Chemotherapeutic Agents

- Antibiotics
- Antifungals
- Antivirals
- Antihelmintics
- Antiprotozoal
- Anticancer drugs
Fungal Growth Patterns

- **Yeast**s
  - Unicellular fungi, reproduce by budding
  - Moist mucoid or waxy colonies that resemble bacteria

- **Molds** (=Filamentous Fungi)
  - Multicellular filamentous, “fluffy” colonies consisting of branching tubular structures called hyphae
  - Collection of intertwined hyphae called mycelium
  - Vegetative hyphae act like roots, penetrating the supporting medium and absorbing nutrients
  - Aerial hyphae project above the surface of the mycelium and bear the reproductive structures of the mold (often spread through the air)
Fungal Growth Patterns

- **Dimorphic Fungi**
  - Grow as molds at ambient environmental temperatures (e.g. 25°C) where they form reproductive spore structures.
  - Spores are aerosolized and infectious
  - Inhaled spores grow as yeasts at body temperature (37°C) in the host

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*Yeast form

*Mold form

*Coccidioides immitis*
Fungal Habitats

- Most clinically relevant fungi reside in the soil, in bird feces, on vegetation, or on the skin and mucous membranes of mammals.
- Some have distinctive ecologic and geographical niches.
Mycosis

• Fungal infections (= mycosis)
  – spread generally from the environment to people (or animals) with limited person-to-person spread.
  – Skin and lungs are prominent entry site for many fungi
  – Patients with impaired cell-mediated immunity (e.g. AIDS, organ transplant) at heightened risk for severe disease.

• Types of fungal infections
  – Superficial: Outer skin layer - no immune response caused mostly by yeasts (Dandruff)
  – Cutaneous: Epidermal layers - evoke immune response Tinea (Ringworm, Athlete’s foot, jock itch) caused by Dermatophytes:
  – Subcutaneous: Chronic infection of subdermal tissues may require surgical intervention
  – Systemic: Mostly originating in the lung caused by virulent dimorphic fungi
  – Opportunistic: In immunocompromised conditions (AIDS; altered mucosal flora due to antibiotics): mostly Candidiasis and Aspergillosis (often cause of epidemic death in birds)
Superficial Mycoses

• **Tinea versicolor (= Pityriasis versicolor)**
  - Caused by a lipophilic yeast, *Malassezia furfur*
  - Normal flora of skin and scalp
  - Growth on media markedly enhanced by adding fat
    (Clinical mycology labs routinely stock olive oil!)

• **Dandruff (= Scurf = Pityriasis capitis)**
  - Caused by a lipophilic yeast, *Malassezia globosa*
  - Accelerated shedding of skin cells
Cutaneous Mycosis

- Also known as “ringworm” and tinea (latin “worm”) because of round shape of lesions
- Infections confined to skin, hair and nails
- Caused by Dermatophyte molds (Trychophytum; Microsporum)

Clinical classification based on location:

- **Tinea capitis**
  - Ringworm of scalp and hair

- **Tinea barbae**
  - Ringworm of beard region
Cutaneous Mycosis

- **Tinea corporis**
  - Ringworm of the smooth skin of the body

- **Tinea cruris**
  - Starts in groin area (“Jock itch”)
  - Causes by *Trychophytum rubrum*
Cutaneous Mycosis

• **Tinea pedis**
  - Classically interdigital ("Athlete’s foot")
  - key risk factor for invasive bacterial infections in diabetics through disruption of normal skin barriers

• **Tinea unguium**
  - Infection of finger and toe nails
  - Often associated with T. pedis
Subcutaneous Mycoses

- **Sporotrichosis**
  - *Sporothrix schenckii* - Dimorphic fungus
  - Found on vegetation, especially rose bushes
  - Introduced into skin by trauma (gardening!)
  - Initial ulcer develops into granulomatous nodule
Systemic Mycosis

- Infections are rare (high natural immunity)
- Usually requires large inoculum
- Often endemic to specific areas

Mostly associated with four fungi:

- *Coccidioides immitis* -> Coccidioidomycosis
  - Soil fungus (dry, dusty soil => inhalation of spores)
  - SW USA (Arizona and Central Valley of CA) and Mexico ("Valley fever")
  - Epidemic after (Northridge) earthquake or sandstorms
  - Considered most virulent fungus (select agent: BSL-3)
  - Starts with flu-like symptoms, meningitis
  - Striking racial/ethnic differences in rate of dissemination: Filipinos>African Americans>Hispanics>Asians>Caucasians (Kern County, Filipinos 0.23% of population but 22% of cases) Likely due to genetic differences in blood group/ HLA
Systemic Mycosis

- **Histoplasma capsulatum** -> Histoplasmosis (“Cave disease”)
  - Soil fungus (soil containing guano (bird, bat droppings))! => spores inhaled
    (In 1890 European starlings were introduced into Central Park, NYC in an effort to bring all of the birds mentioned by Shakespeare to the US => Now there are 200M-1B starlings in N. America, whose droppings are a major route of transmission for histoplasma)
  - S-SE USA (Ohio and Mississippi Valley)
  - Starts with flu-like symptoms, meningitis
  - Fungus lives intracellular in macrophages => immune-evasion
  - 95% of infected individuals asymptomatic (chronic infection can lead to lung fibrosis)
  - In immunocompromised patients systemic infection develops => multiorgan failure, sepsis
Systemic Mycosis

- **Blastomyces dermatitidis** -> Blastomycosis
  - Soil fungus (=> spores inhaled)
  - S-SE USA
  - Predominantly in lung and skin

- **Paracoccidioides brasiliensis**
  - Soil fungus (=> spores inhaled)
  - Central and South America (Brazil—death rate up to 1.5/1000)
Opportunistic Mycosis

- Some fungi are commensal (mucosal flora of mouth, gut, vagina etc.)
- Usually growth balanced by microorganisms (lactobacilli)
- Only a problem in situations of compromised immune responses (AIDS, antibiotics, chemotherapy, radiation, alcoholism, etc.)

- *Candida albicans* -> Candidiasis
  - Dimorphic fungus BUT also mold at 37° C
  - Also other *Candida* species

- *Cutaneous candidiasis*: mostly in moist skin folds (obese patients):
Opportunistic Mycosis

- *Candida albicans* -> Candidiasis (cont.)
  - Oral candidiasis ("Thrush")
    - Babies; denture users
    - Can progress into Candida esophagitis

- Vaginal candidiasis ("Yeast infection")
  - Does NOT require immune dysfunction
  - Severe itching/burning
  - Commonly associated with antibiotic use
  - Bacterial infection often falsely self-diagnosed as candidiasis
    (2/3 of self-diagnosed "yeast infections" actually bacterial!)
Opportunistic Mycosis

- *Candida albicans* -> Candidiasis (cont.)
  - Systemic candidiasis
    - Mucocutaneous barriers breached in patients after surgery, burns
    - Dissemination to kidneys, skin, eye, heart, bone, liver, etc.
    - Often fatal!
Opportunistic Mycosis

- **Cryptococcus neoformans** -> Cryptococcosis
  - Ubiquitous, but especially abundant in pigeon droppings
  - Cryptococcal meningitis most common manifestation
  - Complication in AIDS patients

- **Aspergillus sp.** -> Aspergillosis
  - Mostly pulmonary infections
  - Allergenic
    (Allergic sinusitis and allergic bronchopulmonary aspergillosis)
  - Infections common in birds
## Differences between fungi and mammalian cells

<table>
<thead>
<tr>
<th>Feature</th>
<th>Animals</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell structure</td>
<td>Eukaryotic</td>
<td>Eukaryotic</td>
</tr>
<tr>
<td>DNA</td>
<td>Diploid</td>
<td>Haploid</td>
</tr>
<tr>
<td>Ribosomes</td>
<td>80S</td>
<td>80S</td>
</tr>
<tr>
<td>Cell wall</td>
<td>No</td>
<td>chitin, mannans, glucans</td>
</tr>
<tr>
<td>Cell membrane</td>
<td>Predominantly cholesterol</td>
<td>Predominantly ergosterol</td>
</tr>
<tr>
<td>Microtubule affinity for griseofulvin</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cytosine deaminase</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Squalene epoxidase</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Overview of Antifungal Drugs

<table>
<thead>
<tr>
<th>MECHANISM OF ACTION</th>
<th>Polyenes (Amphotericin, Nystatin)</th>
<th>Azoles (Ketoconazole, Miconazole, Fluconazole, Itraconazole, Voriconazole, Posaconazole)</th>
<th>5-Flucytosine</th>
<th>Griseofulvin</th>
<th>Echinocandins (Caspofungin, Micafungin, Anidulofungin)</th>
<th>Allylamines (Terbinafine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectively bind to ergosterol in fungal cell membrane, altering membrane fluidity and producing pores and osmotic cell death. Much less binding to cholesterol.</td>
<td>Selectively block ergosterol synthesis by inhibiting demethylation of lanosterol. Fungal P450 enzyme much more sensitive than mammalian counterpart.</td>
<td>Converted by fungal cytosine deaminase into 5-fluorouracil; inhibits DNA synthesis. Mammalian cells lack cytosine deaminase.</td>
<td>Inhibit fungal growth by binding to microtubules, disrupting mitotic spindles. Mammalian microtubules less sensitive.</td>
<td>Inhibit fungal Beta glucan synthesis, disrupting cell wall integrity. Mammalian cells have no cell walls.</td>
<td>Selectively blocks ergosterol synthesis by inhibiting squalene epoxidase (not found in animals)</td>
<td></td>
</tr>
</tbody>
</table>
Antifungal Drugs - Polyenes

Polyenes
- bind to fungal membrane sterols (ergosterol)
- alter selectively permeability to K⁺ (and Mg²⁺) => Fungicidal
- Resistance due to altered sterols

• **Amphotericin B**
  - Isolated from *Streptomyces nodosus*
  - Given iv, it (poor oral absorption) and topical
  - Active against most systemic fungi
  - iv not well tolerated (chills, headaches, nausea)
  - Pronounced renal toxicity =>
    Encapsulated into liposomes
    (less drug reaches the kidneys?)

• **Nystatin**
  - Only for topical application
    (Canidida, dermatophytes)
Antifungal Drugs - Azoles

Azoles

- inhibit the synthesis of ergosterol
  (block demethylation of lanosterol by inhibiting fungal CYP3A
  = 14-demethylase)
- Fungistatic
- Active against systemic fungi and dermatophytes
- Resistance due to altered 14-demethylase

- Two groups
  - Imidazoles
  - Triazoles
Antifungal Drugs - Azoles

**Imidazoles**
- **Clotrimazole**
  - Only used topical
  - Candidiasis, tinea

- **Ketoconazole**
  - Tinea, candidiasis, blastomycosis, coccidioidomycosis
  - Also for dandruff (Nizoral®)
  - First oral -azole (mostly replaced by fluconazole and itraconazole)
  - Absorption best at low pH (antacids interfer !)
  - Does not enter CNS well
Antifungal Drugs - Azoles

**Imidazoles**
- **Miconazole**
  - Used topical and p.o.
    (intestinal fungal infections)
  - Also used in E6 slide film processing
- **Tioconazole**
Antifungal Drugs - Azoles

Triazoles
Newer, less toxic, more effective!

• Fluconazole (Diflucan®)
  – Used i.v. and p.o.
  – Reaches high CSF concentrations
  – 90% excreted unchanged
  – t1/2 = 25 hrs
  – Used against Candidiasis, Coccoidosis (meningitis)
  – Well tolerated

• Itraconazole (Sporanox ®)
  – Used i.v. and p.o.(p.o. poor absorption)
  – Absorption increased by acids (Orange juice, Coke!)
  – Absorption decreased by antacids
  – Does not reach CSF
  – Highly lipophilic => fatty tissue accumulation
  – Very broad spectrum

• Voriconazole (Vfend ®)
  – Used for severe systemic infections and emerging fungi (very broad spectrum)

• Posaconazole (Noxafil ®)
  – Very broad spectrum (tested against >18,000 fungi!)
Antifungal Drugs - Antimetabolites

5’-Flucytosine (Ancobon ®)

- Only available antimetabolite drug
- Activated by deamination within the fungal cells to 5-fluorouracil
- 5-fluorouracil inhibits thymidylate synthetase
- Also inhibits fungal protein synthesis by replacing uracil with 5-fluorouracil in fungal RNA
- Resistance common (=> used in combination with other antifungals)
- Broad range (only in the treatment of serious infections caused by susceptible strains of Candida and/or Cryptococcus)
- Well orally absorbed
Griseofulvin (Grisactin®, Fulvicin®)
- Inhibit fungal growth by binding to microtubules => disruption of mitotic spindles => fungistatic
  (mammalian microtubules less sensitive)
- Mainly effective against dermatophytes (tinea)
  (incorporates into keratin => requires several weeks of therapy)
- Oral administration (use declining due to better drugs - e.g. Triazoles)
- Side effects: Nausea, hepato- and renal toxicity, photosensitivity,…
- Veterinary use common
Antifungal Drugs - Echinocandins

- Inhibit synthesis of glucan in the fungal cell wall (likely block 1,3-beta glucan synthase)
- Newest antifungals
- Well tolerated

• Caspofungin
  - Used i.v.
  - Active against Candida and Aspergillus
  - Approved 2001
  - Approved 2005 for invasive Aspergillosis

• Anidulafungin
  - Used i.v.
  - Active against Candida and Aspergillus
  - Approved 2006 for invasive Aspergillosis

• Micafungin
Antifungal Drugs - Allylamines

**Allylamines**
- inhibit fungal sterol synthesis (ergosterol) by inhibiting squalene epoxidase

- **Terbinafine (Lamasil®)**
  - Synthetic antifungal (mostly topical; p.o. for tinea unguium)
  - Lipophilic: accumulates in fat, skin and nails
  - Active against most dermatophytes (tinea, ringworm)

- **Butenafine (Lotrimin® Ultra)**
  - Also anti-inflammatory activity
  - Superior antifungal activity over Terbinafine

- **Naftifine (Naftin®)**
- **Amorolfiné (Loceryl®)**
Antifungals - Summary

Membrane functions: Polymenes bind to ergosterol and disrupt membrane integrity

Cell wall synthesis: Polyoxins inhibit chitin synthesis

Ergosterol synthesis: Azoles and Allylamines inhibit synthesis

Nucleic acid synthesis: 5-Fluorocytosine is a nucleotide analog that inhibits nucleic acid synthesis

Microtubule formation: Griseofulvin disrupts microtubule aggregation during mitosis