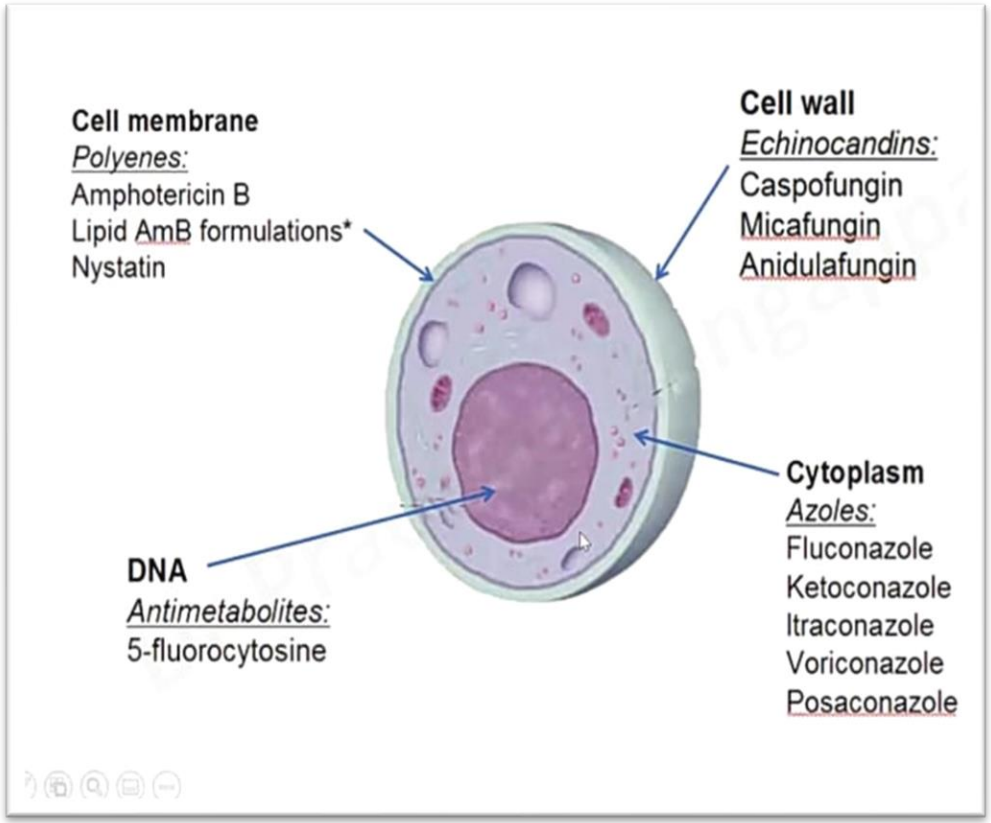
"Cross-Resistance between Fungicides and Antifungals"

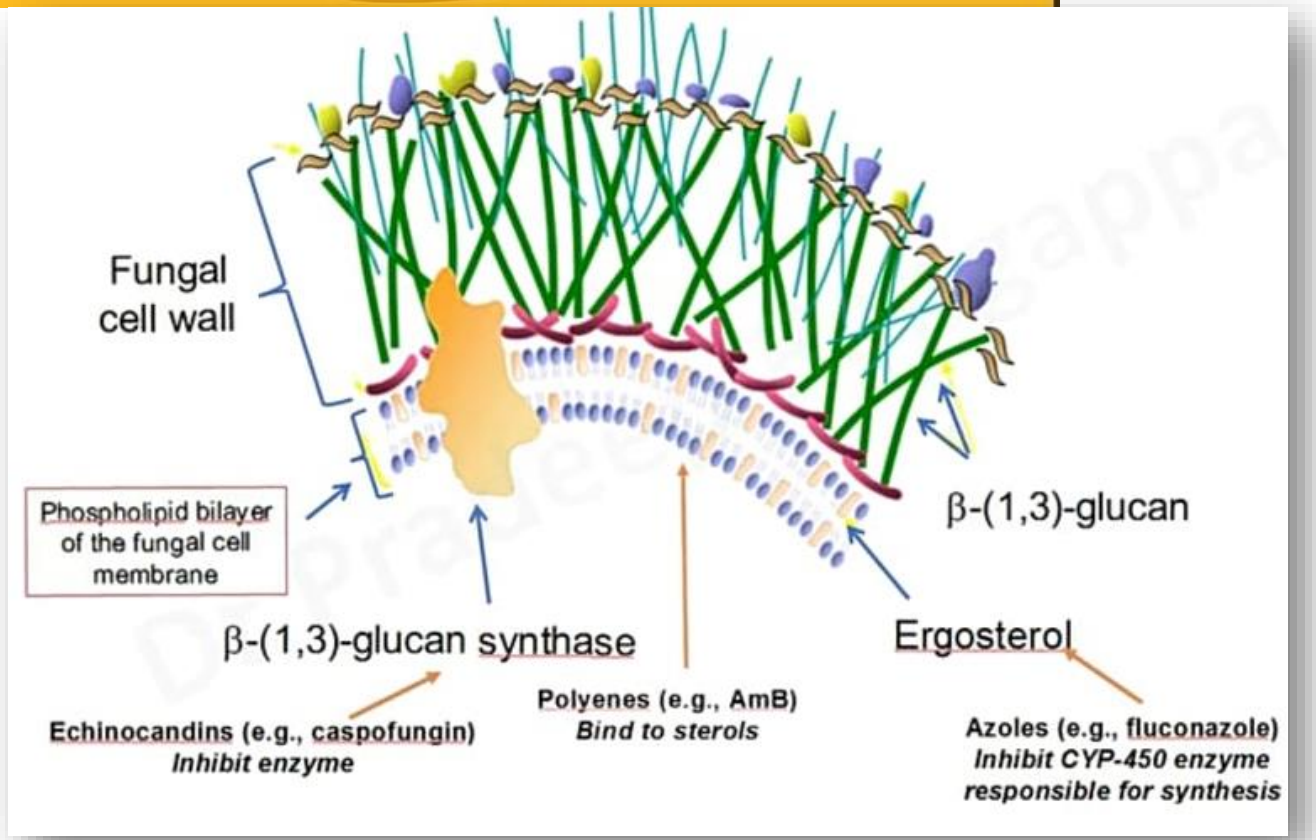


Multidrug resistance *Vs* Cross resistance

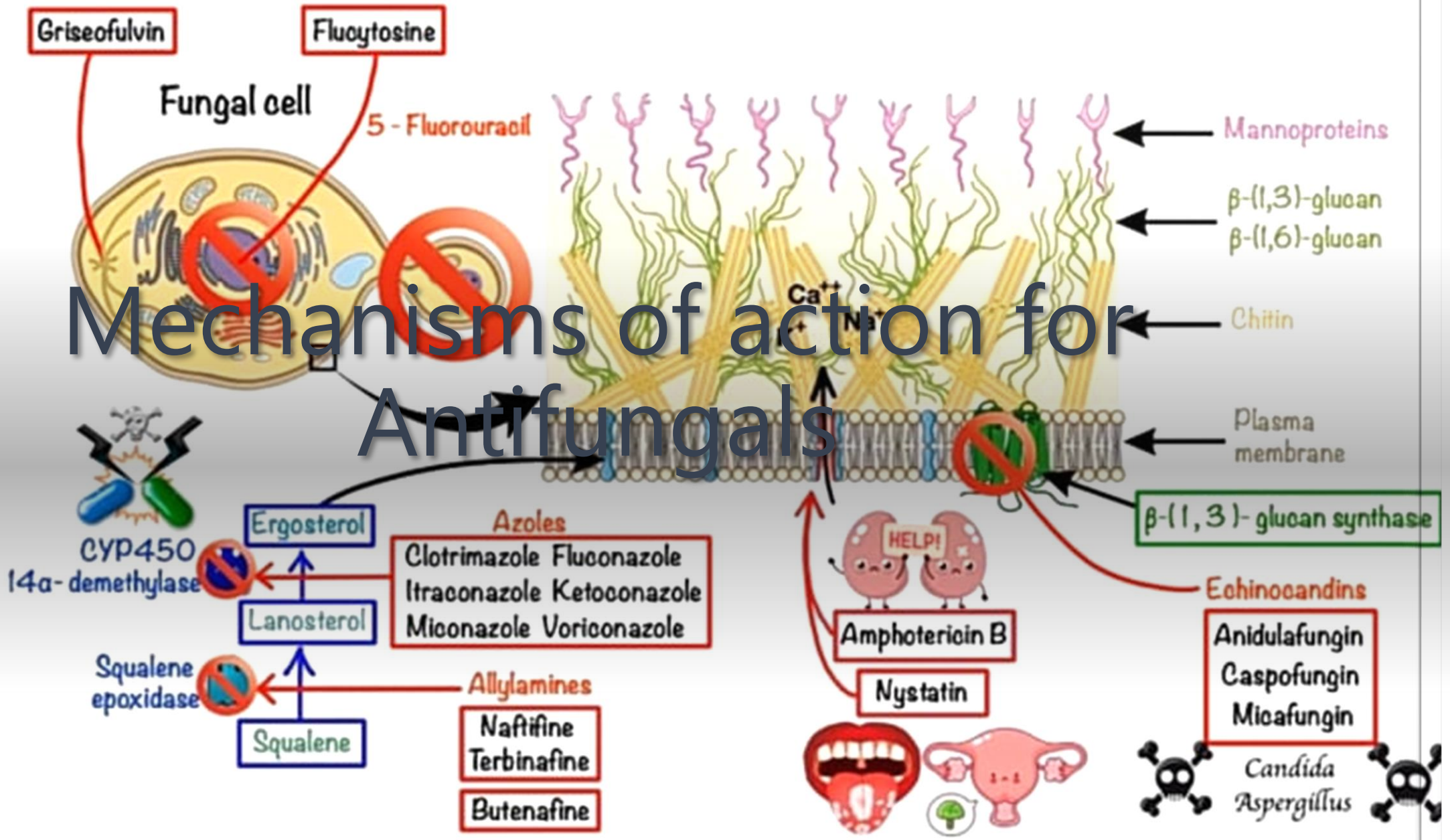



ANTIFUNGALS

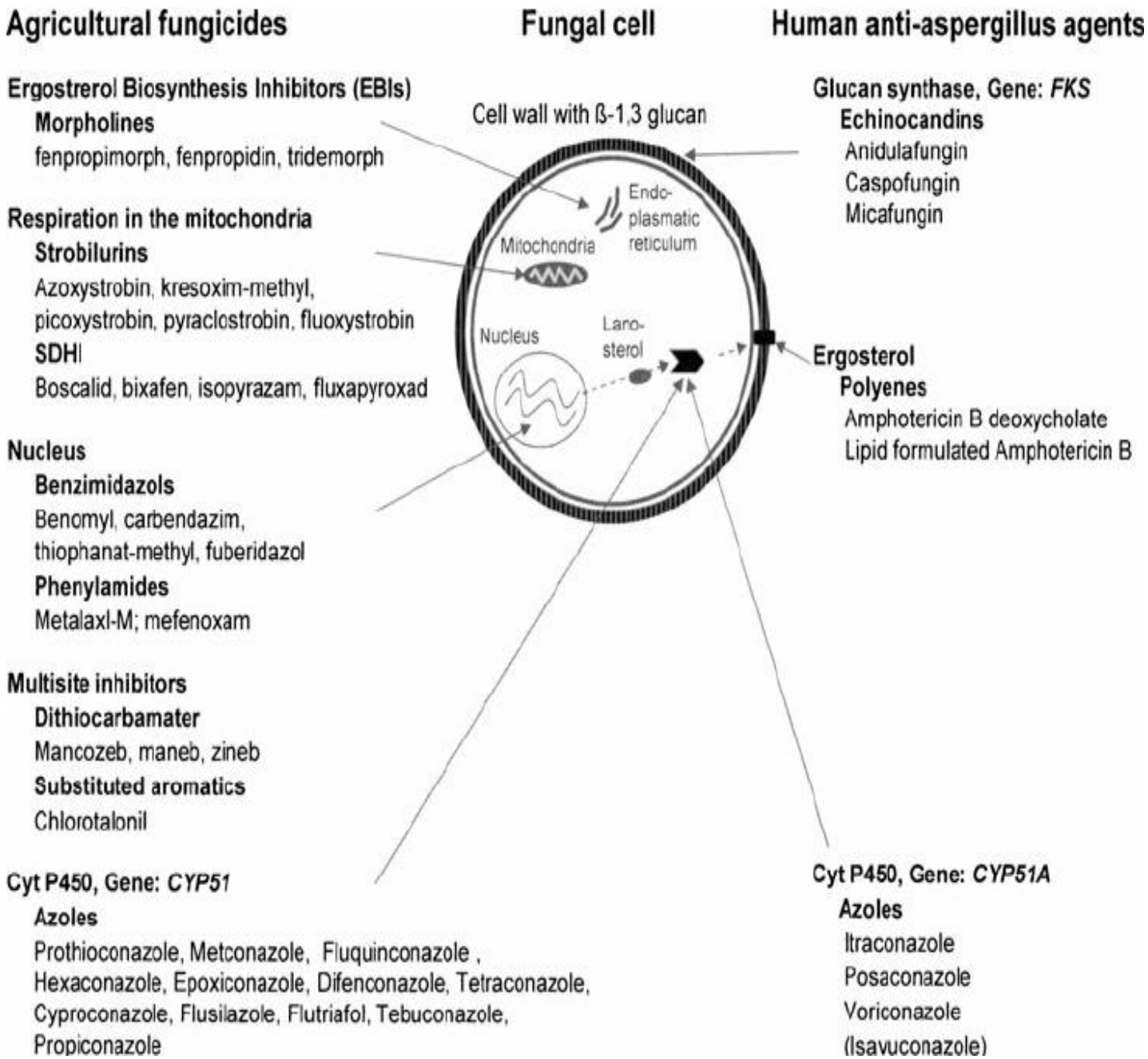

Cell membrane
Polyenes:
Amphotericin B
Lipid AmB formulations*
Nystatin
Cell wall
Echinocandins:
Caspofungin
Micafungin
Anidulafungin
Cytoplasm
Azoles:
Fluconazole
Ketoconazole
Itraconazole
Voriconazole
Posaconazole
DNA
Antimetabolites:
5-fluorocytosine

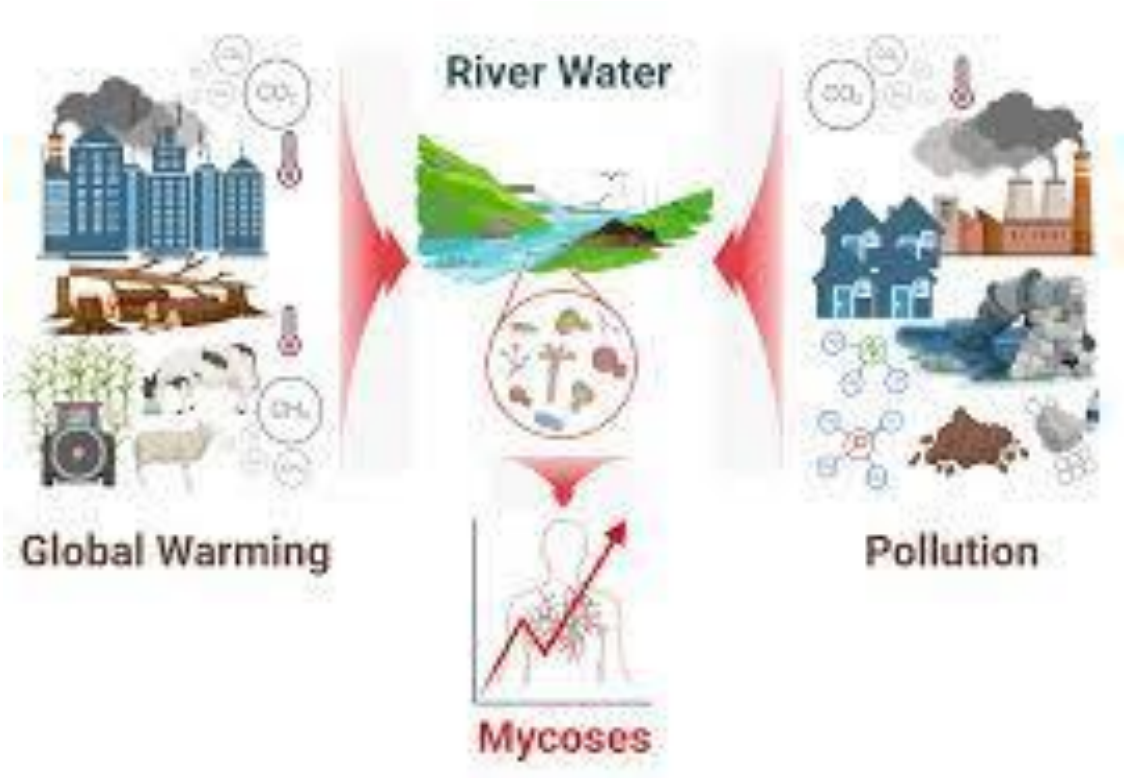

Fungal cell wall
Phospholipid bilayer of the fungal cell membrane
β-(1,3)-glucan
β-(1,3)-glucan synthase
Ergosterol
Echinocandins (e.g., caspofungin)
Inhibit enzyme
Polyenes (e.g., AmB)
Bind to sterols
Azoles (e.g., fluconazole)
Inhibit CYP-450 enzyme responsible for synthesis

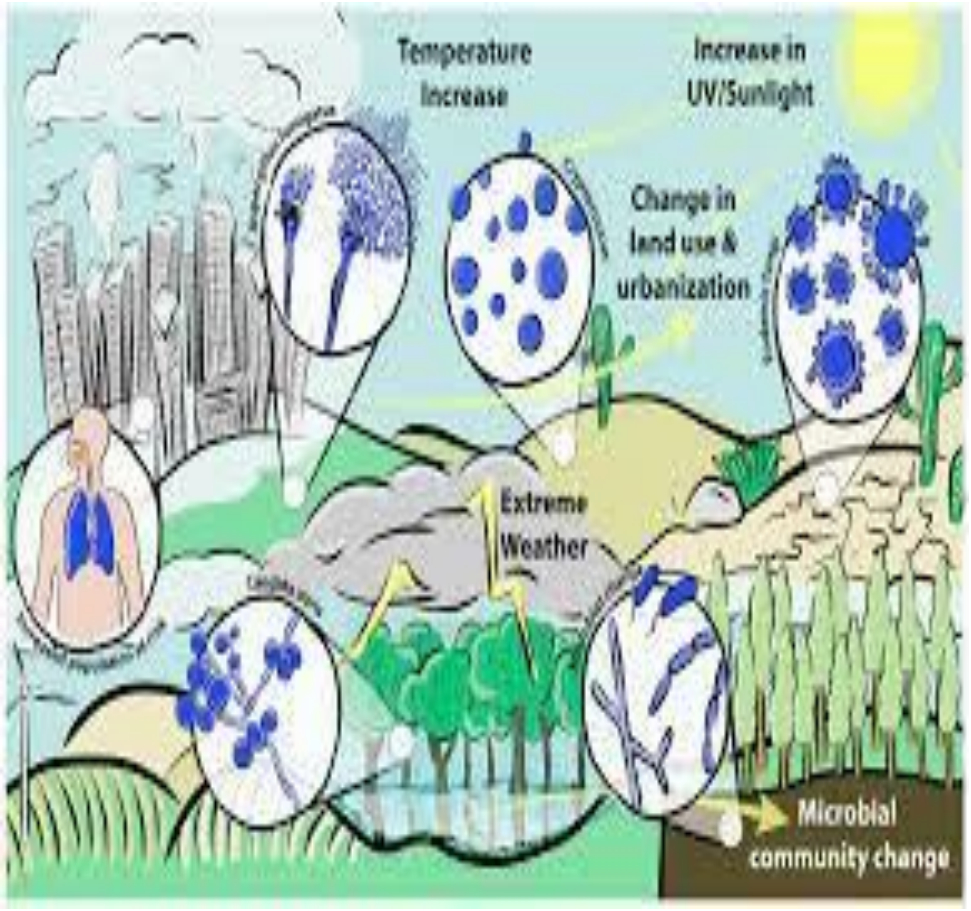
Mechanisms of action for Antifungals



Brief introduction about similarities between fungicides and antifungals

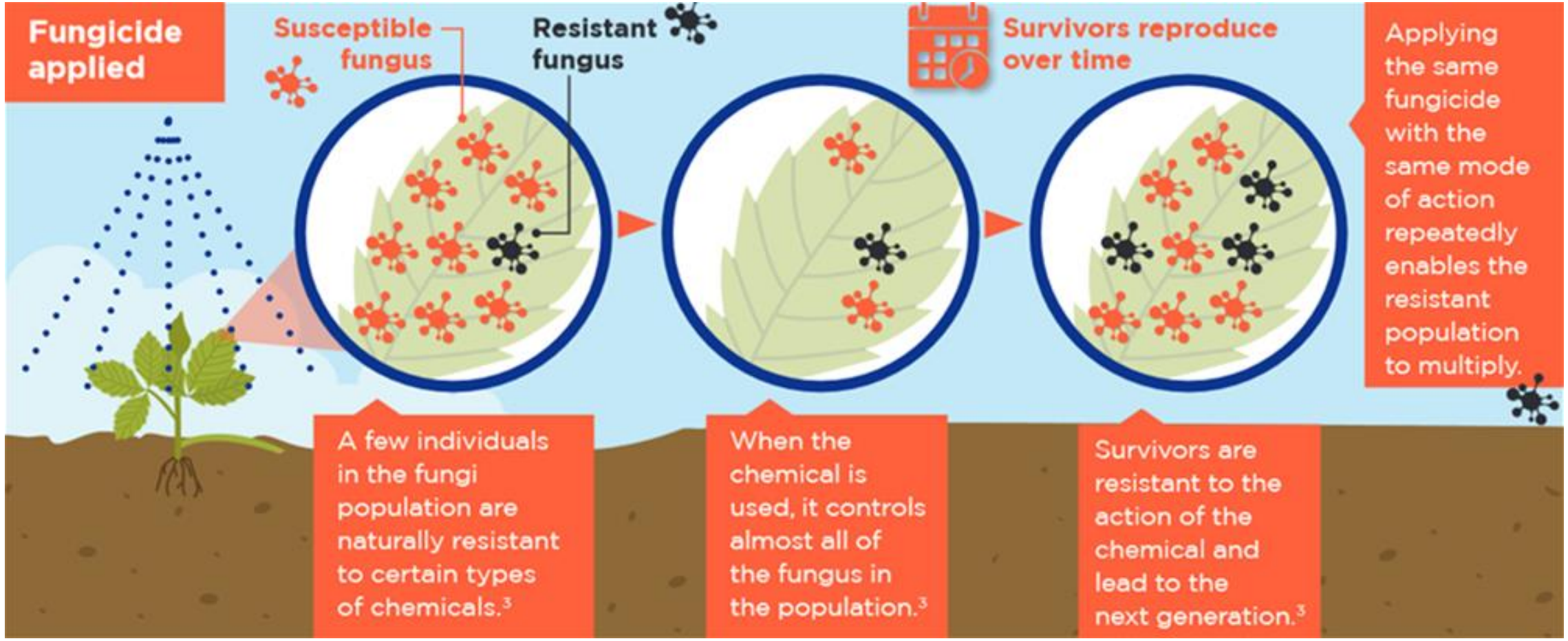






Impact of environmental changes on fungal diseases dissemination

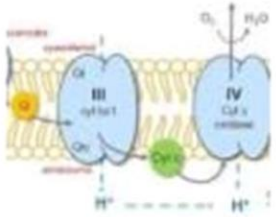
The growing concern about selection pressure



Understanding Mechanisms and Implications

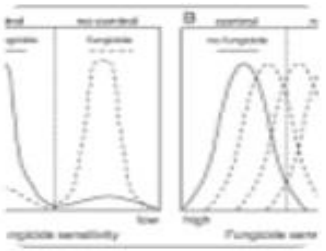
What are the 3 modes of action of fungicides?

In the following, fungicides and their modes of action are classified into three broad groups:

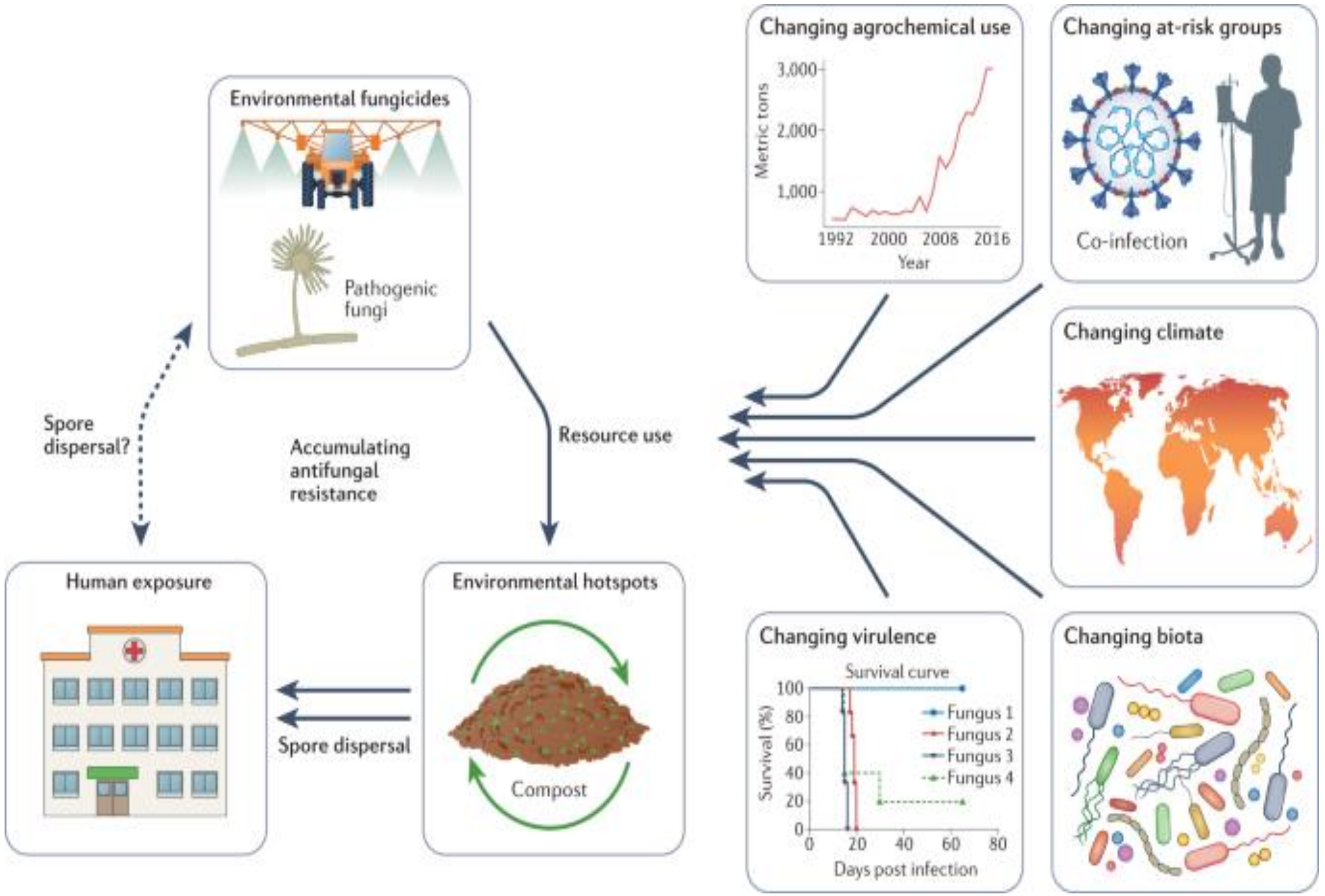


- Inhibitors of sterol synthesis.
- Inhibitors of mitochondrial electron transport (respiration inhibitors).
- Multi-site enzyme inhibitors, nucleic acid and protein synthesis inhibitors.

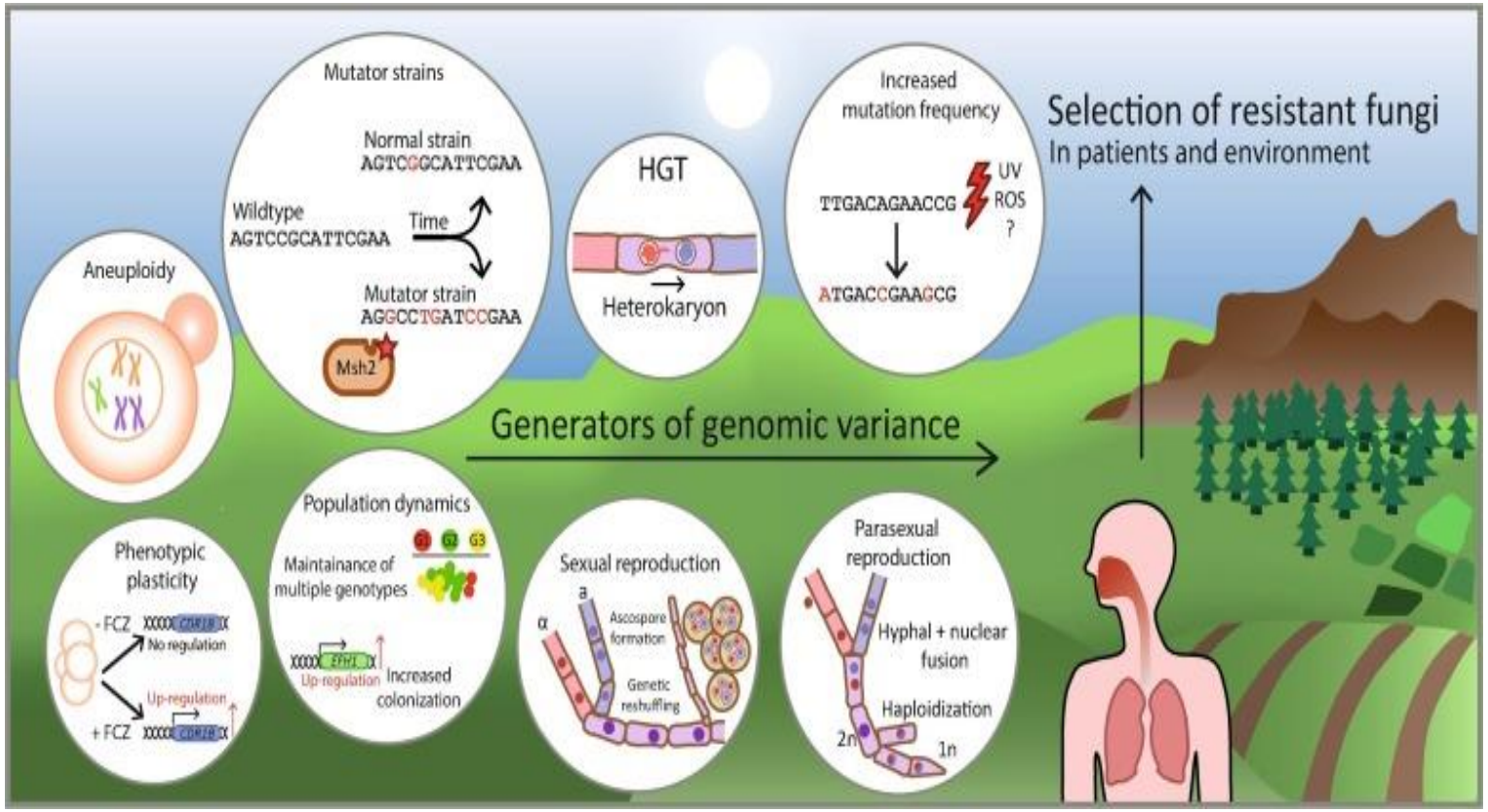
What causes fungicide resistance?



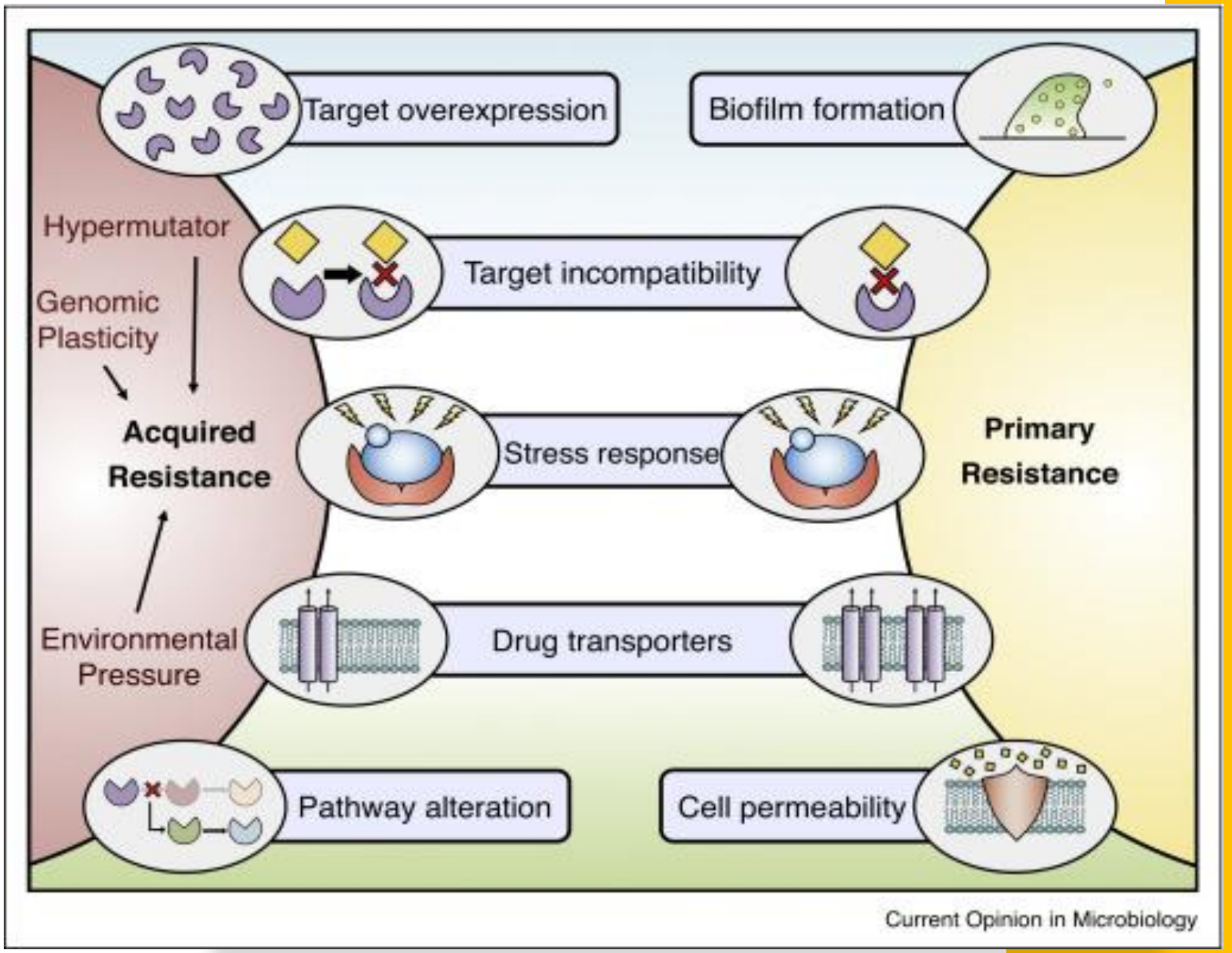
The build-up of resistant strains is caused by **repeated use of the fungicide which exerts selection pressure on the population**. The fungicide selectively inhibits sensitive strains, but allows the increase of resistant strains.


Environmental fungicides
Pathogenic fungi
Spore dispersal?
Accumulating antifungal resistance
Resource use
Human exposure
Environmental hotspots
Spore dispersal
Compost
Changing agrochemical use
Metric tons
3,000
2,000
1,000
1992
2000
2008
2016
Year
Changing at-risk groups
Co-infection
Changing climate
Changing virulence
Survival curve
Survival (%)
100
80
60
40
20
0
0
20
40
60
80
Days post infection
Fungus 1
Fungus 2
Fungus 3
Fungus 4
Changing biota

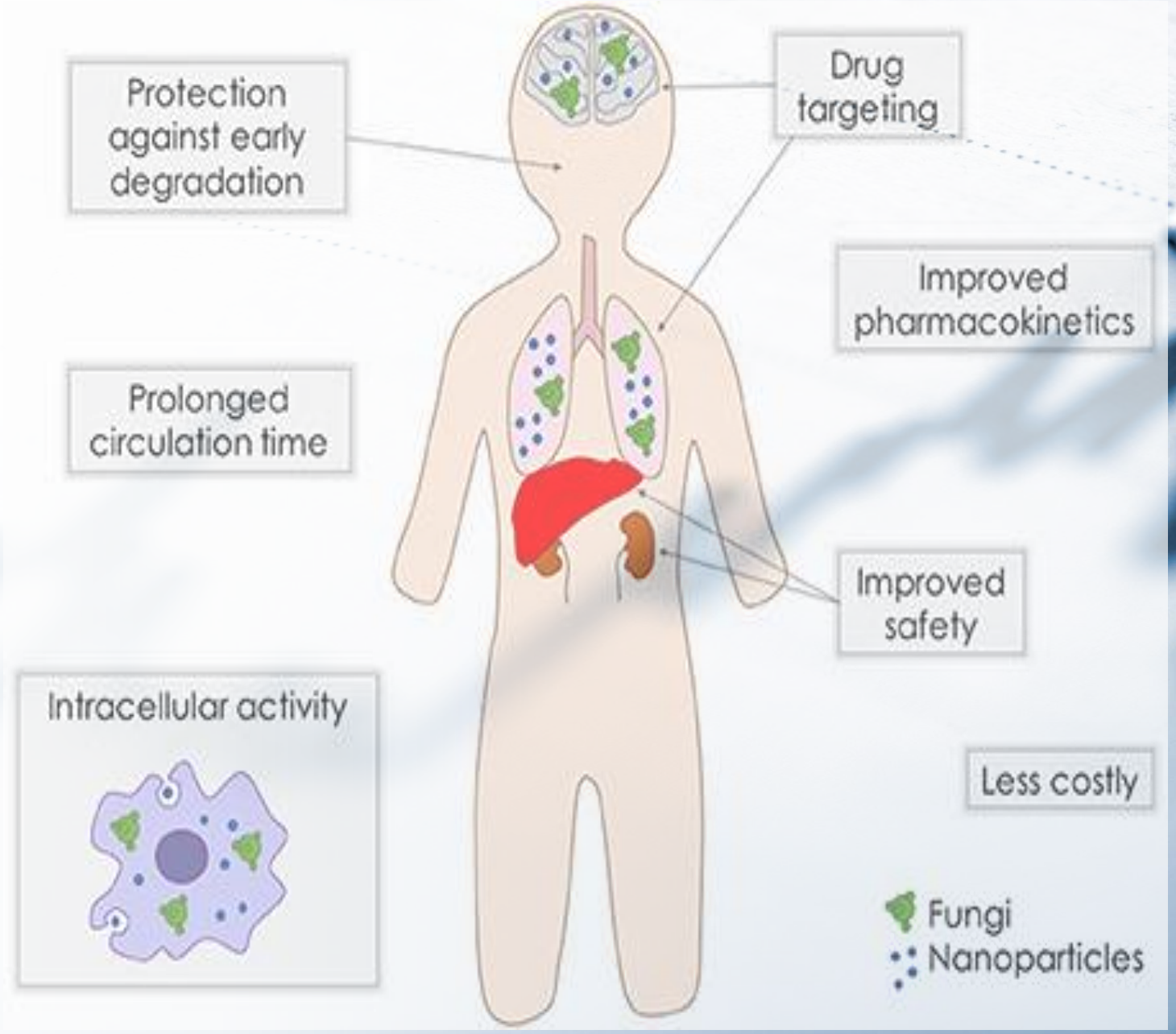
Target site modifications and genetic mutations

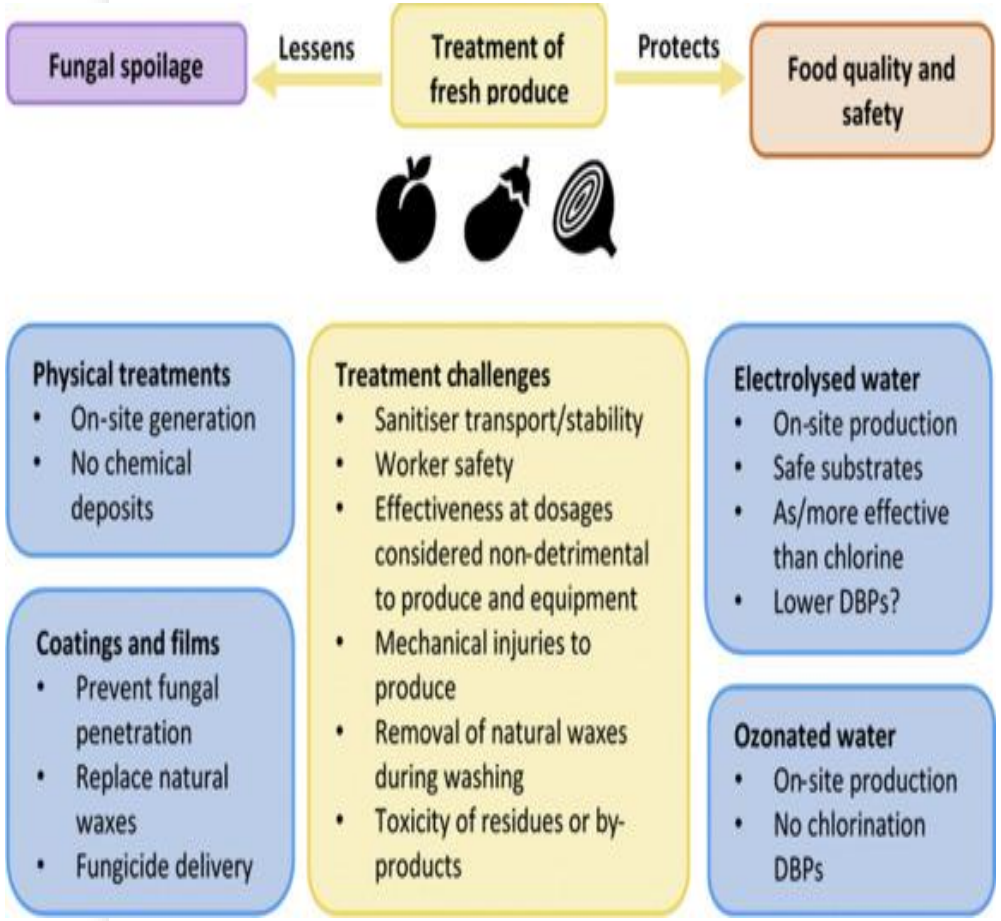


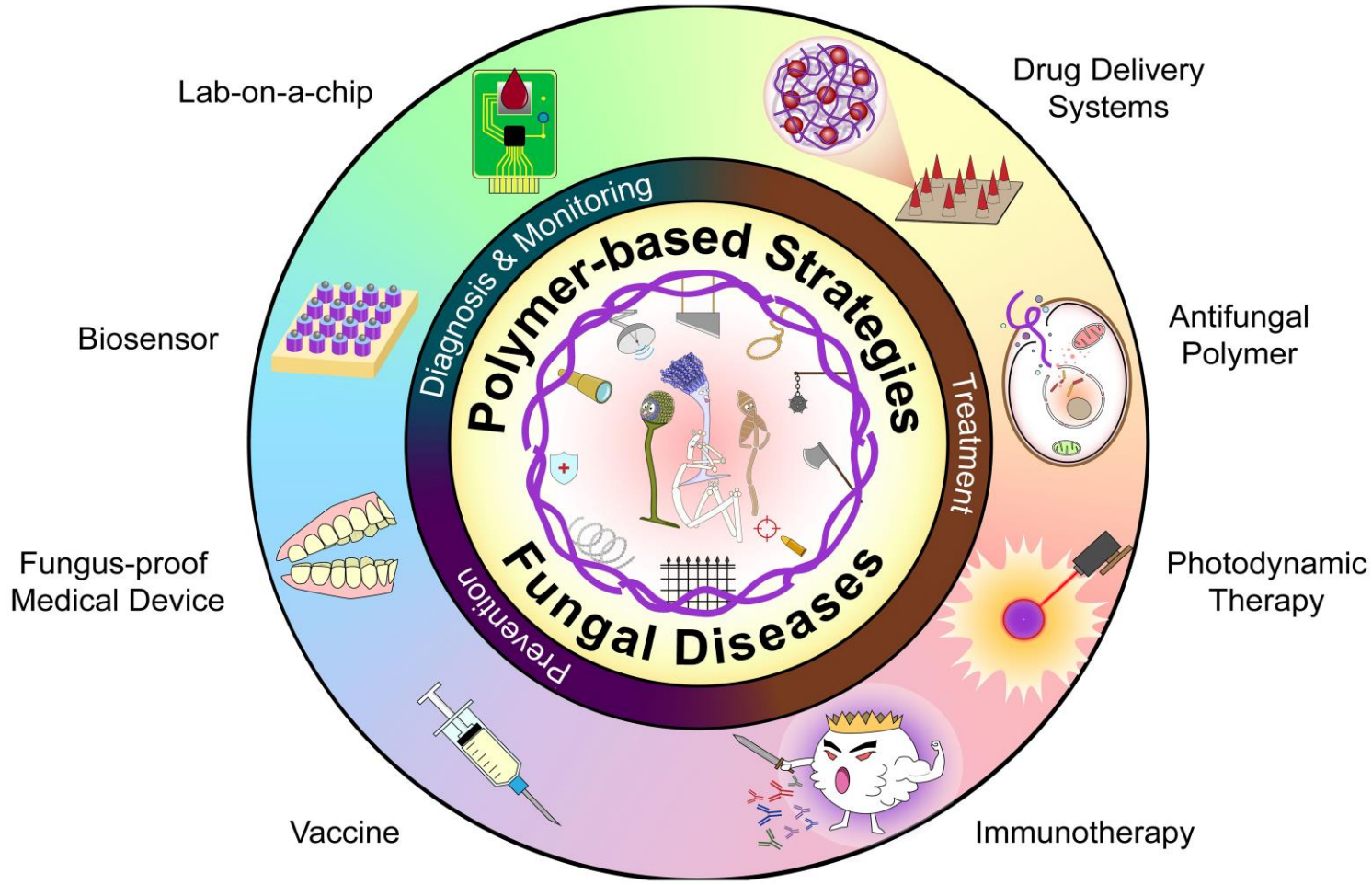
Resistance Mechanisms



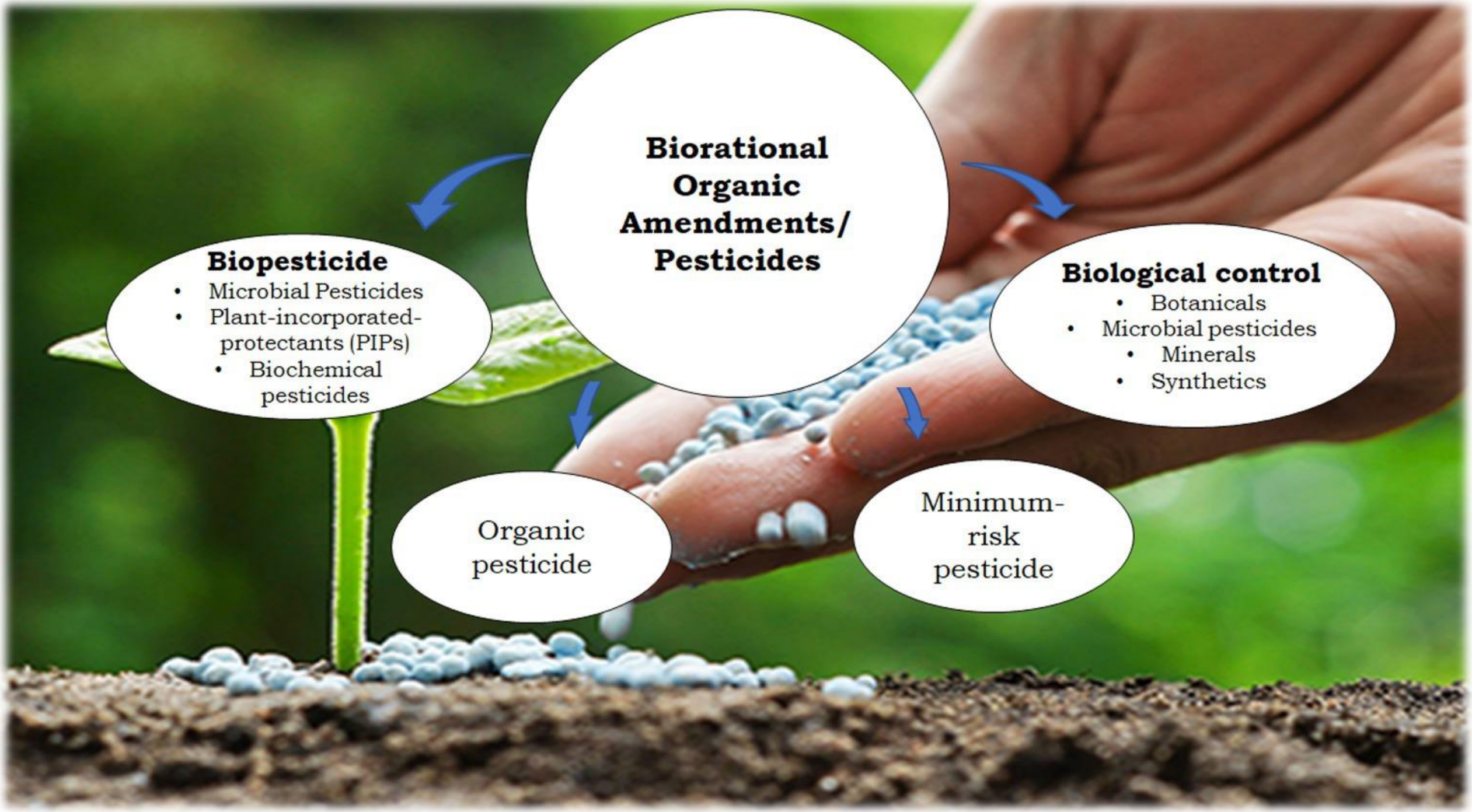
Collaborative efforts in research and development





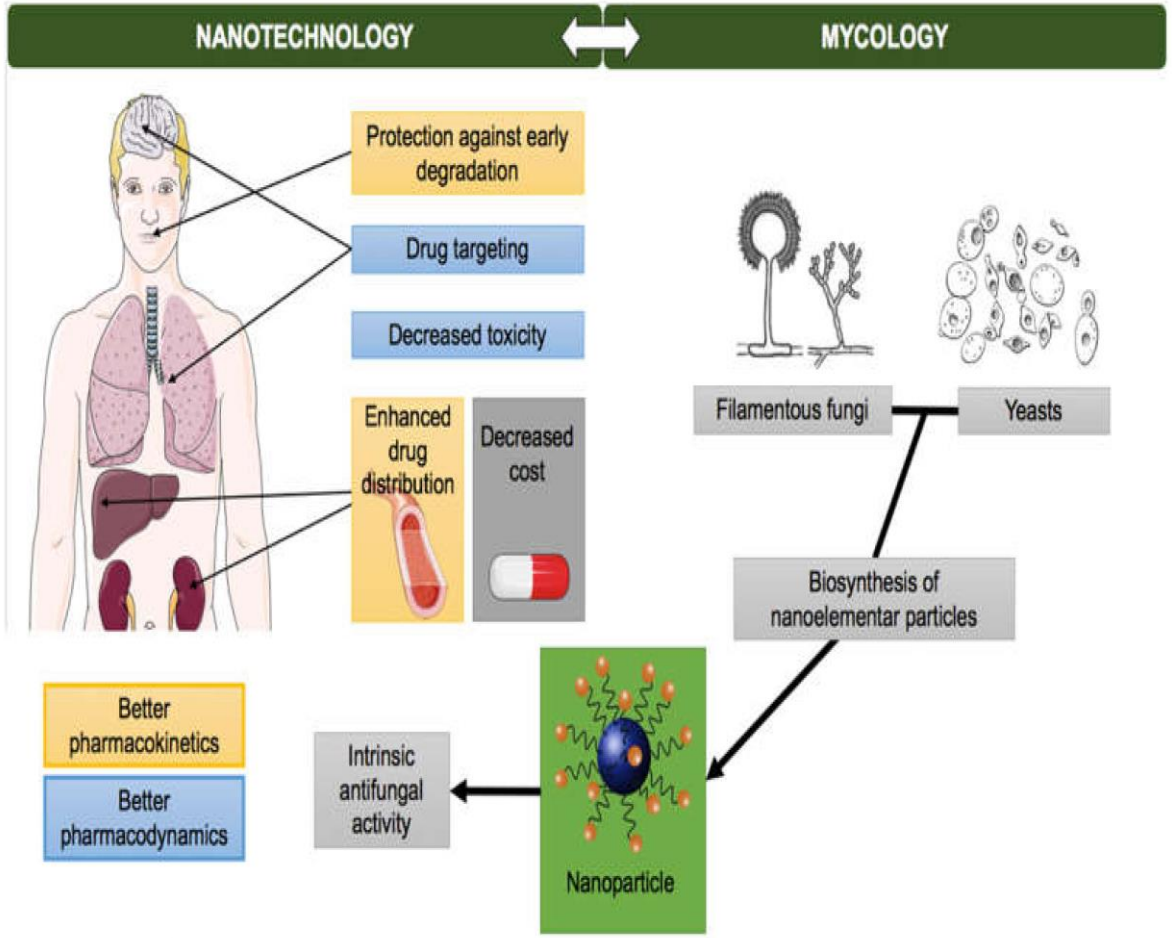


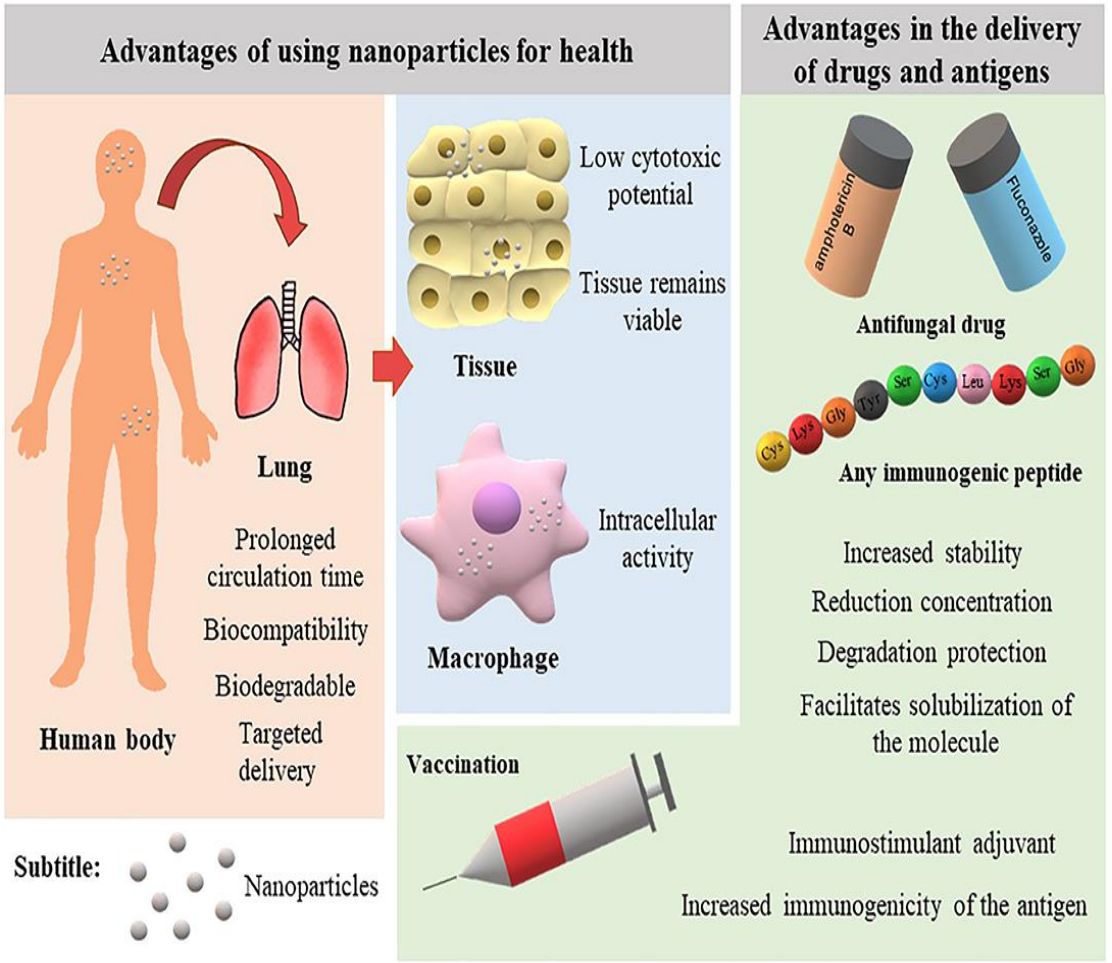
Emerging technologies and approaches


Biorational Organic Amendments/ Pesticides
Biopesticide
• Microbial Pesticides
• Plant-incorporated-protectants (PIPs)
• Biochemical pesticides
Biological control
• Botanicals
• Microbial pesticides
• Minerals
• Synthetics
Organic pesticide
Minimum-risk pesticide

Importance of Fungal Disease Control

New approaches for treatment of invasive mycosis [vaccines, immunotherapy, monoclonal antibodies, nanotechnology applications]





What is the new antifungal drug in 2023?

On March 22, 2023, the US Food and Drug Administration (FDA) approved Cidara's New Drug Application (NDA) for **rezafungin injection** for the treatment of candidaemia and invasive candidiasis (C/IC) in patients 18 years of age or older who have limited or no alternative treatment options. Jun 23, 2023

Mitigation Strategies

- Developing new, effective & less toxic antifungals and fungicides
- Continuous monitoring & Surveillance systems for Invasive mycosis
- Proper disease management *[diagnosis & ttt]*
- Importance of stewardship practices*; [mixed antifungals, cycling, proper selection, dose & duration].*

✓ Summary of key points

- **The incomplete removal or inactivation of antifungals during wastewater treatment led to develop new mutations.**
- **The direct application of the correct dose of fungicides to agricultural crops as a prophylaxis not treatment is a critical point.**
- **The environmental dimension of AFR warrants greater attention.**
- **Invasive mycoses predicted to become more common due to climate changes and increasing human populations, with no effective alternatives to azole fungicides currently available.**
- **It is detrimental to monitor and limit these impacts to secure future food security, healthcare and the global economy.**

Moreover, there is evidence of emerging fungal pathogens in plants, animals, and humans, due to the highly adaptive potential of these fungal pathogens, and also due to the occurrence of climate and ecological changes, globalization, and international commerce.

Furthermore, the emergence of resistant strains to antifungals due to their generalized use result in higher mortality due to severe fungal infections.

Hence, it is necessary to invest more in research and development and innovation targeted at evidence gaps and areas of unmet need.

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We don't grow when
things are easy,
we grow when we face
challenges.
THANK YOU!
THANK YOU!
THANK YOU!
THANK YOU!
THANK YOU!