

Cryptococcosis

Infectious disease pathology | Organism, virulence, tissue response, and CNS disease

Encapsulated yeasts

Host response

Diagnostic morphology

Clinicopathologic correlation

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Learning objectives

- Distinguish the disease profiles of *C. Neoformans* and *C. Gattii*.
- Explain how capsule, melanin, enzymes, and cell-wall biology influence infection.
- Recognize pulmonary, CNS, and disseminated patterns of cryptococcosis.
- Link host immune status to histologic inflammation and diagnosis.

Where cryptococcosis fits among mycoses

Fungal disease

Mycosis = infection produced by a fungus

Growth form

Cryptococcus: An encapsulated budding yeast in human tissue

Disease category

Often opportunistic; Also occurs without recognized immunodeficiency

Organ emphasis

Pulmonary entry; Characteristic major lesions in the CNS

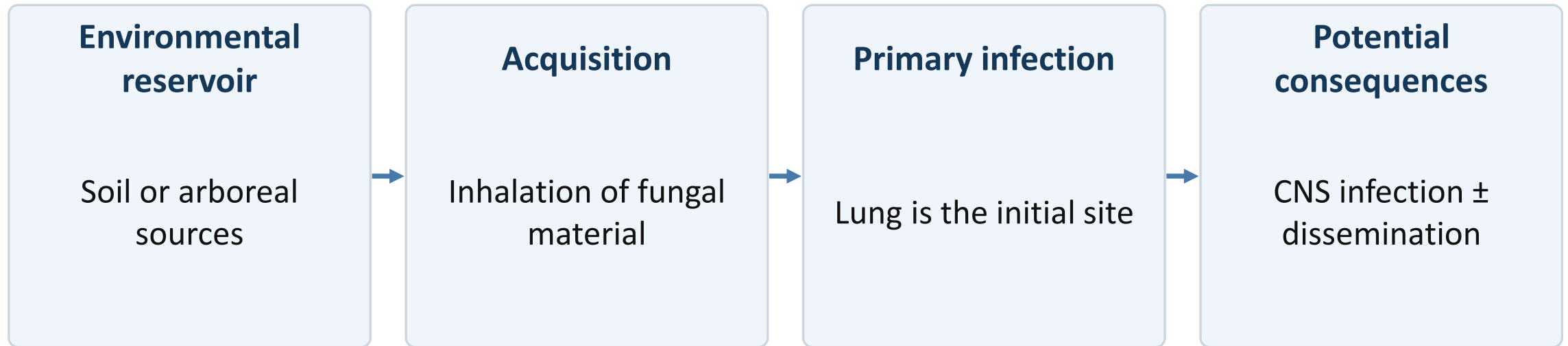
Yeast morphology is the starting point

Yeast biology	Cryptococcus in human tissue
Single-cell growth	Rounded to oval yeast forms
Budding	Yeasts reproduce by budding
Hyphae / pseudohyphae	Neither form in human hosts
Diagnostic implication	Search for encapsulated yeast, not filamentous fungi

Two human pathogens in the source

C. Neoformans	C. Gattii
Commonly opportunistic	Can affect immunocompetent hosts
Pigeon-guano–associated soil	Trees and soil reservoirs
Major CNS infection	May form bulky pulmonary or CNS lesions
Occurs worldwide	Reported in several temperate and tropical regions

Inhalation links environment to host



The lung can conceal early infection

- The pulmonary portal of entry is established in the source.
- Pulmonary disease is often mild or clinically asymptomatic.
- Important CNS involvement may arise despite modest lung symptoms.
- Therefore pulmonary symptom burden need not indicate organism burden elsewhere.

C. Neoformans: Predisposing conditions

Acquired immunodeficiency

AIDS

Hematologic disorders

Leukemia and lymphoma

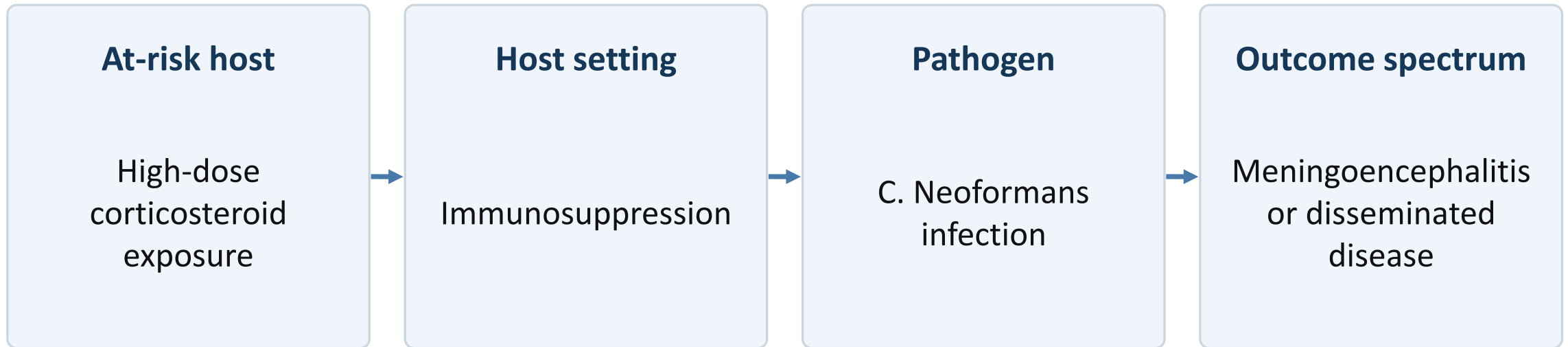
Immune-mediated diseases

Systemic lupus erythematosus and sarcoidosis

Therapy-related suppression

Transplant immunosuppression; High-dose corticosteroids

High-dose corticosteroids matter



Cryptococcosis is not exclusively opportunistic

Immunosuppressed host	Apparently immunocompetent host
High susceptibility to C. Neoformans	C. Neoformans disease is still possible
May have few inflammatory cells	Granulomatous response may predominate
Wide dissemination may occur	C. Gattii disease warrants immune evaluation
Subtle inflammatory histology	Large mass-like lesions may occur

Historical global burden in HIV

152,000

Estimated cryptococcal
meningitis cases

112,000

Associated deaths

19%

AIDS-related mortality
attributed

All figures are Robbins-reported 2020 worldwide estimates in HIV-infected people; Not current surveillance.

C. Neoformans: Ecological exposure

Environmental source

- Found in soil, notably where pigeon guano accumulates.
- Exposure occurs by inhalation.
- Environmental exposure does not establish clinical disease.

Schematic exposure model; No quantitative dose–response asserted.

C. Gattii: Arboreal reservoirs

Tree associations

Oak, baobab, and especially eucalyptus

Additional niche

Also identified in soil

Route of acquisition

Inhalation

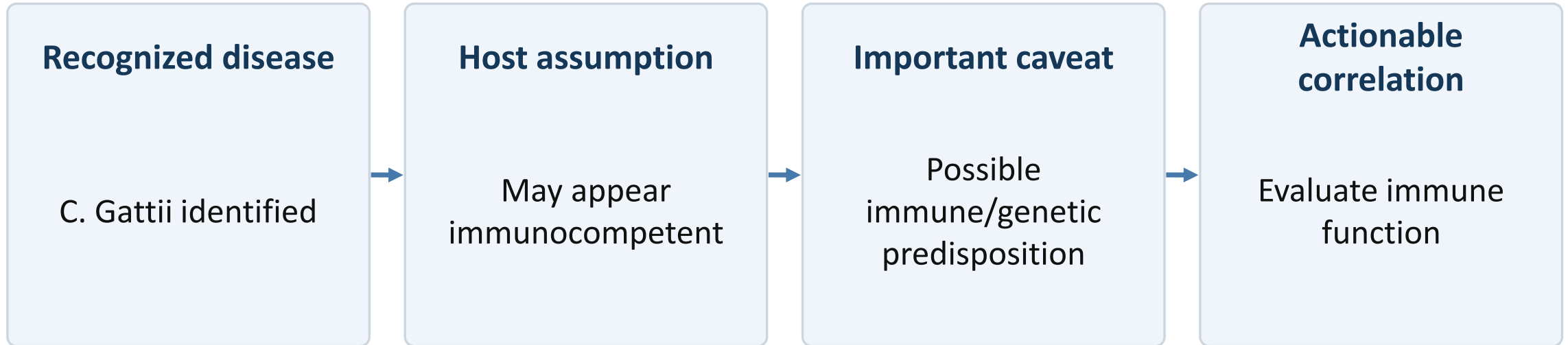
Clinical teaching point

Environmental setting can differ from C.
Neoformans

C. Gattii: Geographic range

- Historically considered a tropical or subtropical pathogen.
- Now reported in Australia and British Columbia / other Canadian regions.
- Additional reports include the U.S. Pacific Northwest, South America, and Africa.
- C. Gattii as responsible for 11%–33% of global infections.

C. Gattii: Why evaluate immunity?



C. Gattii can simulate a tumor

Pulmonary lesion	CNS lesion
Solitary circumscribed granuloma	Large cryptococcoma / mass
May resemble a coin lesion	May cause pressure and mass effects
Can resemble histoplasmosis	May resemble neoplasm on imaging
Evaluate tissue and organism	Do not infer diagnosis from imaging alone

Virulence factors: Organizing framework

Surface structures

Polysaccharide capsule; Chitin cell wall

Cell adaptation

Titan cells and small microcells

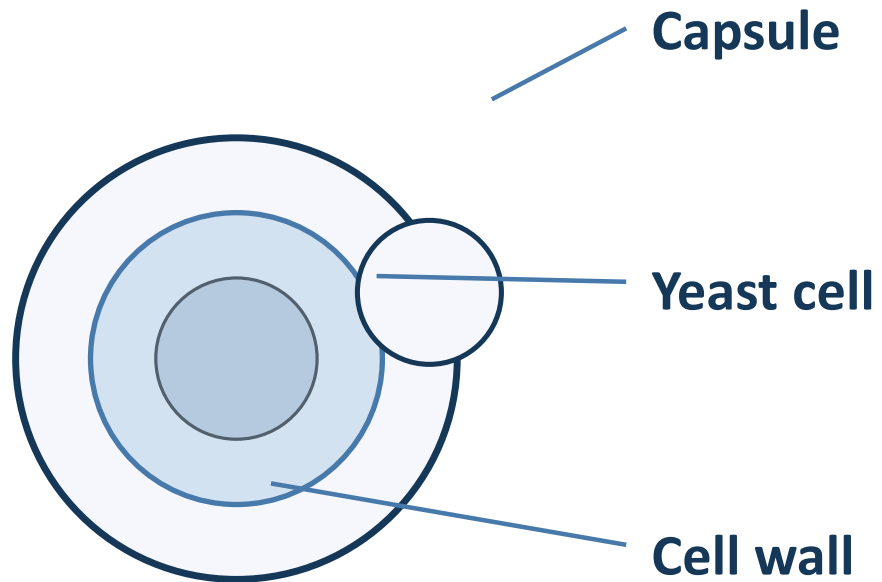
Biochemical defenses

Melanin generated by laccase

Enzymes / secreted proteins

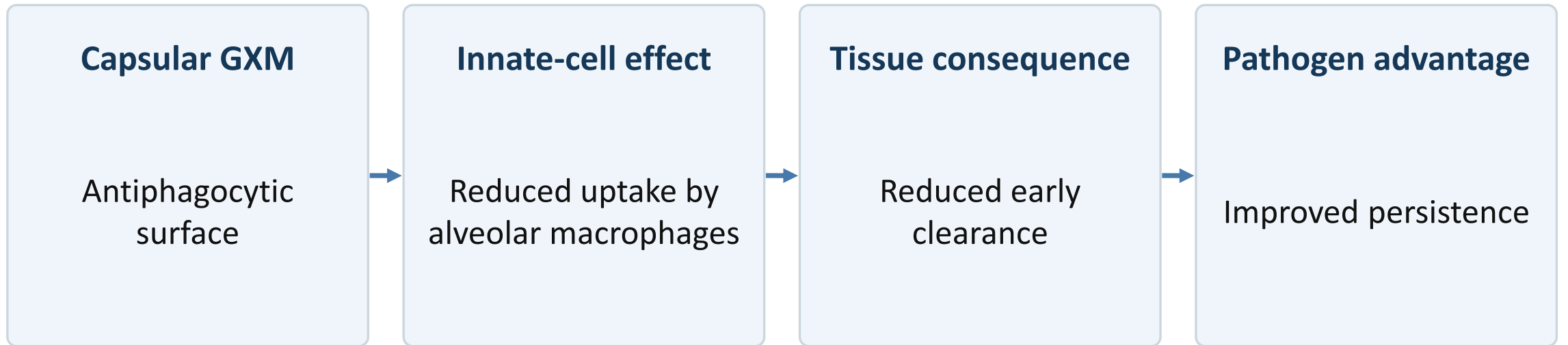
Phospholipases, urease, CPL1

The polysaccharide capsule

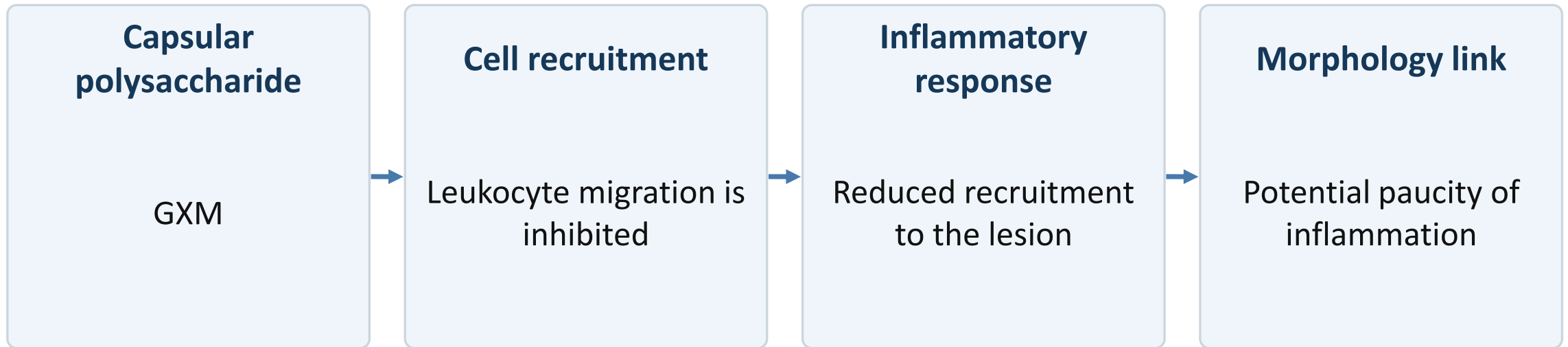


Schematic — proportions and cell shape are illustrative, not microscopy.

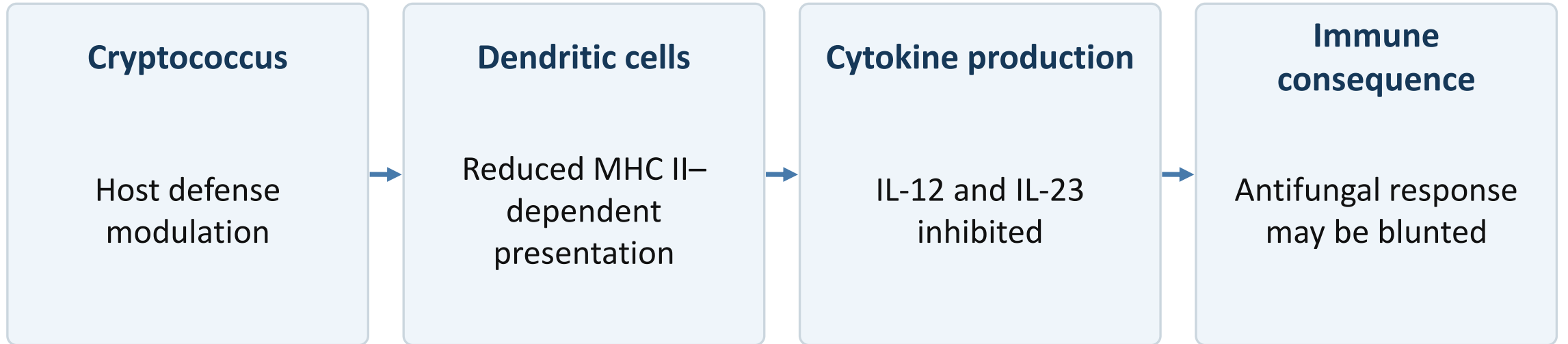
GXM interferes with phagocytosis



Capsule affects leukocyte recruitment



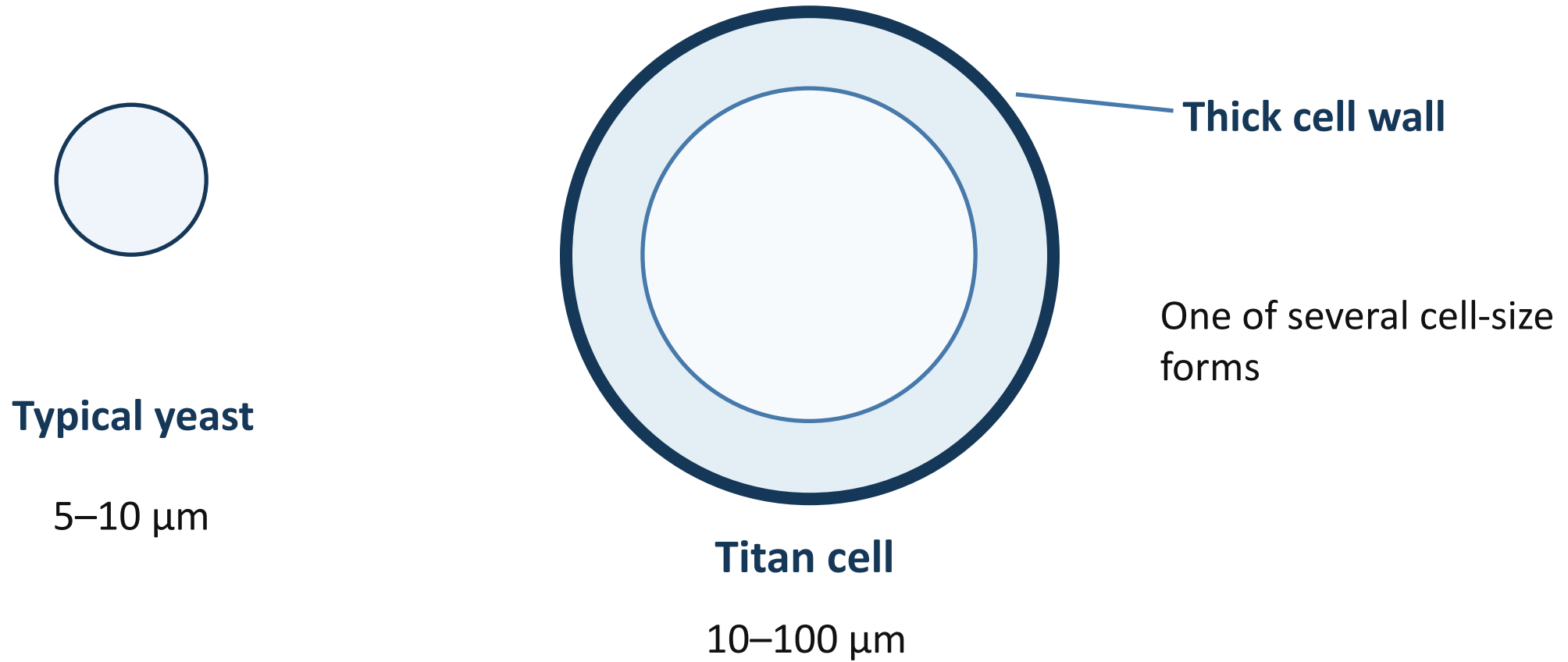
Dendritic-cell antigen presentation



IL-12 and IL-23 are suppressed

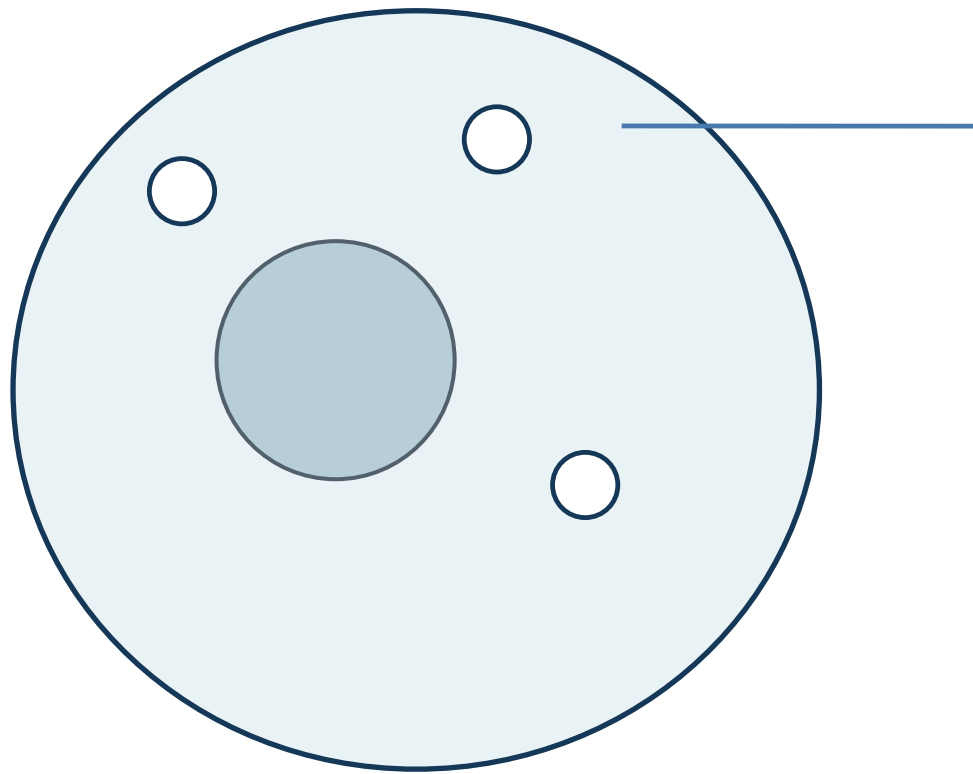
- The source links cryptococcal infection to inhibition of dendritic-cell IL-12 production.
- IL-23 production is also reduced.
- The same passage identifies reduced MHC class II antigen presentation.
- These are experimentally described immune-evasion effects, not a clinical cytokine panel.

Titan cells: Unusually large yeasts



Schematic — relative diameters do not depict exact size scaling.

Microcells: Very small fungal forms



Microcells: 2–4 μm

May be adapted for growth in macrophages

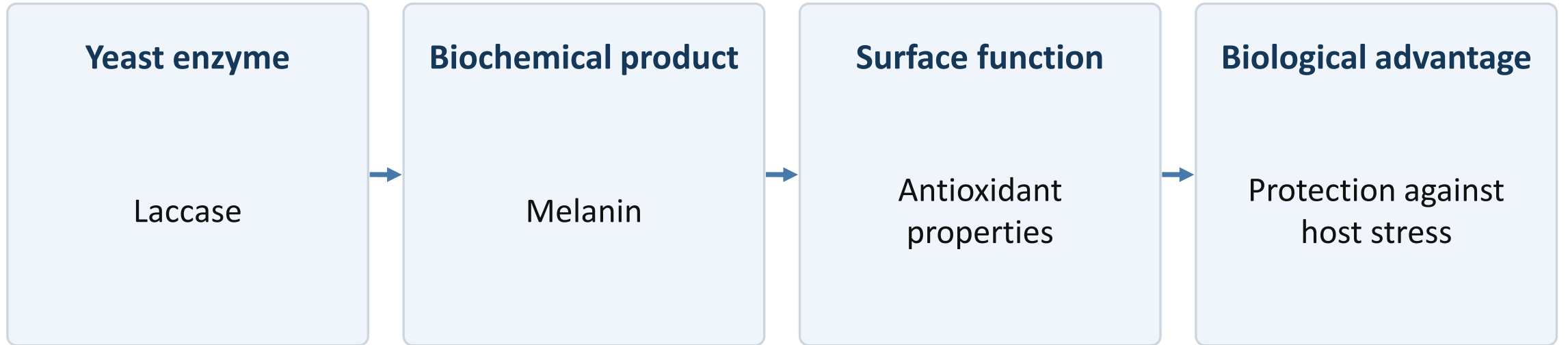
Host-cell schematic; This relationship is proposed, not established in the excerpt.

Schematic macrophage containing small yeast forms; Not a photomicrograph.

Size heterogeneity complicates recognition

Cryptococcal form	Textbook-reported size
Microcell	2–4 μm
Typical yeast	5–10 μm
Titan cell	10–100 μm
Interpretation	Compare morphology with capsule and clinical context

Melanin synthesis depends on laccase



Melanin: Multiple protective roles

Oxidative stress

Antioxidant activity

Antibody defense

Decreases antibody-mediated phagocytosis

Antifungal exposure

Counteracts antifungal-agent effects

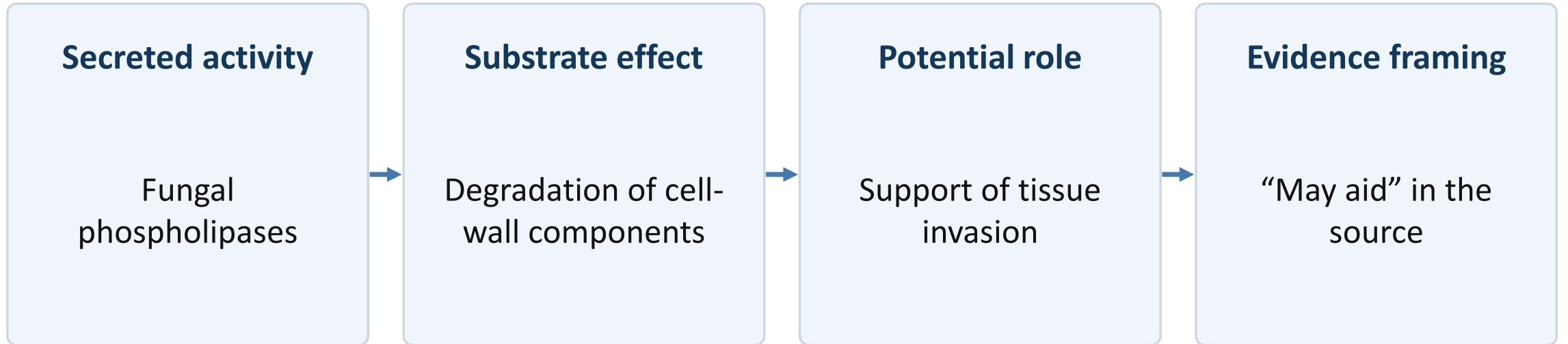
Cell biology

Binds iron and provides wall integrity

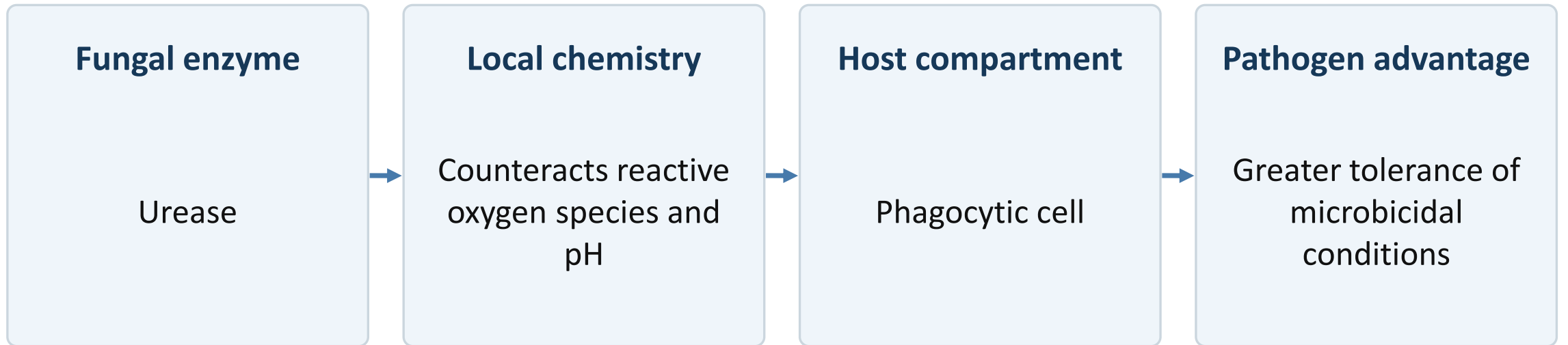
Melanin and the phagocyte encounter

Host defensive pressure	Melanin-associated countermeasure
Oxidant-mediated attack	Antioxidant properties
Antibody-mediated uptake	Reduced phagocytosis
Chemical stress from treatment	Interference with antifungal effects
Cell wall stress	Support of structural integrity

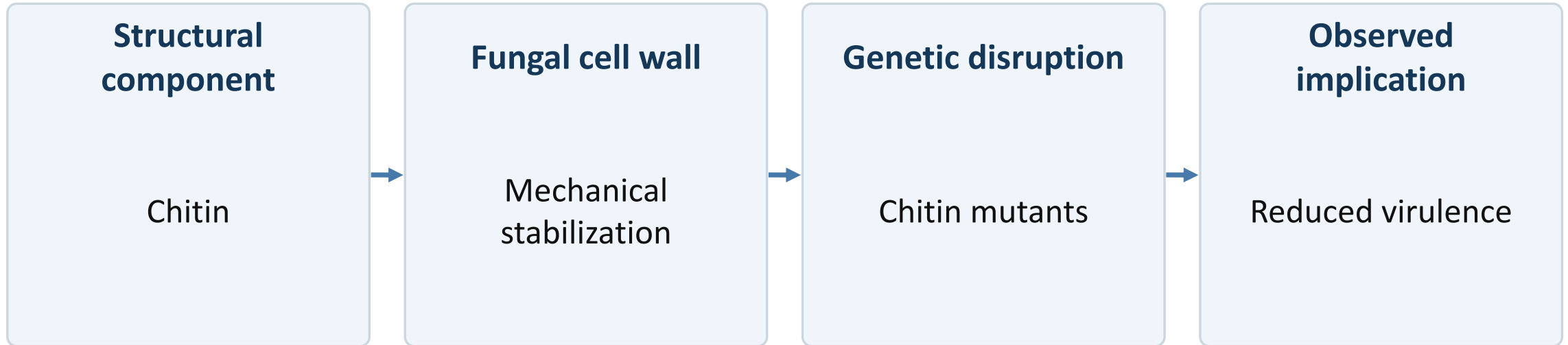
Phospholipases may aid invasion



Urease modifies phagocytic conditions



Chitin maintains wall stability



CPL1: A secreted immune modulator

- CPL1 is a cysteine-rich secreted cryptococcal protein.
- The Robbins passage associates CPL1 with macrophage activation.
- Macrophage activation should not automatically be labeled immunosuppression.
- Distinguish this described function from the antiphagocytic effect of capsule.

Virulence acts through distinct routes

Escape uptake

Capsule, GXM; Melanin

Modify host signaling

Dendritic-cell pathways; CPL1

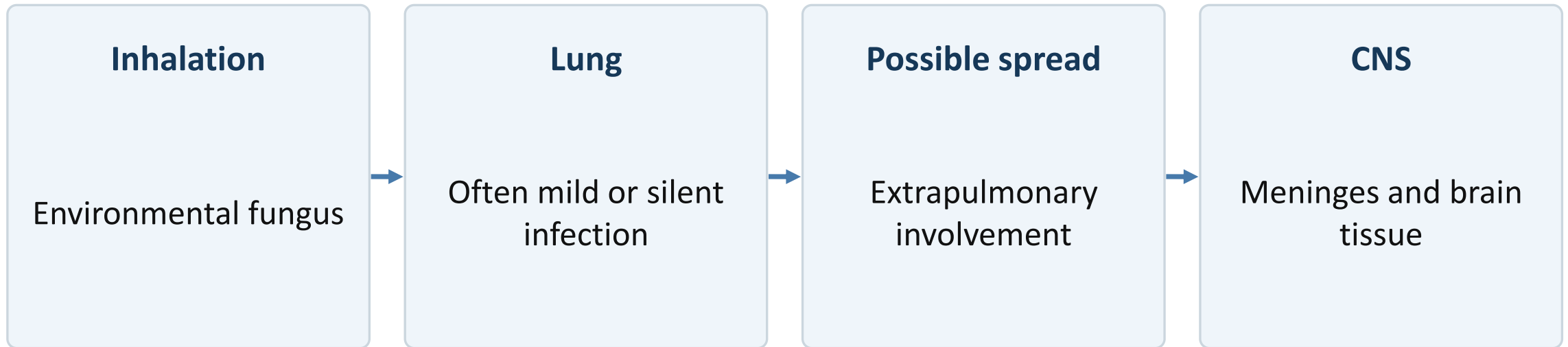
Tolerate damage

Melanin; Urease; Chitin-dependent wall

Interact with tissue

Phospholipases and organism morphology

Primary lung infection to major CNS disease



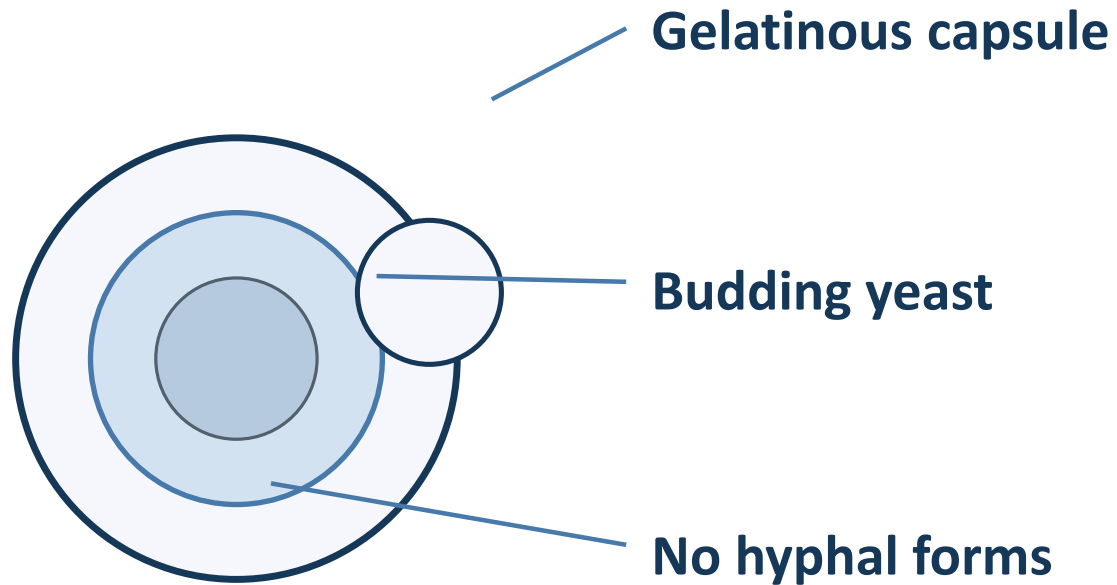
Pulmonary cryptococcosis: Pathology

- The lung is the primary portal of infection.
- Visible or clinically obvious lung disease may be limited.
- *C. Gattii* may produce a solitary pulmonary granuloma.
- A focal lesion can be radiologically similar to a “coin” lesion.

Pulmonary coin lesions require context

Cryptococcal possibility	Diagnostic interpretation
C. Gattii granuloma	An infectious cause of a solitary nodule
Circumscribed lung focus	Can resemble a Histoplasma-associated lesion
Imaging appearance	Morphology alone may not define species
Tissue assessment	Search for encapsulated yeast if infection suspected

The diagnostic organism is a yeast

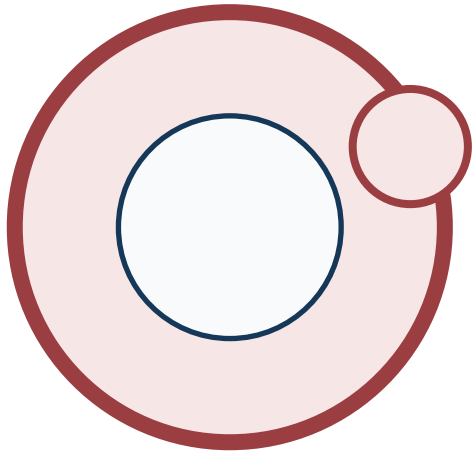


Schematic — proportions and cell shape are illustrative, not microscopy.

Capsular histochemistry

Periodic acid–Schiff (PAS)	Mucicarmine
Capsular material stains intense red	Capsule stains intense red
Shows polysaccharide-rich fungal structures	Especially emphasizes gelatinous capsule
Part of histologic recognition	Robbins Figure 8.44 uses this stain
Interpret with tissue morphology	Interpret with tissue morphology

What mucicarmine demonstrates



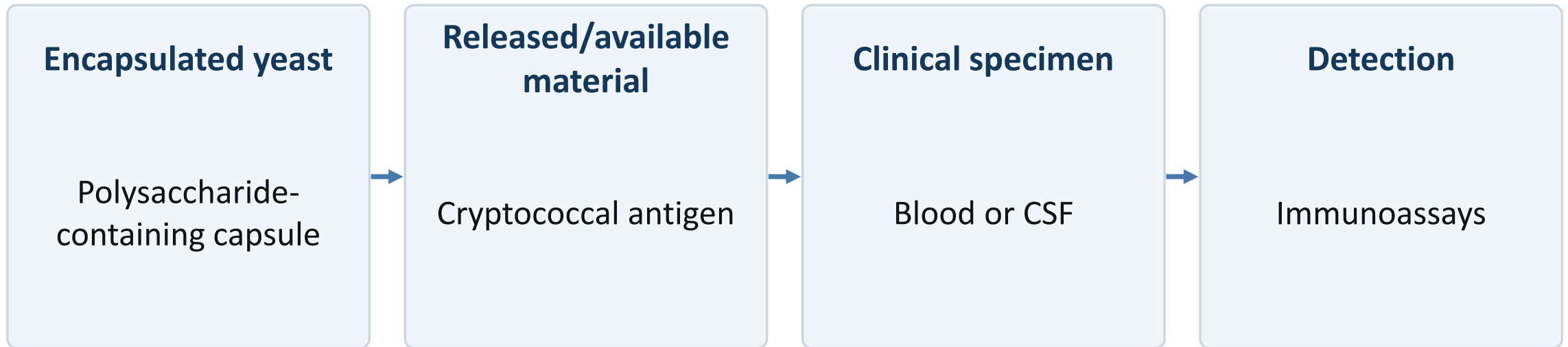
Red-staining capsular polysaccharide

Mucicarmine / PAS (as)

Yeast-shaped organism with thick capsule

Schematic teaching illustration; Not a stained tissue section.

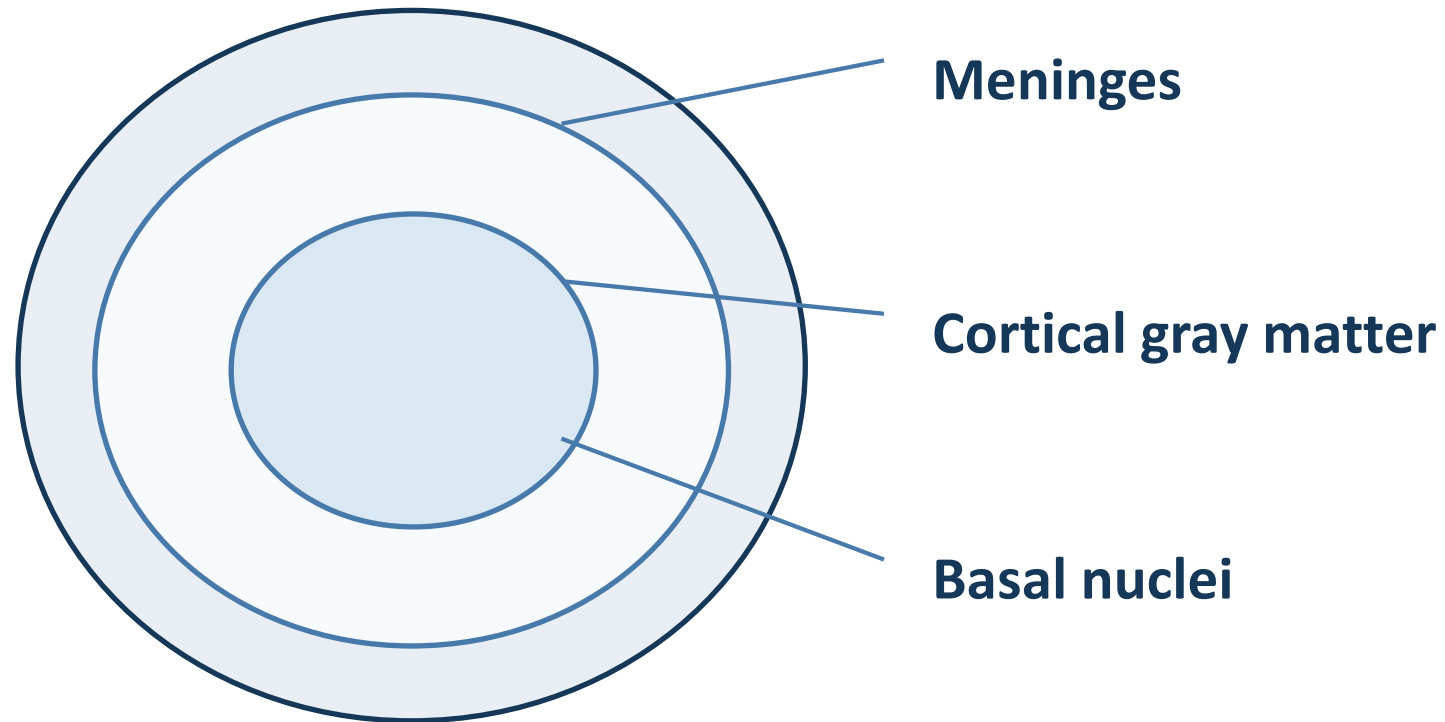
Cryptococcal antigen detection



Histology and antigen tests answer different questions

Tissue morphology	Fluid antigen assay
Visualizes organism and tissue response	Detects cryptococcal polysaccharide antigen
Allows localization in lesions	May support infection in blood or CSF
Stains include PAS / mucicarmine	Immunoassay is not an image of fungal cells
Shows inflammation and distribution	Does not directly document tissue architecture

Major CNS anatomic sites

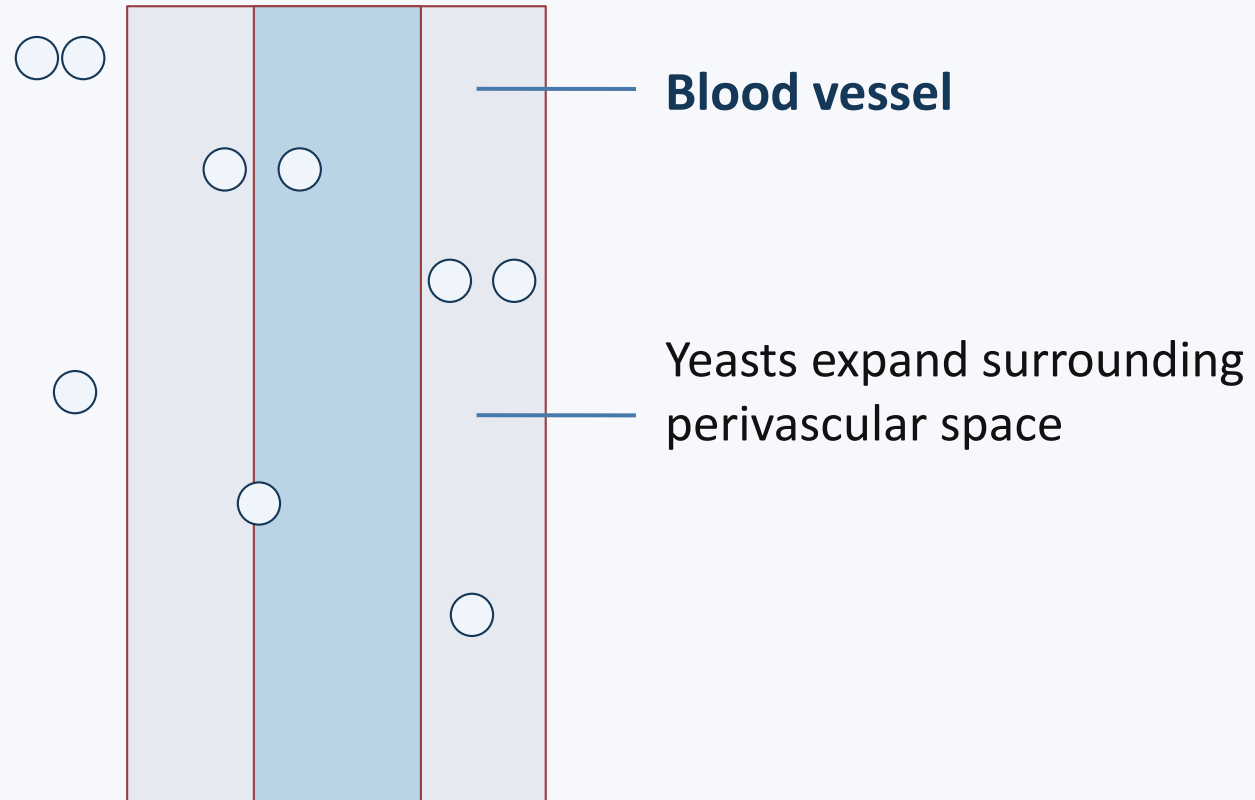


Anatomic schematic — relative dimensions and boundaries are not imaging anatomy.

Meningeal involvement

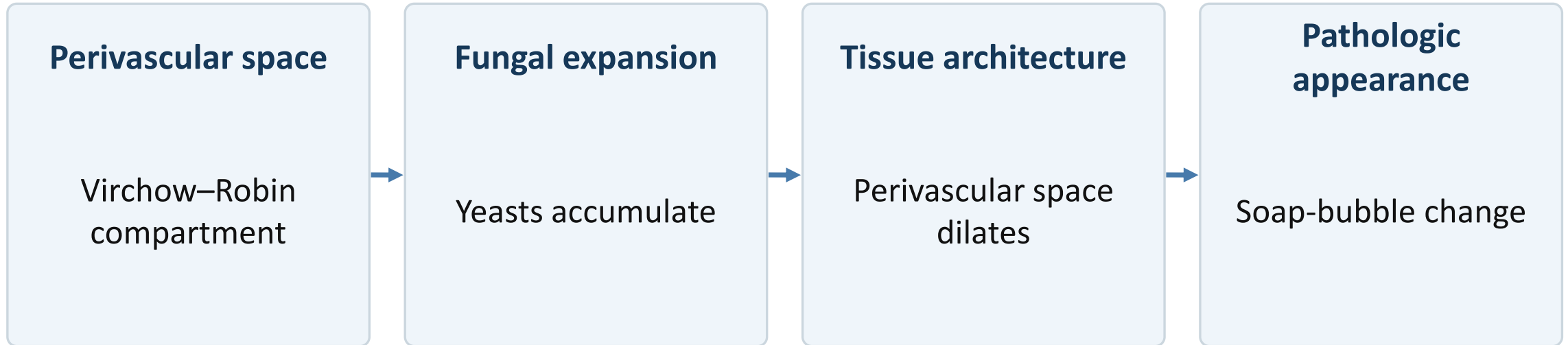
- Cryptococcal infection can involve the meningeal surfaces.
- In immunosuppressed people, abundant organisms may collect as gelatinous masses.
- Inflammatory reaction may be minimal despite the organism burden.
- Clinical presentations include meningitis and meningoencephalitis.

Virchow–Robin spaces are a key compartment



Simplified schematic of Virchow–Robin space expansion; Not a brain histologic section.

Soap-bubble lesions: Mechanism



A large fungal burden can elicit little response

Abundant cryptococci	Weak host inflammatory reaction
Gelatinous aggregates	Few inflammatory cells
Meningeal masses	Limited meningeal cellular response
Dilated perivascular spaces	Minimal gliosis may be present
Severe disease	Inflammatory appearance can be deceptively mild

Disseminated disease in immunosuppression

Cutaneous

Skin

Reticuloendothelial

Liver and spleen

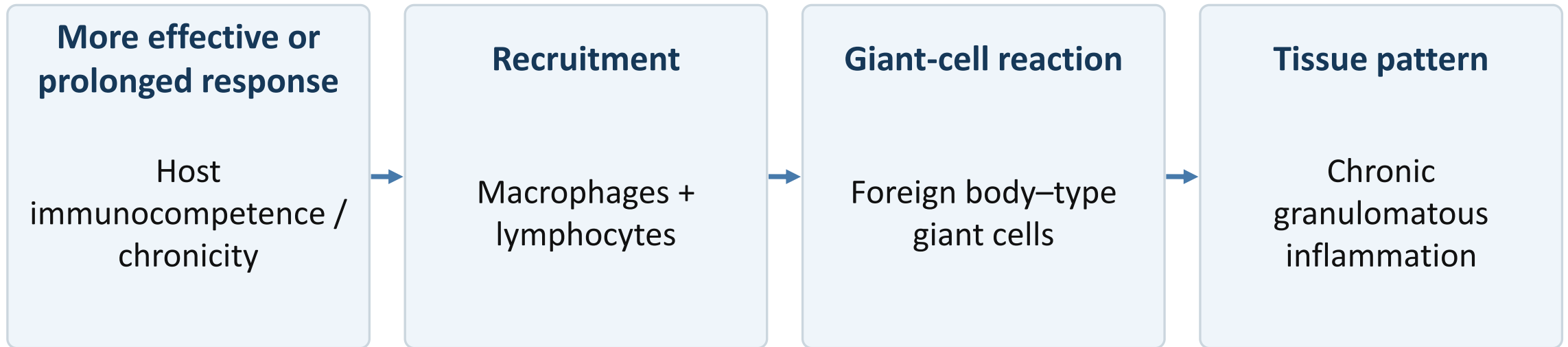
Endocrine

Adrenal glands

Musculoskeletal

Bones

Granulomas reflect a different host response



Cells in cryptococcal granulomas

Macrophages

Predominant mononuclear phagocytes

Lymphocytes

Chronic inflammatory infiltrate

Giant cells

Foreign body–type multinucleated cells

Organisms

Yeasts within or around granulomatous reaction

Other CNS inflammatory patterns

- Suppurative inflammation may occur.
- Granulomatous arteritis may involve the circle of Willis.
- The tissue reaction is therefore not invariably gelatinous or noninflammatory.
- A pattern should be interpreted in the context of immune status and duration.

Immune status changes histopathology

Marked immunosuppression	Immunocompetence / prolonged disease
Many yeasts, limited inflammation	Granulomatous inflammation
Gelatinous meningeal collections	Macrophages and lymphocytes
Virchow–Robin enlargement	Foreign body–type giant cells
Potential dissemination	Other reactions may include suppuration

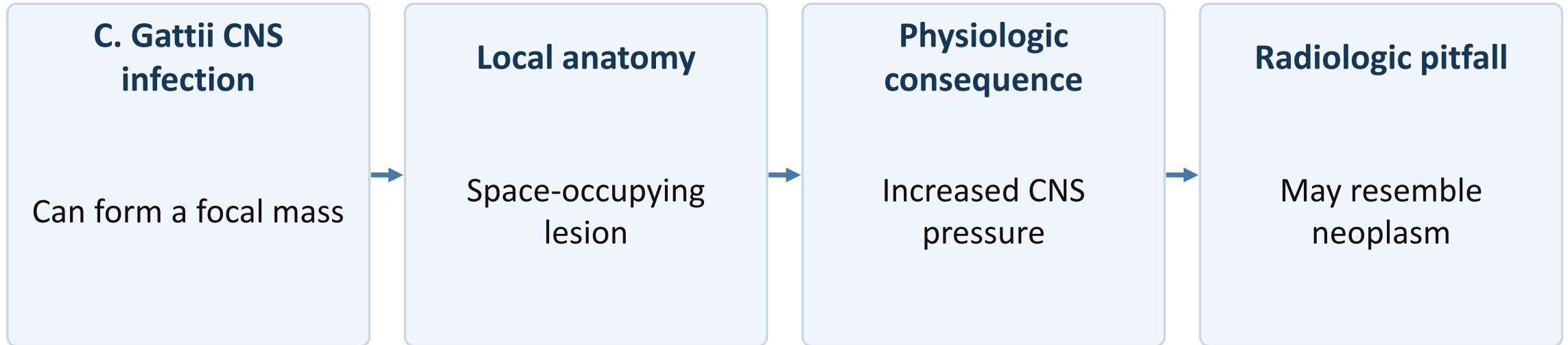
Cryptococcal meningitis: Clinical tempo

Rapid course	Indolent course
May be fulminant	May evolve over months or years
Can be fatal within approximately 2 weeks	Course may remain prolonged
Recognized in AIDS and other immunosuppression	Also occurs outside severe immunosuppression
Tempo does not replace organism testing	Tempo does not replace organism testing

CSF findings may understate inflammation

- CSF can contain few cells despite cryptococcal meningitis.
- Protein concentration is usually increased CNS discussion.
- Encapsulated yeasts may be identified with special stains.
- Cryptococcal antigen assays offer a separate diagnostic route.

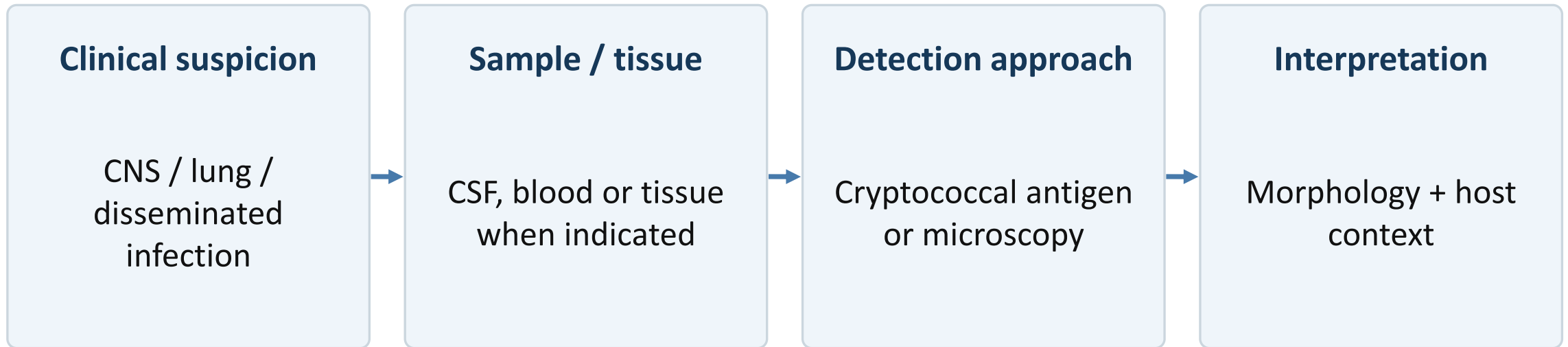
Cryptococcomas can generate mass effect



Cryptococcus versus Candida in the CNS

Cryptococcus	Candida
Often expanded perivascular spaces	Often multiple cerebral microabscesses
Yeast aggregates may evoke little gliosis	Suppurative foci may predominate
Meningitis may be prominent	Microabscesses ± granulomas
Capsulated yeasts	Budding yeasts and pseudohyphae in candidiasis

Diagnostic synthesis: Choose the right sample



Diagnostic pitfalls to avoid

Pitfall 1

Minimal inflammation does not exclude severe infection

Pitfall 2

A solitary nodule may be fungal rather than neoplastic

Pitfall 3

No hyphae is expected in tissue cryptococcosis

Pitfall 4

Organism size varies across microcells, typical yeasts, and Titan cells

Case: Advanced AIDS and meningeal disease

A patient with advanced AIDS develops meningoencephalitis. CSF contains relatively few cells despite severe illness.

Reason through the findings

- Which fungal disease is strongly suggested?
- Why might the cellular response be scant?
- Which source-supported assay could aid diagnosis?

Suggested answer and teaching rationale are available in presenter notes.

Case: A pulmonary coin lesion

An adult with a solitary pulmonary nodule has a tissue granuloma. An encapsulated yeast is identified.

Reason through the findings

- Which cryptococcal species is especially associated with a solitary pulmonary granuloma?
- What other fungal infection is specifically compared?
- Why is imaging alone insufficient?

Suggested answer and teaching rationale are available in presenter notes.

Case: CNS mass without known immunodeficiency

A patient thought immunocompetent has a focal CNS lesion resembling a tumor.
Tissue shows cryptococcal infection.

Reason through the findings

- Which species deserves particular attention?
- What is the reason for pressure-related symptoms?
- What aspect of the host requires assessment?

Suggested answer and teaching rationale are available in presenter notes.

Case: Interpreting a red capsular stain

A pathology section shows rounded budding fungi with intense red capsular material on mucicarmine.

Reason through the findings

- What key organism feature is highlighted?
- What tissue growth form is expected?
- Which two compartments frequently show major lesions?

Suggested answer and teaching rationale are available in presenter notes.

Morphology and biology: Integrate the evidence

Encapsulated yeast

Capsule contributes to evasion + stains with mucicarmine/PAS

Sparse inflammation

Consistent with immune impairment / reduced recruitment

Soap-bubble spaces

Organisms distend cerebral perivascular spaces

Granulomas / giant cells

Reflect sustained host response

Five mechanistic conclusions

- Inhalation produces a pulmonary portal, but the CNS may dominate disease.
- Capsule and host-signaling effects attenuate early antifungal defenses.
- Melanin, chitin, and enzymes support fungal survival and pathogenicity.
- Host immune function strongly influences the histologic pattern.
- Correct diagnosis integrates fungal morphology, specimen findings, and clinical setting.

Selected references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Infectious Diseases: fungal infections and cryptococcosis.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. The Central Nervous System: fungal infections.