

**An Introduction to Antifungal Drugs**  
 **$\beta$ -1,3-Glucan Synthase As a Target**

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# Fungi - Classification By Reproduction

## ➤ Chytridiomycetes

- Group of primitive aquatic fungi that have motile sexual and asexual spores with posterior flagella

## ➤ Zygomycetes

- Zygomycetes have thick-walled resting sexual spores called zygospores; their asexual spores are produced in a sporangium and called sporangiospores. Example is the common black bread mold, *Rhizopus nigricans*.

## ➤ Ascomycetes

- Ascomycetes produce sexual spores (ascospores) in a sack-like body called an ascus, their asexual spores are produced externally, borne on a conidiophore. *Aspergillus nidulans* and *Sporothrix schenckii* are members of this class.

## ➤ Basidiomycetes

- Basidiomycetes produce their spores externally from a club-like structure called a basidium, these generally have no asexual spores. Members include some of the most complex fungi, including mushrooms and puffballs.

## ➤ Deuteromycetes

- Also called the “fungi imperfecti”. *Candida*, an example of a deuteromycete, is a dimorphic fungus responsible for “yeast infections” in humans. Deuteromycetes do not produce spores.

# Pathogenic Fungi – Classification by Morphology

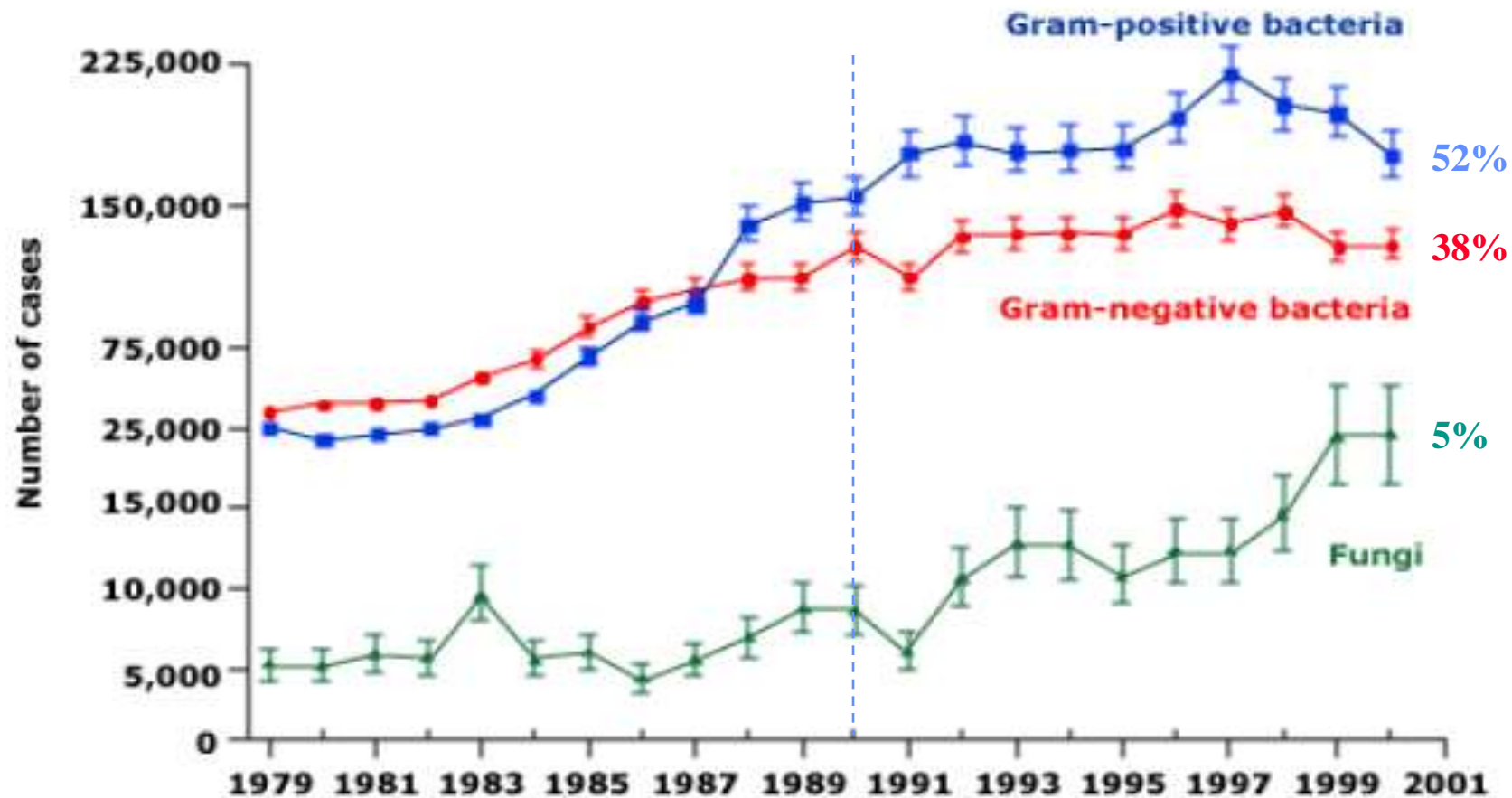
- **Yeasts (Unicellular - buds)**
  - *Saccharomyces cerevisiae* (Baker's yeast)
  - various *Candida* species
  - *Cryptococcus neoformans*
- **Moulds (Multicellular – hyphae and spores)**
  - *Aspergillus fumigatus*, *A. terreus*, ... (soil-borne pathogen)
  - *Fusarium* spp., ... (infects both plant and animal species)
  - *Trichophyton* (dermatophyte)
- **Dimorphic Fungi**
  - Capable of growing in mould or yeast form
  - *Candida albicans* (part of common skin flora ~50%)
  - *Blastomyces dermatitidis*, *Histoplasma capsulatum*, ... (outbreaks in Southwest US of lung infections)

# Fungi Are...

- **Ubiquitous**
  - in soil, air, water, food, ...
- **Part of the natural flora**
  - skin, mucous membranes, GI tract, ...
- **Typically not a problem unless compromised immunity or invasive procedures**
  - AIDS, BMT, broad spectrum AB therapy, burn patients, cancer and associated chemotherapy, invasive surgeries, organ transplant therapy
- **Increasing in frequency as pathogens**
  - More invasive therapies, resistance to existing antibiotics

# Increasing Incidence of Fungal Sepsis

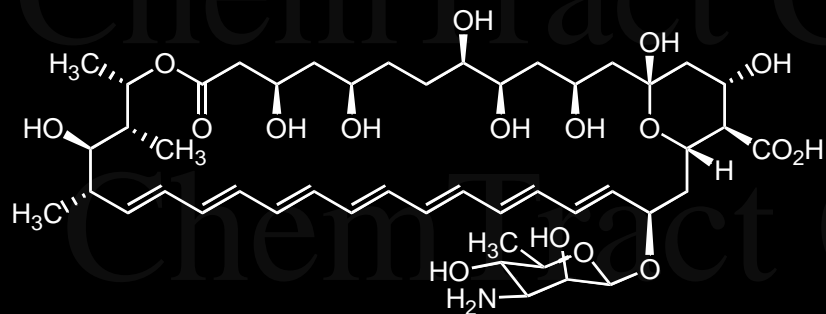
Number of cases of sepsis in the United States, according to causative organism, 1979 - 2000



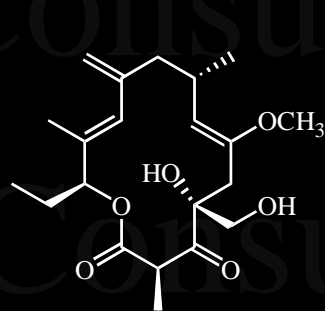
# It's a Tough World Down There!

- **Fierce Competition**
  - ~ 5000 to 10000 species of microorganisms in a handful of dirt
- **Limited Resources**
  - microorganisms are competing for nutrients
- **Chemical Warfare (they never signed a treaty!)**
  - fungi and bacteria are a rich source of antifungal and antibacterial agents
  - most anti-infectives are derived from natural products
  - Many other classes of natural product-derived drugs were first identified because of their antibiotic properties
    - cyclosporin, rapamycin (immunomodulants)
    - compactin, mevastatin (statins)
    - taxol (anticancer)

# Antifungal Natural Products From Bacteria and Fungi



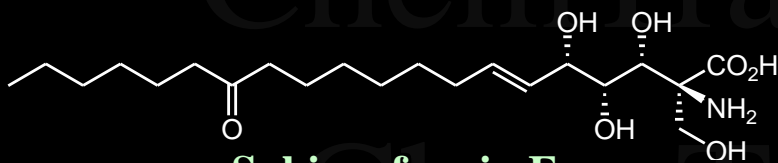
**Amphotericin B**  
(*Streptomyces nodosus*)



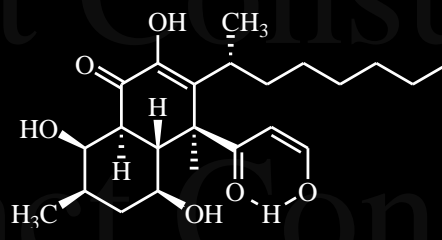
**Galbonolide A**  
(*Streptomyces galbus*)



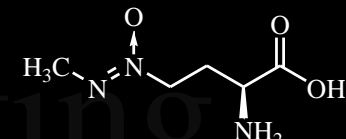
**Enfumafungin**  
(*Hormonema* spp.)



**Sphingofungin F**  
(*Paecilomyces variotii*)



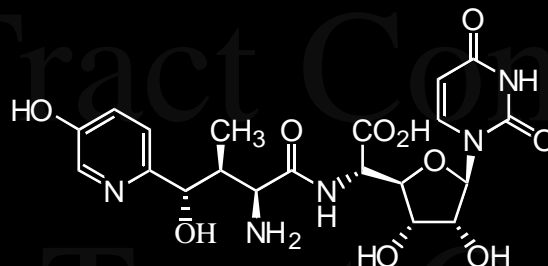
**Australifungin**  
(*Sporormiella australis*)



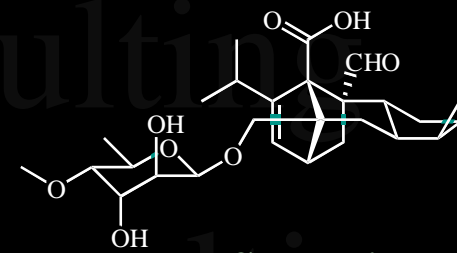
**Azoxbacilin**  
(*Bacillus cereus*)



**Benanomycin A**  
(*Actinomycete*)

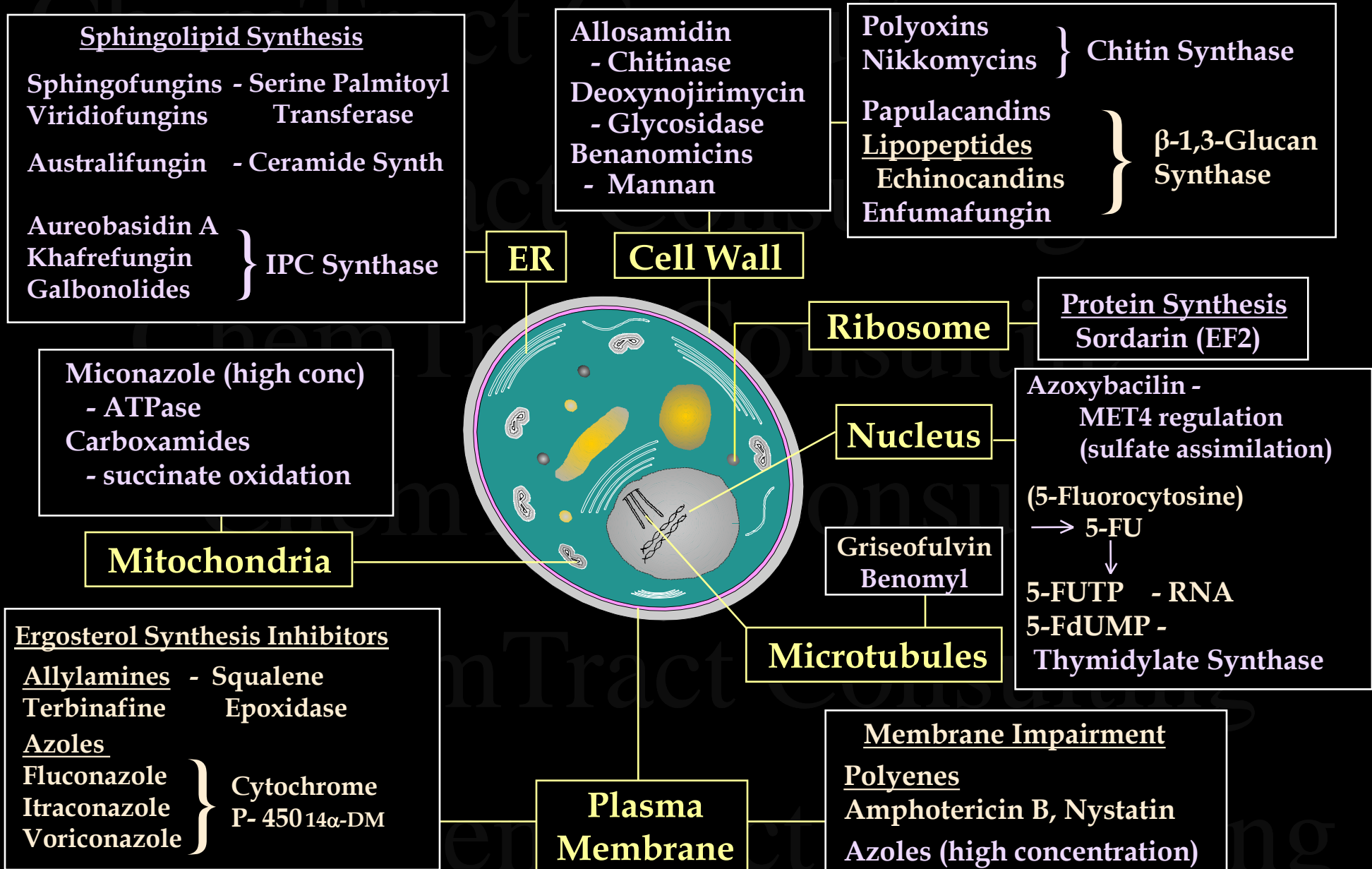


**Nikkomycin Z**  
(*Streptomyces* spp.)



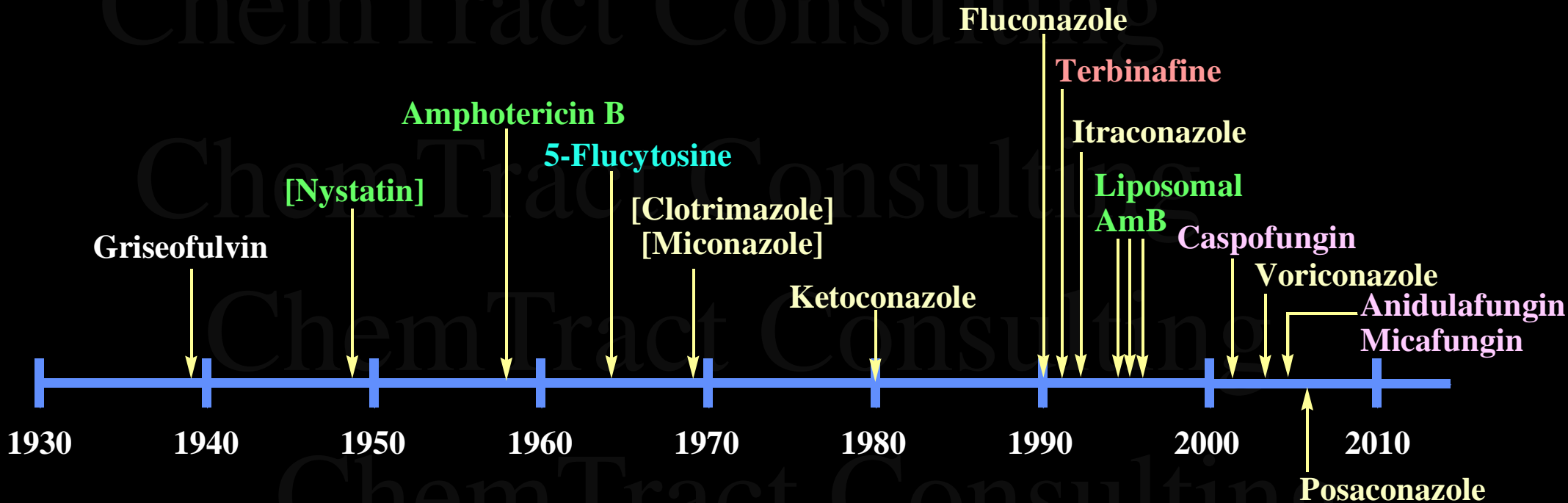
**Sordarin**  
(*Sordaria araneosa*)

# Many Antifungal Targets...





# Some Clinically Important...

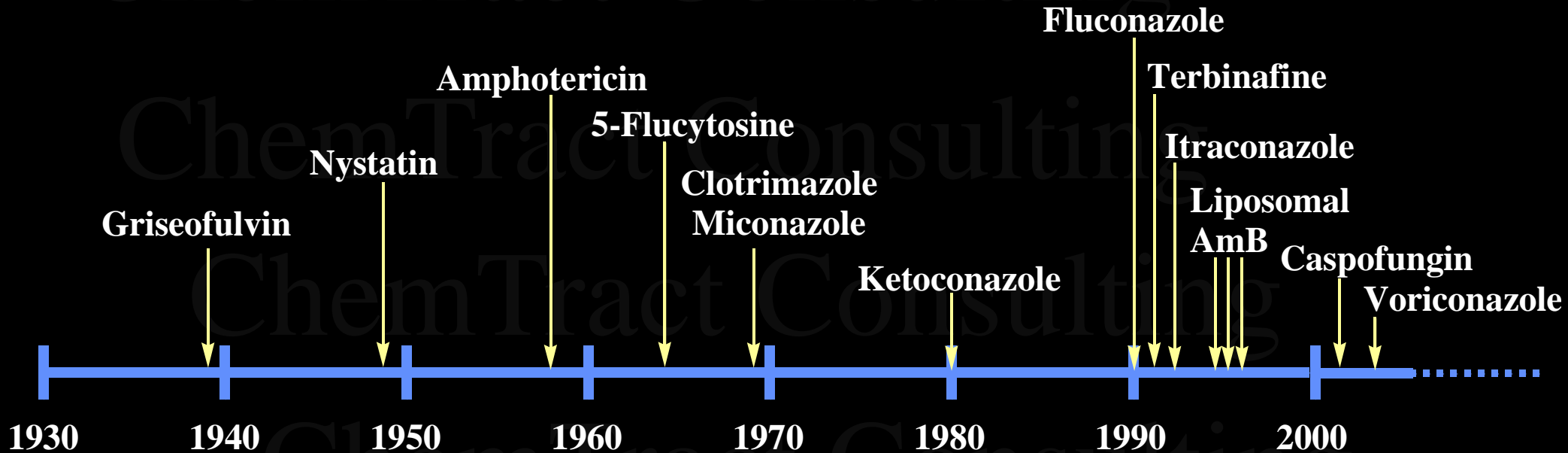


- Ergosterol binding - polyenes
- RNA/DNA synth - pyrimidines
- 14 $\alpha$ -Demethylase - azoles
  - Squalene epoxidase - allylamines
  - $\beta$ -1,3-Glucan synthase - echinocandins

Baum *Postgrad. Med. J.* **55**, 587 (1978)

Andriole *Inf. Dis. Clin. Practice* **7** (supp 1), S2 (1998)

# Chronology of Antifungal Therapy



- Polyenes

- Pyrimidines

- Azoles

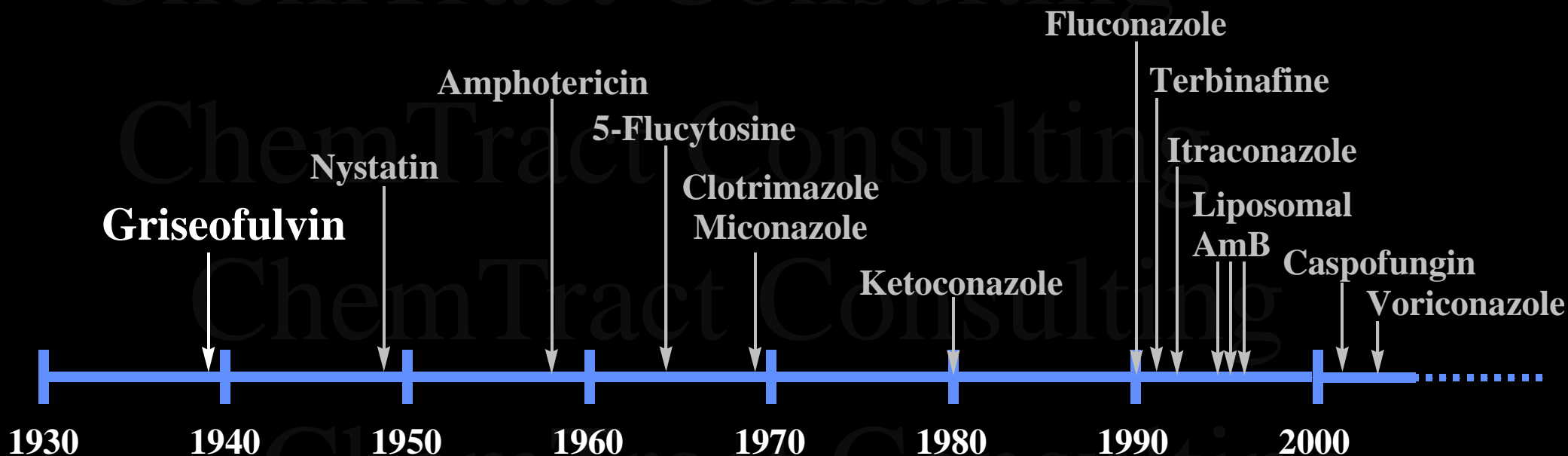
- Allylamines

- Echinocandins

Baum *Postgrad. Med. J.* **55**, 587 (1978)

Andriole *Inf. Dis. Clin. Practice* **7** (supp 1), S2 (1998)

# Chronology of Antifungal Therapy

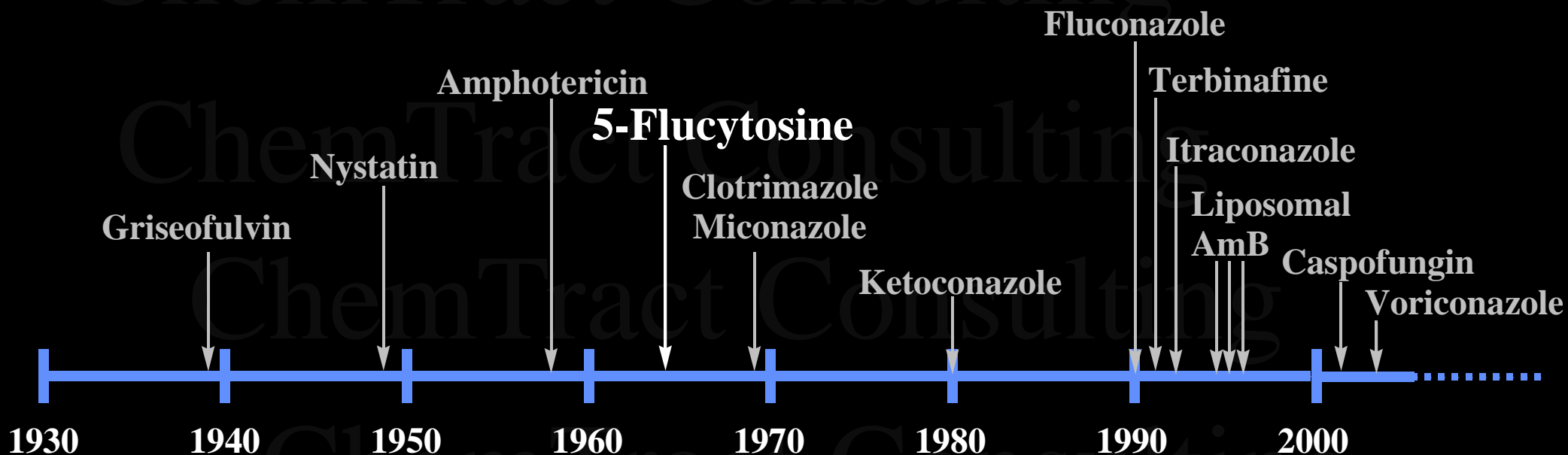


(from *Penicillium griseofulvin*)

- First treatment available for the specific treatment of fungal infections
- Inhibits fungal mitosis by disrupting the mitotic spindle through interaction with polymerized microtubules
- Activity limited to dermatophytes



# Chronology of Antifungal Therapy

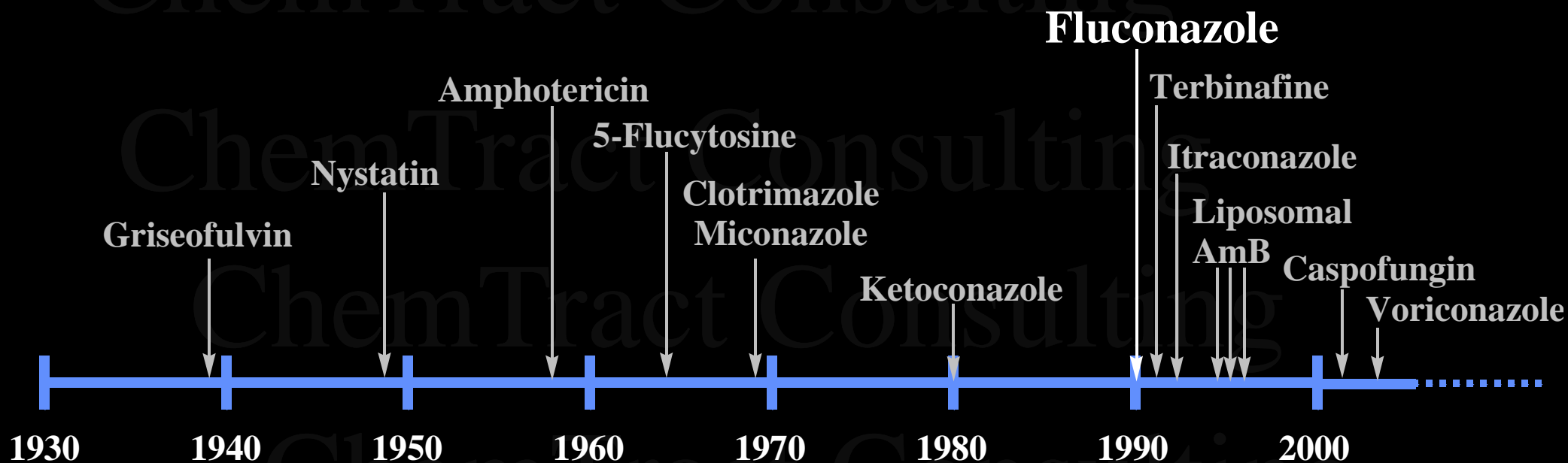


fungal  
cytosine  
deaminase

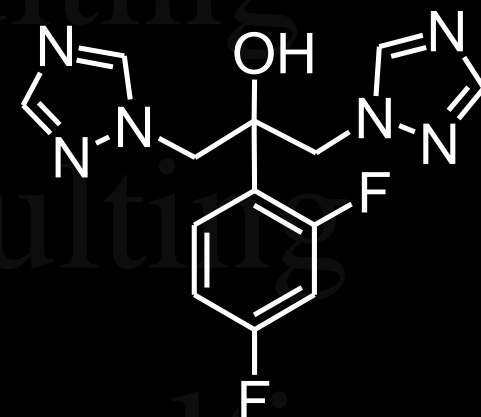


- Inhibits RNA and protein synthesis
- Narrow spectrum
- Resistance an issue: must be used in combination therapy
- Can cause myelosuppression and hepatotoxicity

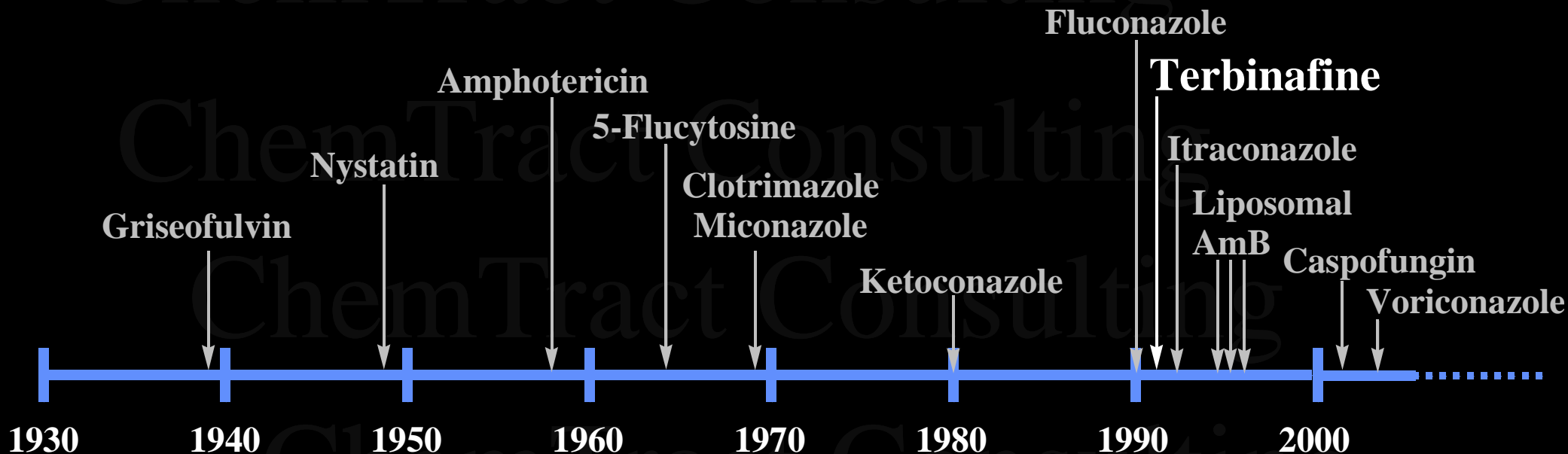
# Chronology of Antifungal Therapy



- Inhibits ergosterol biosynthesis
  - CYP450-dependent  $14\alpha$ -lanosterol demethylase
- Excellent PK and tolerability
- Resistance an issue (intrinsic *vs* acquired)
  - *C. krusei*, *C. albicans*
- Inactive against *A. fumigatus*



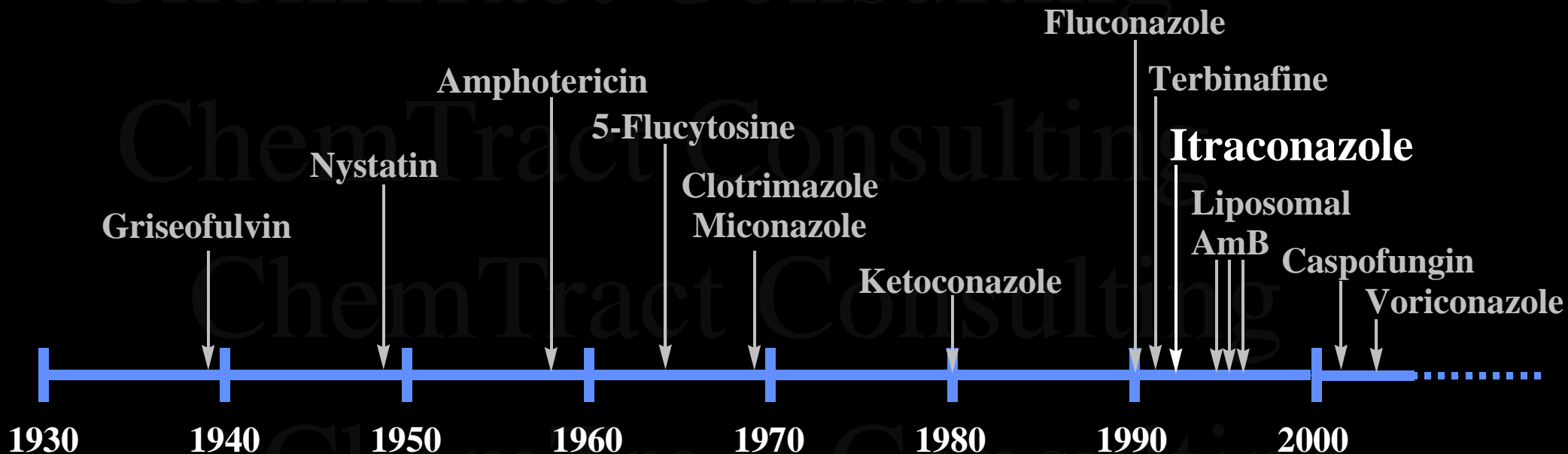
# Chronology of Antifungal Therapy



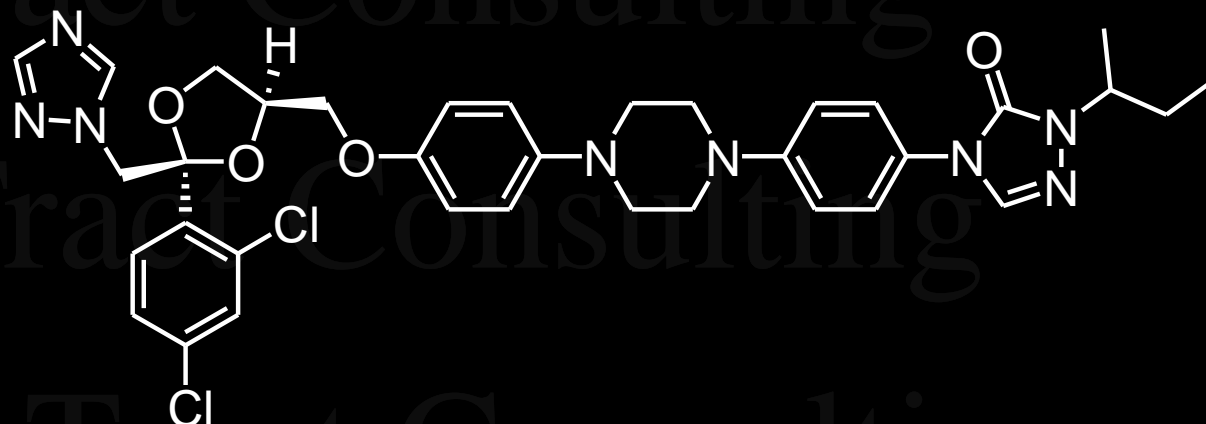
- Squalene epoxidase inhibitor
- Potent dermatophyte activity
- *Aspergillus* activity
- Modest *Candida* activity



# Chronology of Antifungal Therapy

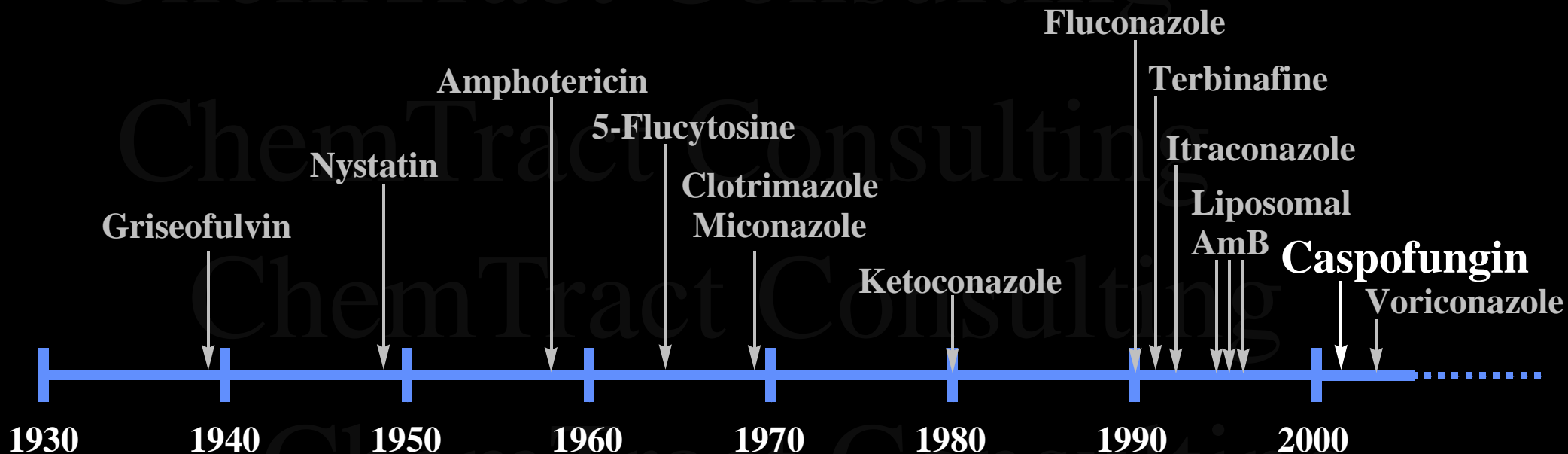


- Ergosterol biosynthesis inhibitor
- Improved potency
- Activity against moulds
- Poor solubility





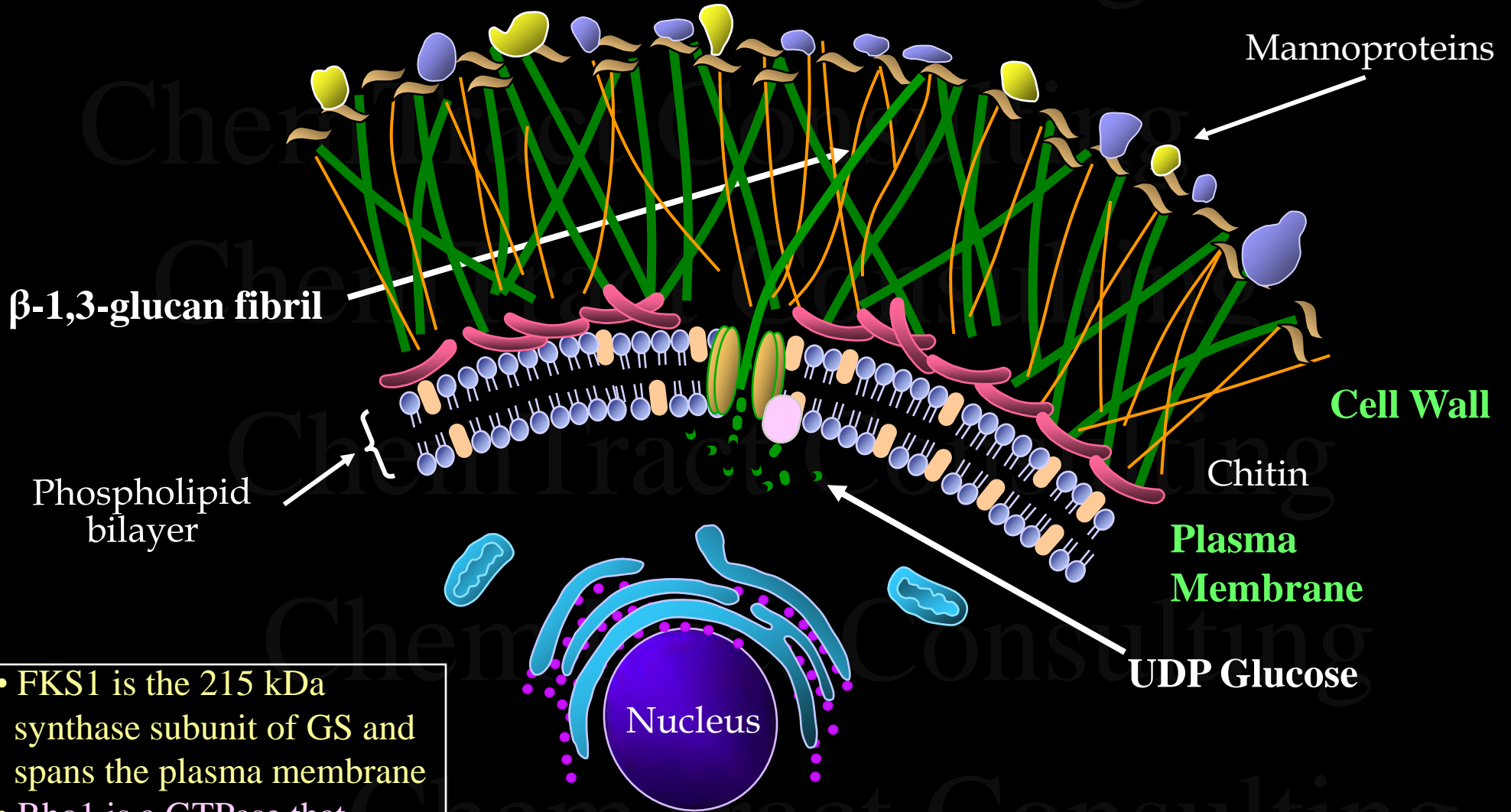
# Chronology of Antifungal Therapy



- Inhibitor of fungal cell wall synthesis
- Semi-synthetic derivative of pneumocandin B<sub>0</sub>



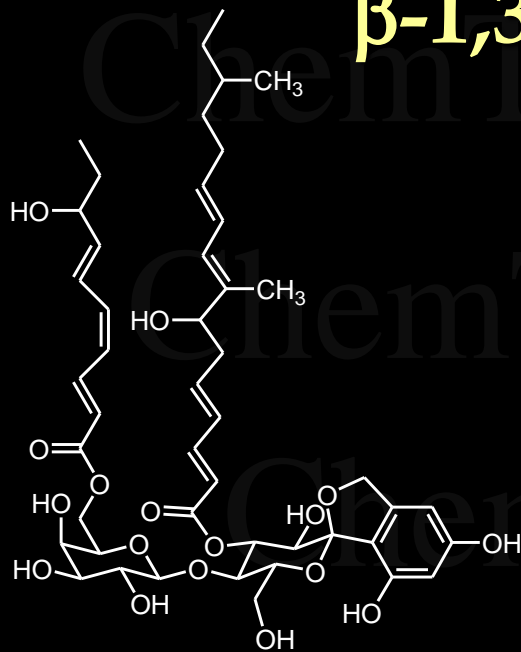
# $\beta$ -1,3-Glucan As a Cell Wall Target



- FKS1 is the 215 kDa synthase subunit of GS and spans the plasma membrane
- Rho1 is a GTPase that upregulates glucan synthesis

spatial and temporal orchestration of cell structure

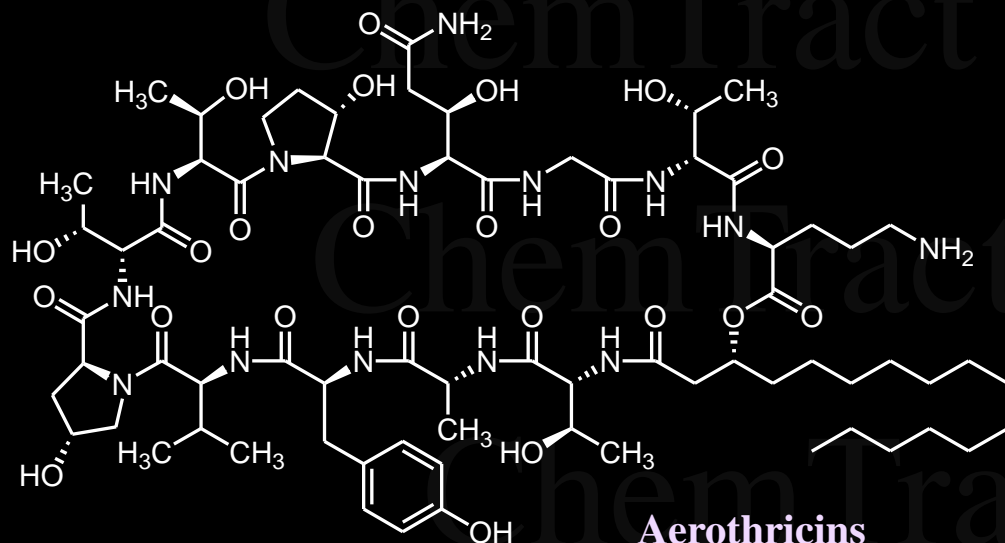
# $\beta$ -1,3-Glucan Synthesis Inhibitors



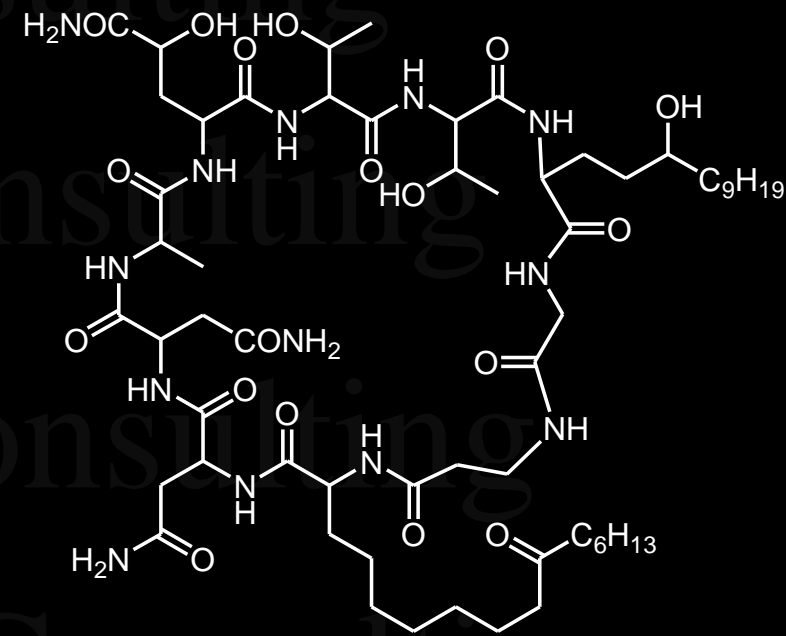
**Papulacandins**



**Echinocandins**

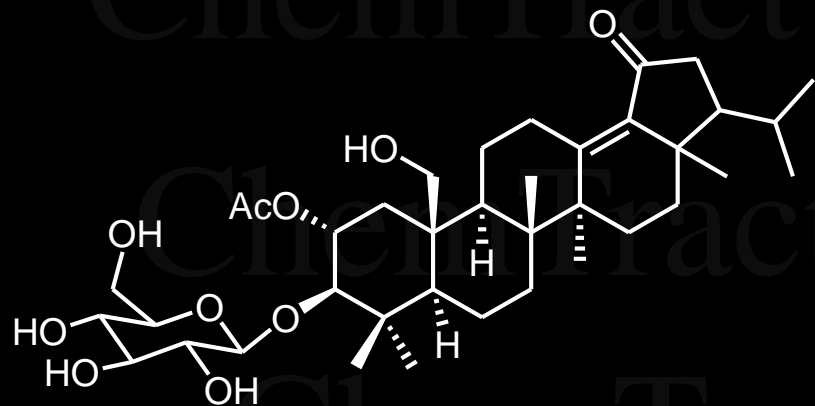


**Aerothricins**

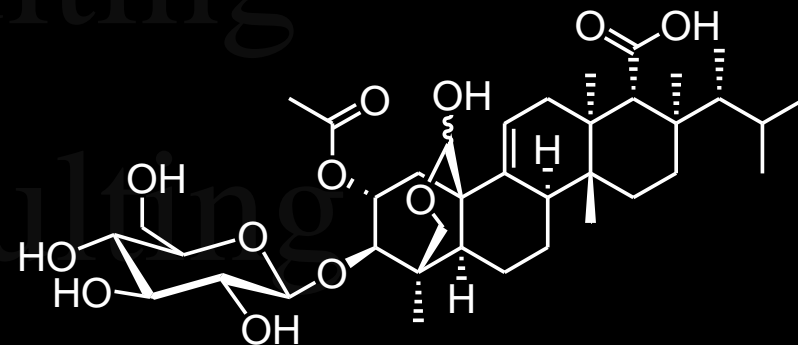


**Sankyo Lipopeptides**

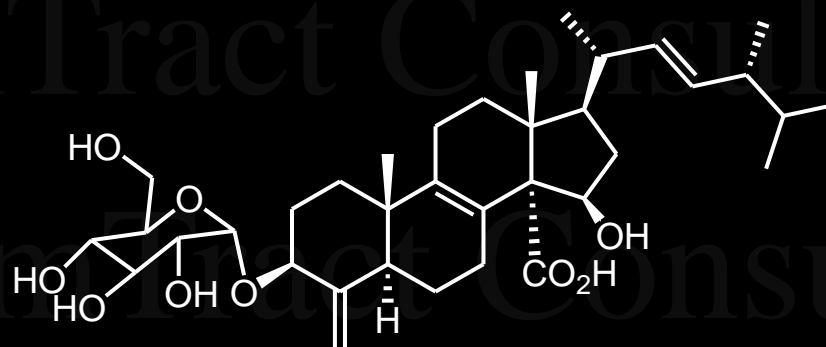
# $\beta$ -1,3-Glucan Synthesis Inhibitors



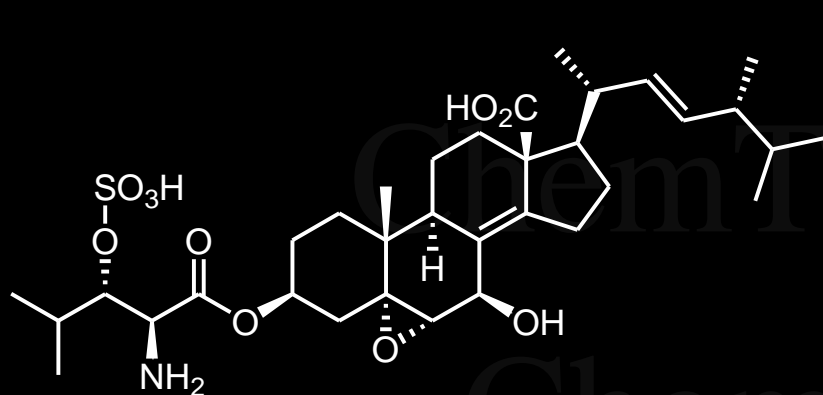
**Hyalodendrosides**



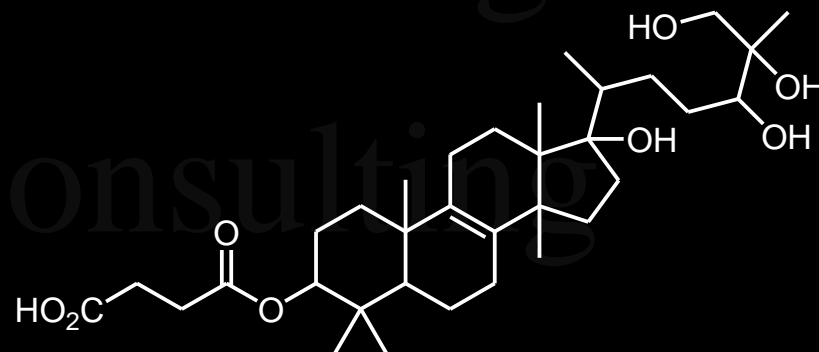
**Enfumafungin**



**Ascosteroside**



**Ergokinins**



**Arundifungins**

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**Stay tuned for the story of how  
the echinocandins developed**

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