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HYPOTHESIS

Immune Camouflage in *Pythium insidiosum* Keratitis: A Hypothesis on Molecular Mimicry and Host Pattern Recognition Receptor Evasion

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Abstract: Pythium insidiosum keratitis is a vision-threatening corneal infection that often mimics fungal keratitis, yet it responds poorly to standard antifungals. Historically, approximately 80% of cases have required surgical excision of the cornea. Unlike fungi, *P. insidiosum* lacks ergosterol in its cell membrane and possesses a cellulose-rich wall with minimal β-1,3-glucan exposure, reducing Dectin-1–mediated detection. Surface hydroxyproline-rich glycoproteins structurally resemble host collagen, potentially engaging inhibitory lectin receptors and dampening early innate immune responses. Delayed Toll-like receptor (TLR4) activation, limited TLR2 signaling, and altered complement activation contribute to subdued inflammatory recruitment, allowing the pathogen to establish deep stromal infection before overt clinical signs emerge. We hypothesize that the organism's aggressive behaviour stems from immune camouflage. *P. insidiosum* evades early host immune detection by masking its pathogen-associated molecular patterns (PAMPs) and mimicking host molecules. This allows the oomycete to establish infection with minimal initial inflammation. Supporting evidence includes the atypical, cellulose-rich cell wall (with minimal β-glucan and no ergosterol) of *P. insidiosum* blunts early cytokine responses. Moreover, the corneal cells infected with Pythium initially produce very low levels of IL-1β, underscoring the potential need for adjunctive immunotherapies to effectively clear the infection. If validated, this immuno-evasion hypothesis has major implications: diagnostic assays could incorporate host immune response patterns, and novel treatments might combine cell wall–degrading enzymes or Pattern Recognition Receptor (PRR) agonists with immunotherapy to "unmask" the pathogen for immune elimination. Ultimately, viewing *P. insidiosum* as an immuno-camouflaged pathogen offers a new paradigm to explain its clinical course and to improve outcomes in this often-devastating keratitis.

Keywords: *Pythium insidiosum*, keratitis, molecular mimicry, pattern recognition receptor evasion, immuno-camouflage

Background

Pythium insidiosum is an aquatic oomycete (fungus-like organism) that causes Pythiosis – an infection previously known mainly in horses and dogs, but now increasingly recognized in humans.[1] In the eye, *P. insidiosum* causes suppurative keratitis (corneal ulceration) that closely mimics fungal keratitis in appearance, earning it the nickname "parafungus".[2] Patients often have a history of corneal trauma in water or soil environments and present with features resembling severe fungal ulcer – such as reticular infiltrates and peripheral "tentacle" extensions in the cornea.[2] Critically, however, standard antifungal medications are ineffective against Pythium due to its unique cellular structure. Unlike true fungi, *P. insidiosum* lacks ergosterol in its cell membrane and instead incorporates cellulose in its cell wall.[3] Its cell wall is composed primarily of cellulose with some β-glucans and even hydroxyproline-containing proteins,[4] whereas fungal pathogens have chitin and abundant β-glucan. This fundamental difference explains why conventional antifungals (targeting ergosterol or fungal cell wall synthesis) often fail and why extreme measures, such as therapeutic keratoplasty (corneal transplantation), have been required in a high proportion of cases.[5] Beyond the lack of therapeutic targets, *P. insidiosum* keratitis poses a diagnostic and immunological challenge. Clinically, it can be mistaken for fungal or amoebic keratitis, delaying appropriate therapy.[6] Microbiologically, *Pythium* grows as broad, aseptate

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hyphae in tissue that can resemble zygomycete fungi.[7] However, an astute clue is that corneal scrapings show ribbon-like hyphae that fail to stain with chitin-specific fungal stains but bind calcofluor white (which highlights cellulose). This indicates that the pathogen's cell wall composition differs markedly from that of fungi, potentially affecting how the host's immune system recognizes it.[8]

The host immune response to *P. insidiosum* in the cornea is not yet fully elucidated, but emerging studies show distinctive patterns. In fungal keratitis, resident macrophages and dendritic cells rapidly detect fungal cell wall components via Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), triggering an intense neutrophil influx.[9] For example, in Aspergillus keratitis, TLR4 and the CLR Dectin-1 (β-glucan receptor) are critical for fungal killing and neutrophil recruitment, respectively.[10] By contrast, the immune response to *Pythium* appears initially muted. An in vivo study in a rabbit model of P.insidiosum keratitis found that key innate inflammatory cytokines (IL-1β, IL-6, IL-8) in the cornea did not surge until days 3–7 post-infection,11 suggesting a delay in robust immune activation. In in vitro experiments, human corneal epithelial cells stimulated with *P. insidiosum* failed to upregulate IL-1β, in stark contrast to their response to typical pathogens.[12] *Pythium* induced IL-6 and IL-8 in these cells, indicating partial host recognition, but the absence of early IL-1β suggests that certain innate pathways (e.g., inflammasome activation) may be bypassed.[13] Monocyte-derived macrophages likewise produce a distinct cytokine profile in response to Pythium: IL-1β and IL-8 are produced, partly via TLR2-dependent signalling, but neutralizing TLR2 only modestly reduced these cytokines.[14] This implies that *Pythium* triggers multiple receptors sub-optimally. Intriguingly, patients with predisposing immunological conditions – for example, individuals with β-thalassemia – are disproportionately susceptible to systemic Pythiosis.[15] Monocytes from such patients show deficient TNF-α and IFN-γ responses to *Pythium* zoospores, which may explain their vulnerability. All these observations point toward an organism that, unlike typical corneal pathogens, initially "flies under the radar" of the host immune system.[16] Despite increasing recognition of *Pythium insidiosum* as a major cause of infectious keratitis, its immune evasion mechanisms remain poorly understood compared to fungal and protozoal keratitis. While fungi primarily exploit β-glucan shielding and Acanthamoeba employs cyst-mediated resistance, Pythium exhibits a unique cellulose-dominant cell wall and potential molecular mimicry, suggesting a distinct form of immune camouflage. Understanding these differences is crucial for developing targeted immunomodulatory therapies and improving diagnostic precision.

Given this background, we explore the hypothesis that *P. insidiosum* keratitis is severe not only because of diagnostic delays or drug resistance, but because the pathogen actively evades and subverts the host's innate immune recognition. Furthermore, we propose an immuno-camouflage hypothesis: P. insidiosum avoids triggering full-blown immune responses by molecular mimicry of host tissues and by concealing its PAMPs from pattern recognition receptors (PRRs). We discuss how this hypothesis diverges from conventional thinking and examine supportive and contrary evidence. If Pythium has evolved to evade the immune system, unravelling this could open new avenues for diagnosis (e.g., immune-based assays) and treatment (e.g., therapies to expose or counteract the camouflage).

The Hypothesis

Pythium insidiosum keratitis represents an infection in which the pathogen's success is due to immuno-evasion. We hypothesize that *Pythium* acts as an "immuno-camouflaging" oomycete. It employs molecular mimicry of host structures and strategic evasion of PRRs to dampen early innate immune detection in the cornea (**Figure 1**). In essence, *Pythium* disguises itself as "self" or at least as a non-threatening presence, buying time to invade tissue unchecked. This concept diverges from the traditional view that corneal infections cause pathology primarily by *overwhelming* the host response; here we propose the opposite – that *Pythium* causes such extensive damage because it initially underwhelms or misdirects the host response, leading to delayed containment and subsequent uncontrolled spread (**Figure 2**).[17] The pathogenicity of *Pythium insidiosum* appears to result from a complex interplay between microbial persistence and host-mediated stromal damage. Unlike fungi that produce potent proteases or keratolytic toxins, Pythium exhibits a silent invasion pattern with limited enzymatic degradation yet extensive stromal infiltration. Recent evidence indicates that host-derived matrix metalloproteinases (MMP-2 and MMP-9) become upregulated in response to delayed immune recognition, leading to progressive stromal melt and perforation. This supports our hypothesis of immune camouflage, in which early evasion of pattern recognition receptors (PRRs) leads to a dysregulated secondary inflammatory cascade once the pathogen is detected. Thus, corneal damage in Pythium keratitis results not only from direct invasion but also from an exaggerated host response driven by sustained MMP activity and delayed immune activation.

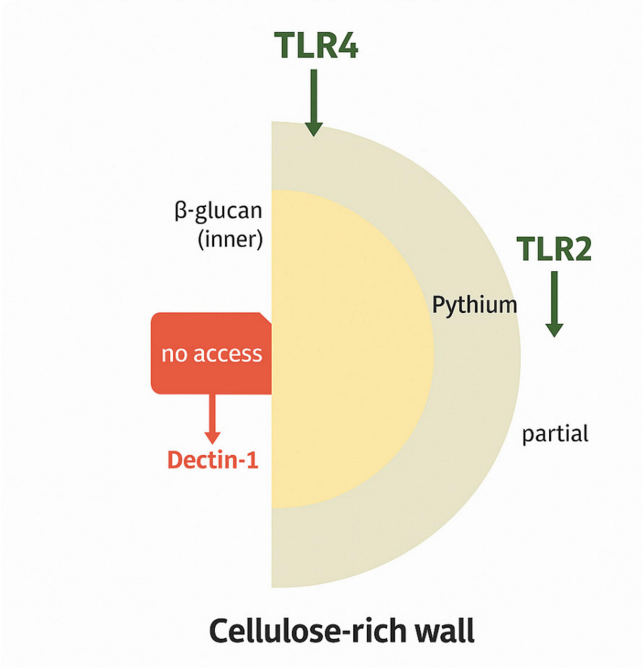

Figure 1 *Pythium insidiosum* PRR Evasion Model—The cellulose-rich outer wall limits immune recognition by masking inner β-glucan layers, preventing access to Dectin-1 and allowing only partial engagement of Toll-Like Receptor 2 (TLR2) and Toll-Like Receptor 2 (TLR4). This structural adaptation facilitates evasion of host pattern recognition receptors (PRRs) and contributes to immune evasion.

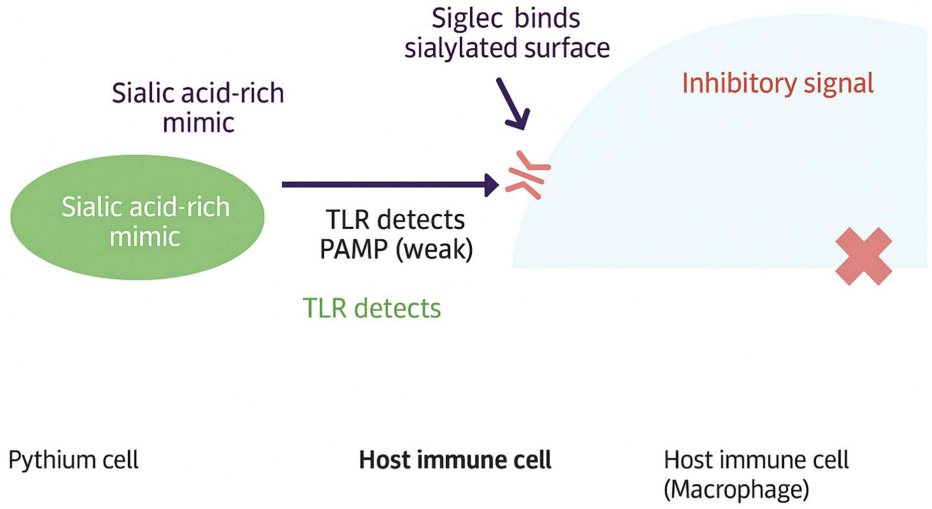

Figure 2 The diagram depicts molecular mimicry by *Pythium* through a sialic acid-rich surface that engages host Siglec receptors, delivering inhibitory signals to macrophages. This interaction weakens Toll-like receptor (TLR) recognition of pathogen-associated molecular patterns (PAMPs), allowing immune evasion.

Key Immunological Steps in the Proposed Mechanism

Failure of Early PAMP Recognition

Upon entering corneal tissue (eg via a small wound), *P. insidiosum* zoospores encyst and germinate into hyphae. Unlike fungal conidia or hyphae, which carry exposed β-glucans and mannans, *Pythium* presents an outer cell wall rich in cellulose and possibly mucilaginous polymers. Cellulose is not a common component of human pathogens and correspondingly, humans lack dedicated PRRs for cellulose[18] Important fungal PAMPs like β-1,3-glucan may be present in *Pythium*'s wall but are buried beneath the cellulose-rich outer layer.[19] We propose that this architecture conceals β-

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glucan of *Pythium* from Dectin-1 on host phagocytes, at least in the early phase. Similarly, *Pythium* contains little or no chitin, so chitin-sensing pathways are not triggered. The net effect is that crucial receptors such as Dectin-1, TLR4, and NOD-like receptors that would normally signal an alarm in response to a fungal invader are either not engaged or only weakly engaged initially.[20] Corneal epithelial cells and resident macrophages thus mount an attenuated response – for example, releasing some IL-8 for neutrophil recruitment, but minimal IL-1β or TNF-α (key drivers of inflammation). This mechanistic step explains the empirical finding that IL-1β is low in early *Pythium* infection despite the presence of a large organism in the cornea. Essentially, *Pythium* is like an "invisible intruder," sneaking past the cornea's pattern recognition system by wearing an atypical cell wall cloak.[21]

Molecular Mimicry of Host Molecules

In addition to concealing its microbial signatures, we hypothesize that P. insidiosum actively mimics host tissue components to mislead the immune system. Oomycete cell walls and secreted proteins may contain epitopes that resemble those found in the human cornea or extracellular matrix.[22] For instance, the presence of hydroxyproline-rich proteins in *Pythium*'s cell wall is notable – hydroxyproline is abundant in human collagens. *Pythium* could produce a collagen-like glycoprotein that the host immune system perceives as "self." Another potential mimicry target is in glycosylation patterns: *Pythium* might decorate its surface with sugars commonly found on human cells. One candidate is sialic acid (N-acetylneuraminic acid), a terminal sugar on many mammalian cell surface glycoproteins. Some pathogens (notably certain bacteria) coat themselves with sialic acid to engage host inhibitory receptors such as Siglecs on immune cells, thereby inhibiting immune activation.[23] We propose *Pythium* may employ a similar strategy – by displaying host-like carbohydrates or other antigens, it engages negative regulators on macrophages and dendritic cells, further dampening their response. This molecular mimicry could induce immune tolerance or confusion: pattern recognition receptors are not triggered effectively, and any immune cells that do bind might interpret the signal as "self" and activate inhibitory pathways. The result is an inappropriate lack of acute inflammation at a time when the pathogen is actively spreading through the corneal stroma.[24]

Delayed and Misdirected Inflammation

By evading early detection, *Pythium* gains a foothold. The organism's hyphae infiltrate extensively, often reaching the sclera or causing ring infiltrates in the cornea. Eventually, as the infection load increases and tissue damage accumulates, the immune system is inevitably alerted – necrotic cells may release damage signals or *Pythium* PAMPs become exposed (for instance, as hyphae age or are partially damaged, β-glucan could become accessible to Dectin-1).[25] When the immune system finally recognizes the invader, it may do so explosively: neutrophils flood in (correlating with high corneal IL-8 levels by day 7) and pro-inflammatory cytokines like IL-1β and IL-17 surge in later stages.[21] By this point, however, the infection is well established, and the inflammatory response, though finally robust, can cause collateral tissue damage (corneal melts, scarring). In essence, the host response is "fashionably late" – arriving so delayed that it must react with overwhelming force, which unfortunately harms the delicate cornea. This is a departure from typical fungal keratitis, in which early immune detection often reveals infection confined to a focal ulcer (with some tissue damage from inflammation), with the pathogen at least constrained early. In *Pythium* keratitis, immune evasion leads to a scenario where, by the time the alarm is fully raised, the infection is widespread, and the ensuing inflammation contributes more to pathology (rapid perforation, for example) than to adequate clearance [26]

Immune Exhaustion or Deviation

We further speculate that *Pythium*'s mimicry might not only delay immunity but also skew it. If *Pythium* antigens mimic host proteins, the adaptive immune system may avoid targeting those antigens strongly (to prevent autoimmunity). There is precedent in infectious diseases for such mimicry, which can lead to inadequate immune responses or even tolerance. While this aspect remains speculative for *Pythium*, it raises the question of whether repeated exposure to *Pythium* (in environmental settings) could induce some immune deviation in susceptible individuals. Clinically, some patients with *Pythium* keratitis fail to mount high antibody titers until given immunotherapeutic vaccines, again hinting that the pathogen is not immunologically conspicuous (Figure 3).[27]

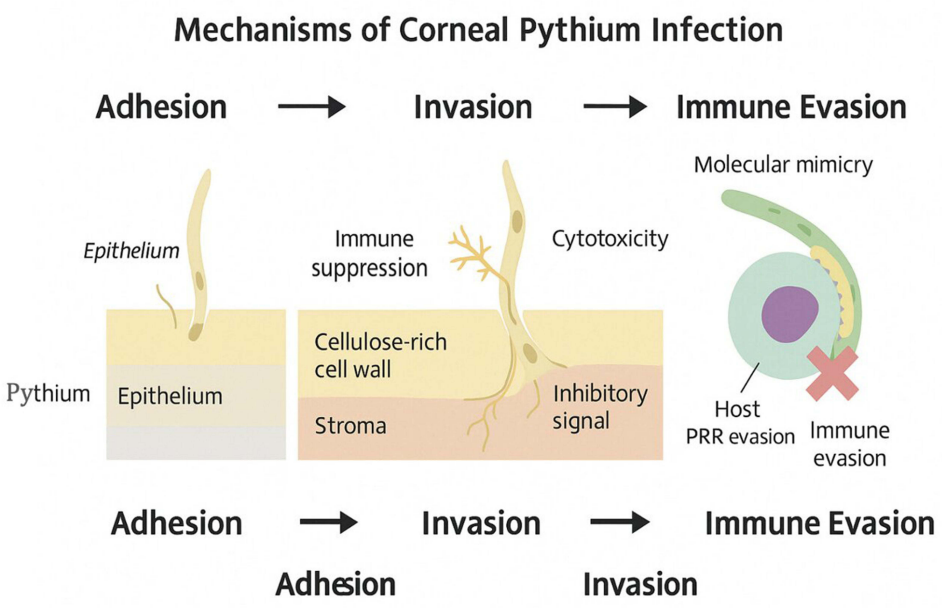

Figure 3 Schematic representation of the mechanisms of corneal *Pythium* infection, progressing through adhesion, invasion, and immune evasion. The organism adheres to the corneal epithelium, invades the stroma via a cellulose-rich cell wall, and induces immune suppression and cytotoxicity. Immune evasion is facilitated by molecular mimicry and host pattern recognition receptor (PRR) evasion, enabling persistence within the corneal tissue.

In summary, the hypothesis posits a stepwise subversion of host defences by *P. insidiosum*. Initially, through structural camouflage (an atypical cell wall) and active molecular disguise, Pythium establishes infection with only a mild immune response. A delayed hyperinflammatory phase follows this silent invasion phase once the immune system finally recognizes the threat. This two-phase immunopathology – stealth then storm – could explain why *Pythium* keratitis often progresses rapidly to perforation and why treatments that target the organism pharmacologically have limited success if the immune system is not appropriately engaged. It diverges from existing thinking by suggesting that the host's failure to mount an early defense, rather than the organism's inherent virulence or the lack of drugs, is a key driver of disease severity.[18]

Evaluation of the Hypothesis

This is a hypothesis-driven conceptual framework intended to propose potential mechanisms and future experimental directions. The assays and models described herein, including PRR activation studies and cell wall unmasking experiments, are proposed for future validation. These experiments will be undertaken in subsequent studies. To evaluate this immuno-camouflage hypothesis, we consider evidence from the literature that supports or challenges each component of the proposed mechanism, and we suggest experimental approaches to test these ideas.

Supporting Evidence for Immune Evasion

Unique Cell Wall and PRR Evasion

There is strong biochemical and experimental evidence that *P. insidiosum* is not recognized by the host in the same way as fungal pathogens. The cell wall composition (summarized in Table 1) provides the first clue. Unlike Candida or Aspergillus, *Pythium* incorporates cellulose and only a small amount of β-glucan, and it lacks chitin.[28] This means key fungal PAMPs are either absent or shielded. Indeed, studies have shown that TLR4 and Dectin-1, which are crucial for immune detection of fungi (TLR4 drives fungal killing, Dectin-1 triggers neutrophil recruitment), are not robustly activated at the onset of *Pythium* infection.[29] Ahirwar et al found that in vitro exposure of human corneal cells to *P. insidiosum* led to upregulation of Dectin-1 and TLR4 transcripts only after 12 hours, implying that initial contact (0–6 hours) did not strongly engage these receptors.[11] In contrast, fungal components often trigger Dectin-1 within

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Table 1 Comparative Analysis of Immune Evasion Strategies of *Pythium insidiosum* versus Typical Fungal Keratitis Pathogens, Highlighting Differences in Cell Wall Composition, Pattern Recognition Receptor Engagement, Cytokine Responses, Neutrophil Recruitment, Intracellular Survival, Adaptive Immunity Bias, and Disease Outcomes

S. No	Feature	Pythium insidiosum (Oomycete)	Typical Fungal Pathogen (eg Fusarium)
1	**Cell Wall Composition**	Cellulose-rich; little or no chitin; low β-1,3-glucan exposure Contains hydroxyproline-rich proteins (collagen-like).[31]	Chitin and β-1,3-glucan abundant in wall; no cellulose. Mannan glycoproteins on surface. Ergosterol in membrane.
2	**Early PRR engagement**	Weak early engagement. Minimal Dectin-1 signalling (β-glucan masked)[11]; TLR4 engagement delayed; some TLR2 signalling. Possibly engages inhibitory lectins (eg Siglecs) via host-like sugars (hypothesized).[12]	Strong immediate engagement. Dectin-1 binds exposed β-glucan triggering IL-1β; TLR4 and TLR2 recognize fungal mannans and other PAMPs, activating TNF/IL-1 pathways. Inhibitory receptors not prominently engaged by fungal cell wall.[7]
3	**Innate cytokine response (early)**	**Blunted**: Low IL-1β, TNF-α in first 24–48h. Moderate IL-6, IL-8 induction. Potentially higher IL-10 (tolerogenic skew) (proposed).[12]	*Robust*: High IL-1β, TNF-α, IL-6 within hours of infection. IL-8 also high, driving neutrophil influx. Low IL-10 in early stage (pro-inflammatory skew).[7]
4	**Neutrophil recruitment**	Delayed and often insufficient to contain infection early (neutrophils accumulate once infection is widespread). Neutrophils may arrive but fail to halt progression, contributing to tissue damage later.[11]	Rapid and intense neutrophil infiltration at infection site, often forming an abscess that helps contain the fungus locally. Early neutrophils can limit spread, though they also cause some collateral damage.[7]
5	**Survival inside phagocytes**	Can survive transiently inside macrophages; zoospores germinate inside and can kill the phagocyte. Suggests phagosome evasion or delayed acidification (consistent with poor activation of macrophage microbicidal functions).[32]	Generally killed upon phagocytosis if opsonized properly – macrophages/neutrophils activated by strong PAMP signals produce ROS and enzymes that kill fungi. Intracellular survival is limited for most fungi (except specialized ones like Histoplasma).[33]
6	**Adaptive immunity**	Th2/regulatory bias observed in natural infection (high IL-10, low IFN-γ). Antibodies against *Pythium* antigens can cross-react (some antigens not strongly immunogenic). Immunotherapy (PIA vaccine) needed to shift toward Th1 and effective clearance.[32]	Tends to induce Th1/Th17 responses (IFN-γ, IL-17) important for fungal clearance. Antibodies form against fungal cell wall components (eg mannans) in most cases. Vaccines are not typically used clinically, as normal adaptive response often suffices with antifungal help.
7	**Outcome if untreated**	Progressive stromal destruction with peripheral spread ("tentacles"); often perforation or need for enucleation. Host inflammation eventually becomes excessive but too late to save tissue.[2]	Localized ulcer with inflammation; can still progress, but if untreated for long can also lead to perforation. However, many fungal ulcers stay localized longer, giving more time for intervention.

minutes, leading to rapid IL-1β release. The delayed engagement of Dectin-1/TLR4 in *Pythium* aligns with our hypothesis that early during infection these PRRs "see" little to react to. Additionally, *Pythium* does stimulate TLR2 to some extent (likely via lipoproteins or glycoproteins on its surface),[11] but TLR2 activation tends to induce a more regulatory or IL-10–skewed response in many contexts, and in corneal macrophages TLR2 alone was insufficient to drive IL-6 production.[11] Thus, the pattern of PRR usage by *Pythium* (more TLR2, delayed Dectin-1/TLR4) is consistent with a pathogen that avoids triggering the host's most potent antifungal sensors initially. This supportive evidence comes from both the organism's biochemistry and host gene expression data.[30]

Damped Early Cytokine Response

Clinical reports and animal studies corroborate that *Pythium* fails to elicit a fulminant early immune response. In a rabbit model, the expression of pro-inflammatory cytokines was modest at 3 days post-infection and peaked at 7 days despite significant infection being present. Specifically, IL-1β – a master pro-inflammatory cytokine usually elevated early in infections – was not significantly up on day 3 compared to control, whereas by day 7 it rose substantially.[34] This timing

suggests that the initial immune activation was delayed. For comparison, in fungal keratitis IL-1β can rise within hours as Dectin-1 and TLRs trigger inflammasome pathways.[35] The absence of early IL-1β in *Pythium* infection (despite the organism proliferating in the cornea) strongly supports the idea of early immune evasion. The pattern of chemokines also fits: IL-8 was elevated in *Pythium* infection, but mostly at later time points, mirroring the massive neutrophil influx observed clinically only once the infection is well advanced (often giving the appearance of a "dense infiltrate" days into the disease). Thus, both the in vitro epithelial data and in vivo cytokine profiles indicate a muted early innate response, as predicted by the hypothesis.[36]

Molecular Mimicry and Immune Modulation

Direct evidence of molecular mimicry is more difficult to obtain, but there are tantalizing clues. One clue comes from comparative immunology: *Pythium* and a phylogenetically distant fungus, *Basidiobolus*, share cross-reactive antigens that can confuse diagnostic tests[37] If *Pythium* shares antigens with *Basidiobolus*, it is conceivable it also shares epitopes with mammalian proteins (given that convergent mimicry is possible). More directly, the composition of *Pythium*'s extracellular matrix includes hydroxyproline, an amino acid prevalent in collagen and plant cell wall glycoproteins but rare in most pathogens.[38] This unusual feature suggests cell wall of *Pythium* proteins might resemble host structural proteins (like collagen or mucins), potentially reducing their immunogenicity. Additionally, studies of *Pythium* immunotherapy give hints about baseline immune skewing. Untreated patients with vascular *Pythiosis* often show a Th2-biased immune profile (high IL-5, IL-10, low IFN-γ), whereas after receiving the *Pythium* antigen vaccine, they shift toward a Th1 profile (high IFN-γ, IL-12) and improved macrophage activity.[39] This implies that *Pythium* infection in its natural course might promote a non-protective Th2/regulatory environment – possibly via IL-10 induction or lack of strong Th1 cues – which would be consistent with immune evasion. For example, if *Pythium*'s surface mimicry engages macrophage Siglec receptors, it could drive an anti-inflammatory, IL-10^high phenotype in those cells, echoing what is seen in certain chronic parasitic infections that exploit similar mechanisms.[40] While specific Siglec-Pythium interactions have not been documented, the concept is supported by analogies in microbial pathogenesis (several pathogens coat themselves in host-like sialic acid to evade complement and neutrophils). Our hypothesis is that *Pythium* similarly decorates itself in such a way to appear as "self" to the innate immune system, and this is indirectly supported by the need to artificially boost Th1 immunity via a vaccine to clear the organism in disseminated cases (Figure 4).[41]

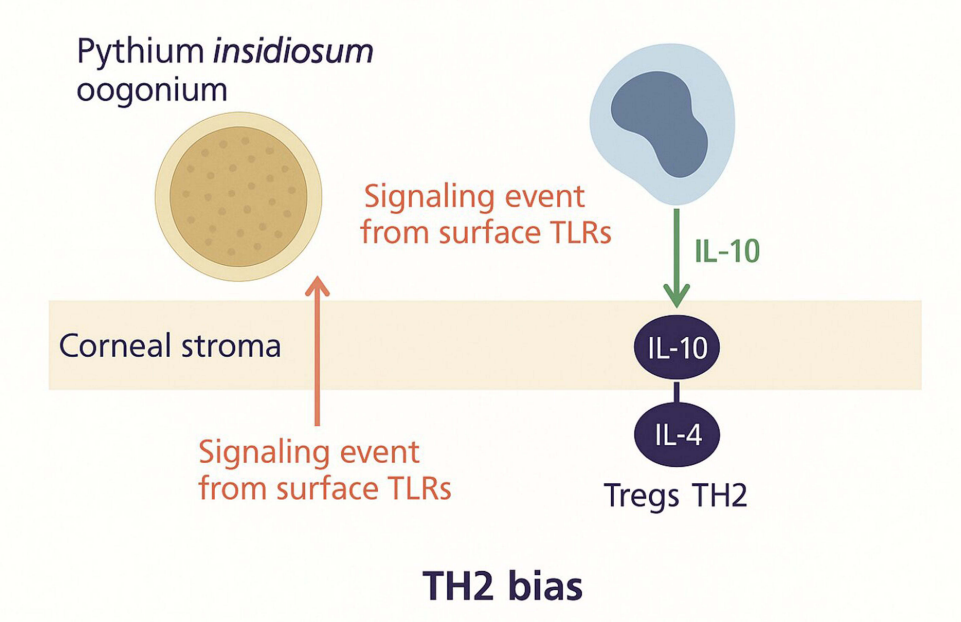

Figure 4 Illustration of stromal immune deviation in *Pythium insidiosum* infection, where signaling events from surface Toll-like receptors (TLRs) in the corneal stroma promote a T-Helper cells-2 (TH2)-biased immune response. The process involves Interleukin-10 production, leading to regulatory T cell (Treg) and TH2 cell activation with increased Interleukin-4, facilitating immune modulation and persistence of infection.

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Survival Inside Phagocytes

A hallmark of many immune-evasive pathogens is the ability to survive phagocytosis (eg *Mycobacterium tuberculosis* in macrophages). There is evidence that *Pythium* zoospores can survive after being engulfed by phagocytes.[42] Medhasi et al (2024) observed that even when patient-derived macrophages phagocytosed *Pythium* zoospores, the zoospores were able to germinate inside the macrophages and ultimately kill the host cells.[32] This implies that not only does *Pythium* initially avoid activation of the macrophage's microbicidal arsenal, but it can also resist or delay destruction within the phagosome. One reason could be that the usual phagolysosomal responses (eg production of reactive oxygen species or acidification) are not effectively triggered without strong PRR signals. If the macrophage does not "realize" it has engulfed a dangerous pathogen (due to mimicry), it might not activate the full spectrum of killing mechanisms, allowing *Pythium* to persist intracellularly temporarily.[43] While *Pythium* is primarily extracellular in tissues, this intracellular phase could help it disseminate or at least survive initial contact with immune cells. The ability to germinate inside a macrophage and kill it is direct evidence of a failure of innate immunity – something one would not expect if the macrophage were properly activated. This observation strongly supports the notion that *Pythium* can disarm or evade cellular immunity at least for a window of time (Figure 5).[44]

Clinical Correlations

Certain clinical features of *Pythium* keratitis make more sense under the immuno-camouflage hypothesis. One example is the frequent necessity of enucleation or evisceration in advanced cases despite intense inflammatory response in the eye. By the time the immune system fully responds, the infection has often involved most of the cornea and even beyond, making immune-mediated clearance without destroying the eye nearly impossible.[45] Another correlation is the risk factors: patients with iron overload or thalassemia have impaired neutrophil and macrophage function and are at higher risk of fulminant Pythiosis. If *Pythium* relies on slipping past a suboptimal immune system, then those with any baseline immune defect (even subtle, like iron-overloaded phagocytes) would be at a marked disadvantage, which matches clinical observations.[46] In fungal keratitis, by contrast, otherwise healthy individuals mount a vigorous response and usually wall off the infection unless pathogen load is very high or virulence is extreme. The fact that *Pythium* often requires such drastic intervention suggests that, in essence, the immune system "drops the ball" early on – aligning with our hypothesis.[16]

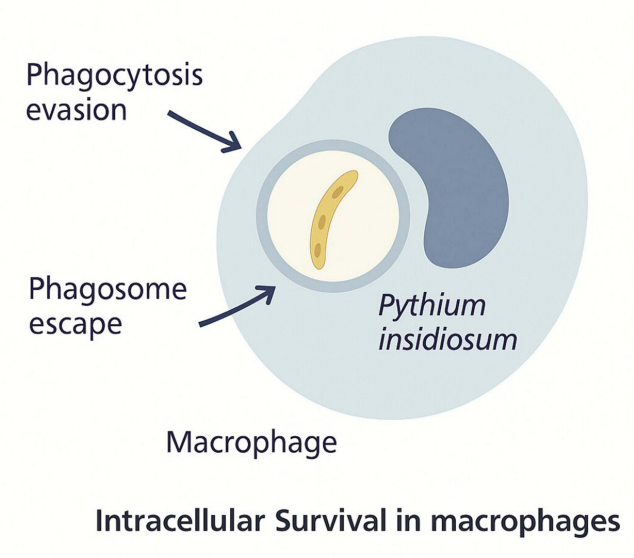

Figure 5 Diagram illustrating intracellular survival of *Pythium insidiosum* within macrophages. The organism evades phagocytosis and escapes from the phagosome, enabling persistence inside host immune cells and contributing to immune evasion.

Contradictory Evidence or Alternate Explanations

While the above points support the hypothesis, it is important to acknowledge evidence that could challenge it.

Intensity of Inflammation

One might argue that *Pythium* keratitis is actually characterized by too much inflammation rather than too little – corneas can undergo rapid melt with extensive neutrophil infiltration (sometimes described as a "sterile" immune ring). Could this not indicate that the immune system is responding strongly to *Pythium*, rather than being fooled by it? Indeed, by mid to late infection, the host response is extreme.[47] However, our hypothesis does not claim *Pythium* lacks immunogenicity entirely; rather, it suggests an initial delay or blunting. The later excessive inflammation is not contradictory – it's expected once the immune system catches up. Another interpretation of the excessive inflammation is that it results from the immune system suddenly recognizing the pathogen after a period of unopposed growth, leading to an over-reactive response (analogous to an immune reconstitution phenomenon). Thus, the presence of inflammation in *Pythium* keratitis is not evidence against immune evasion; it may actually be a consequence of it. Nevertheless, it will be important to quantify the timing of immune events carefully in experimental models to confirm this sequence.

No Known Pythium Immune Effector Molecules

In plant-pathogenic oomycetes (like *Phytophthora*), numerous secreted effectors help the pathogen evade plant immunity. For *P. insidiosum*, such virulence factors are less studied. We currently lack identified *Pythium* proteins that actively disable human immune signaling. The hypothesis of molecular mimicry is somewhat speculative in this regard – we infer its presence from outcomes, not from having isolated a "stealth protein." This is a gap that future research must address.[22] It is possible that *Pythium*, being an evolutionary generalist (infecting plants, animals, humans), has not evolved highly specific immune suppressors for humans, and that its immune evasion is more due to passive lack of PAMPs than active immune suppression. In evaluating the hypothesis, one should consider the simpler explanation: *Pythium* might evade detection simply because our immune system is not adapted to recognize oomycete features (an evolutionary blind spot), rather than *Pythium* specifically *mimicking* us. This is a valid alternative interpretation.[1] The hypothesis would still hold in spirit (immune evasion), but the emphasis would shift from active mimicry to passive "stealth" by unusual biochemistry. Testing this will require deeper analysis of *Pythium*'s genome and secretome for known immune-modulating motifs (eg does it have proteins with host motif domains, or known inhibitor domains?).

Adaptive Immunity Eventually Clears Infection

Another point to consider is that many patients do eventually seroconvert and can clear *Pythium* with appropriate treatment (including immunotherapy). If *Pythium* were completely camouflaged, one might expect it to cause chronic infection indefinitely (like some parasites that establish latency). Instead, in many cases of keratitis that undergo therapeutic keratoplasty combined with aggressive medical therapy, the patient recovers without systemic spread, indicating the immune system can recognize and eliminate residual *Pythium*.[48] This suggests that any immune evasion by *Pythium* is temporary or partial. Our hypothesis accounts for this by the idea that once enough damage occurs or enough antigens are present, the jig is up – *Pythium* gets recognized (albeit late). So this observation does not refute the hypothesis, but it emphasizes that *Pythium*'s camouflage is not perfect or permanent. It buys time, but not infinite time. Experimentally, this could be seen in vitro: if one exposes immune cells to increasing doses of *Pythium* antigen or longer exposure, eventually typical inflammatory responses might appear. This dose-response could be explicitly tested.

Experimental Approaches to Test the Hypothesis

Although this is a hypothesis-driven conceptual study, the proposed experimental framework is designed to be practically implementable Feasibility testing could involve in vitro macrophage stimulation assays with *Pythium* antigens to assess PRR activation, alongside comparative β-glucan unmasking assays. Validation in ex vivo or animal models could subsequently evaluate cytokine responses (IL-1β, TNF-α, IL-6) and confirm immune activation patterns. These

approaches would provide empirical support for the proposed immune camouflage model of *P. insidiosum*. To move from circumstantial evidence to direct proof of immuno-camouflage, the following studies are proposed:

Comparative PRR Activation Assay

Take *P. insidiosum* hyphae and a control fungus (eg *Aspergillus* or *Fusarium* hyphae) and expose them to human or mouse dendritic cells or macrophages in vitro. Measure early signaling events (NF-κB activation, inflammasome activation) and cytokine release (IL-1β, TNF-α, IL-6, IL-10) at very short time points (eg 4, 8, 12 hours) (Figure 6). We predict *Pythium* will induce significantly lower IL-1β and TNF-α than the fungus, but possibly similar IL-8 (since neutrophils do eventually come) and perhaps higher IL-10 (Table 2).[24] Furthermore, using blocking antibodies or knockout cells for specific PRRs can pinpoint differences: for instance, blocking Dectin-1 should have little effect on *Pythium*-stimulated cytokines (since *Pythium* is not effectively using Dectin-1 pathways initially), whereas it would drop cytokines in *Fusarium*-stimulated cells (where β-glucan–Dectin-1 is key). Early results of this kind of experiment would directly confirm if *Pythium* fails to trigger the usual PRR signals (Figure 7).[49]

Cell Wall "Unmasking" Experiment

To test if cellulose is hiding immunostimulatory β-glucan in *Pythium*, we can enzymatically treat *P. insidiosum* hyphae with cellulase (which digests cellulose) or with a β-glucanase control. Treated and untreated hyphae can then be added to immune cells or even injected into a mouse cornea. We hypothesize that cellulase-treated *Pythium* (with cellulose removed, exposing inner β-glucan) will elicit a much stronger immune response – eg immediate neutrophil infiltration, high IL-1β – compared to intact *Pythium*.[50] Preliminary support for this idea comes from a recent proposal to use cellulose synthesis inhibitors in treating *Pythium keratitis*; while that was aimed at directly weakening the organism, an added benefit might be enhancing immune recognition. If our hypothesis is correct, cellulase exposure will "uncloak" Pythium, making it behave more like a fungus immunologically. This can be quantified by an increase in Dectin-1–dependent cytokines after cellulase treatment. A converse experiment is to coat a true fungus (like Candida) with exogenous cellulose or a synthetic polymer and see if its recognition by immune cells is reduced – this would mimic *Pythium*'s strategy and strengthen the concept of physical PAMP masking.[2]

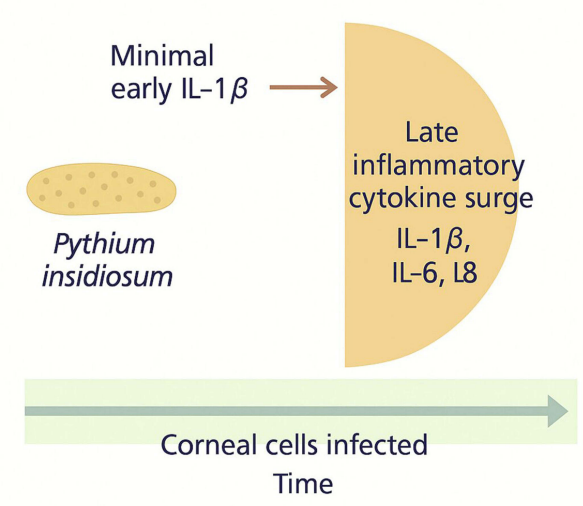

Figure 6 Delayed hyperinflammation model of *Pythium insidiosum* infection, showing minimal production followed by a late surge of inflammatory cytokines, including Interleukin −1β, Interleukin −6, and Interleukin −8, during ongoing corneal cell infection. This delayed response contributes to tissue damage and disease progression.

Table 2 Proposed Omparative Kinetics of PRR Activation and Cytokine Responses in *Pythium insidiosum* versus *Fusarium solani* Keratitis, Highlighting Delayed Innate Immune Engagement and Prolonged Inflammatory Profile in *Pythium* Infections

S. No	Parameter	Pythium insidiosum	Fusarium solani
1	**Dectin-1 mRNA upregulation**	Delayed (12–24 h post-exposure)	Rapid (1–3 h post-exposure)
2	**TLR4 surface expression**	Minimal increase ≤6 h, modest by 24 h	Significant increase within 6 h
3	**IL-1β secretion (pg/mL)**	<20 at 6 h, rises to 100 by 24 h	>80 at 6 h
4	**TNF-α secretion (pg/mL)**	~25 at 6 h, ~150 at 24 h	~200 at 6 h
5	**IL-10 secretion (pg/mL)**	~50 at 6 h	~15 at 6 h
6	**Neutrophil influx in vivo**	Low at day 3, peaks day 7	High by day 2, contained by day 5

Mimicry Detection Assays

To directly detect molecular mimicry, we could perform a proteomic and glycomic analysis of *Pythium* cell surfaces. High-performance liquid chromatography or mass spectrometry can identify if cell wall of *Pythium* contains sialic acids, glycosaminoglycans, or other host-like carbohydrates. We can also test if *Pythium* binds to host immune inhibitory receptors: for instance, a fluorescence binding assay with recombinant human Siglec proteins could show whether

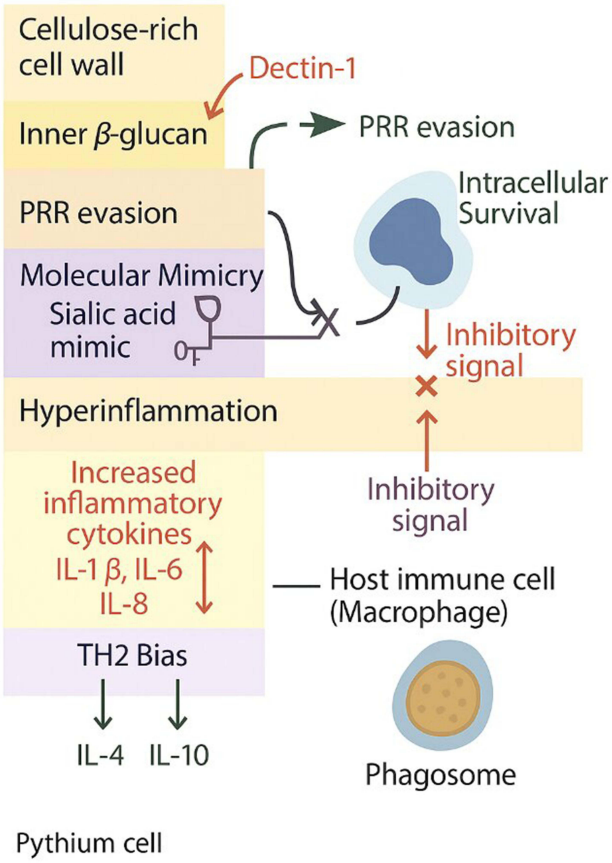

Figure 7 Schematic illustration of the mechanisms of *Pythium insidiosum* immune evasion. Strategies include pathogen recognition receptor (PRR) evasion via a cellulose-rich cell wall and β-glucan masking, molecular mimicry through sialic acid-rich surfaces, and intracellular survival within macrophages with inhibitory signaling. Additional mechanisms involve inducing hyperinflammation with elevated IL-1β, IL-6, and IL-8, and skewing the immune response toward a TH2 bias characterized by increased IL-4 and IL-10 production.

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Pythium extracts have affinity for these receptors. If *Pythium* indeed carries sialylated epitopes, one would see binding to Siglec-7 or Siglec-9 (common on monocytes and neutrophils).[51] We can also treat *Pythium* with neuraminidase (which removes sialic acids) and see if immune recognition improves (similar logic to the cellulase experiment). On the protein side, immunoblotting could be done to see if antibodies against human corneal proteins cross-react with *Pythium* proteins. For example, one might test whether anti-collagen antibodies bind any *Pythium* antigens on a blot – unusual binding could indicate a collagen-like protein in *Pythium*. Additionally, any *Pythium* gene encoding a protein with significant sequence homology to a human protein (detected via BLAST searches) would be a candidate mimic; knocking it out (if feasible) and seeing if immune detection of the mutant improves would be a definitive test. These experiments are more challenging but would directly demonstrate mimicry.[52]

In vivo Immune Challenge Models

An elegant in vivo experiment would be a comparative infection in PRR-deficient vs normal mice. For example, use *P. insidiosum* to infect the corneas of wild-type mice and Dectin-1 knockout mice (or MyD88 knockout mice, etc). If our hypothesis is correct that *Pythium* largely evades Dectin-1, then *Pythium* keratitis outcomes might be *similar* in Dectin-1 KO and wild-type mice (ie knocking out that sensor does not make things drastically worse, because it was not contributing much to defense anyway). In contrast, a fungal keratitis in Dectin-1 KO mice would be much more severe than in wild-type.[49] Such a result – *Pythium* causing severe disease irrespective of certain PRRs – would bolster the idea that it does not trip the normal alarms. Conversely, if knocking out an inhibitory pathway (for instance, mice lacking Siglec-E, the murine equivalent of human Siglec-9) leads to *Pythium* being better controlled (because the inhibitory signal is gone), that would strongly support the mimicry aspect. Measuring bacterial vs *Pythium* load and host damage in these models can pinpoint which immune pathways are bypassed by *Pythium*. Additionally, adoptive transfer experiments (eg transferring macrophages educated in the presence of *Pythium* antigens into naive hosts) could show whether *Pythium* induces a regulatory phenotype that dampens clearance.[53]

Testing Molecular Mimicry

A direct way to evaluate mimicry is to see if disrupting the suspected mimic confers a host advantage. If we suspect, for instance, that *Pythium*'s sialylation of its surface is critical, we could create conditions to grow *Pythium* in presence of sialic acid analog inhibitors (to reduce any sialylation) and then test its virulence or immune recognition. Alternatively, use a Siglec-Fc fusion protein as a decoy in an infection model – if adding a soluble Siglec that binds *Pythium*'s surface leads to greater immune activation (by blocking the pathogen's engagement of inhibitory receptors on actual immune cells), that would strongly validate the mimicry concept.[54] These are sophisticated experiments but feasible with modern immunology techniques. In evaluating contradictory data, we must consider that severe inflammation in *Pythium* keratitis is not evidence against immune evasion but a likely consequence of initial evasion. However, to be thorough, the hypothesis should also be tested in scenarios where immune evasion might not be at play. For example, if we introduce *Pythium* antigens alone (without live organism) into a cornea, do they provoke less response than equivalent fungal antigens? If yes, the antigens themselves are inherently less immunostimulatory (supporting evasion). If no, and the live infection is needed to see the dampening (meaning only live *Pythium* causes low response), it could mean *Pythium* actively secretes an immunosuppressive factor during infection. This distinction – passive evasion via "stealth" PAMPs vs active immunosuppression – is subtle but important, and experiments can be designed to differentiate (eg co-culture *Pythium* with another pathogen to see if it suppresses the response to the second pathogen).[55]

Consequences and Discussion

If *P. insidiosum* is indeed an immuno-camouflaging pathogen, the implications for clinical management and our understanding of host-pathogen interactions are profound. While the Th2-skewed immune response and absence of ergosterol in *Pythium insidiosum* have been recognized as major contributors to its persistence and antifungal resistance, these mechanisms do not fully explain its aggressive corneal behaviour. The present hypothesis introduces an ocular-specific model of immune camouflage, integrating both pathogen and host microenvironmental factors. The corneal surface represents a unique immunological niche characterized by relative immune privilege, avascularity, and localized innate defense through pattern-recognition receptors (PRRs). We propose that *P. insidiosum* adapts to this setting by masking β-glucan with a cellulose-rich outer wall, thereby

limiting Dectin-1–mediated recognition, and by expressing sialic acid–rich surface components that engage Siglec receptors on host immune cells to deliver inhibitory "self-like" signals. This dual strategy of PRR evasion and molecular mimicry blunts early corneal immune activation, explaining the delayed inflammatory onset and rapid stromal infiltration observed clinically. By reframing *P. insidiosum* infection as an active immune-camouflage process rather than passive immune evasion, this model provides a new perspective on ocular pathogenesis and suggests potential therapeutic avenues targeting PRR activation or Siglec blockade to restore effective immune recognition in *Pythium* keratitis. This section discusses the potential consequences, spanning diagnostics, treatment, and broader immunological insight:

Rethinking Diagnostics

Current diagnostic methods for *Pythium* keratitis rely on microbiological culture, PCR, or cytology (eg seeing aseptate hyphae on smear). These can be slow or inconclusive, leading to delays in proper therapy. If the immuno-camouflage hypothesis holds true, it suggests a novel diagnostic approach: detecting the host's *lack* of immune response. For instance, in a patient with a severe corneal ulcer, an unusually low level of IL-1β or TNF-α in the tear fluid or aqueous humor (relative to the size of the ulcer) could raise suspicion for *Pythium*.[56] In contrast, fungal ulcers typically induce a marked inflammatory cytokine milieu. Thus, measuring a panel of inflammatory mediators from tear samples might serve as an "immune fingerprint" – *Pythium* could show an IL-10^high^/IL-1^low^ signature early on, tipping off clinicians that this is not a typical fungus. Additionally, the presence of host-like components in the lesion (eg detecting cellulose in corneal scrapes with fluorescent brighteners, already used, or even finding human collagen fragments bound to *Pythium* – hypothetically if *Pythium* cloaks itself in host debris) could be exploited as indirect markers.[57] A fascinating possibility is the development of a skin test or blood test akin to a delayed-type hypersensitivity test: inoculate a small amount of killed *Pythium* antigen intradermally and observe if the patient mounts a normal Th1 response. A patient with *Pythium* infection might exhibit anergy or a skewed response due to immune deviation, whereas they would respond normally to common antigens. Such immunological tests could complement molecular diagnostics.[58]

Therapeutic Innovations

Recognizing immune evasion opens up entirely new therapeutic strategies beyond simply trying to kill the microbe. One strategy is immunomodulation – essentially, boosting the host's ability to recognize and fight *Pythium*. This could be as straightforward as adding an immunostimulatory adjuvant to the treatment regimen.[59] For example, topical TLR agonists (like a TLR7/8 agonist imiquimod, or a CpG ODN for TLR9) might be applied to the cornea to activate innate immunity broadly, counteracting *Pythium*'s suppression. There is precedence for using imiquimod in difficult fungal or protist infections of the skin; a careful use in the cornea could potentially ramp up local immunity (though with risk of inflammation).[60] Another angle is checkpoint inhibition in the immune sense: if *Pythium* engages inhibitory receptors like Siglecs or PD-1/PD-L1 pathways on macrophages (the latter is speculative), one could use blocking antibodies to those (akin to cancer immunotherapy but locally) to prevent the pathogen from exploiting those "brakes". Of course, safety in the eye is a concern, but short-term local application might be feasible.[61] Perhaps, the most immediately practical idea is to combine *Pythium*-targeted therapy with agents that strip its camouflage. The recently proposed use of cellulose biosynthesis inhibitors (CBIs) falls in this category. Indaziflam or similar agents could weaken the oomycete's cell wall and simultaneously expose its underbelly to the immune system. Our hypothesis provides a second rationale for CBIs: beyond fungistatic effects, they might turn *Pythium* from an invisible foe to a visible one. Likewise, enzymatic adjunctive therapy could be tried – for instance, hourly topical cellulase or chitinase (though *Pythium* has little chitin, cellulase is relevant) might digest the pathogen's protective layer in vivo. This concept parallels how biofilm-degrading enzymes are used to break down bacterial biofilms to improve antibiotic penetration and immune access.[2]

Another therapy inspired by mimicry would be to target the mimicry itself. If we confirm *Pythium* uses host-like sialic acids, we could use neuraminidase eye drops to remove those sugars. Neuraminidase (sialidase) eye drops are not standard, but interestingly, certain bacteria produce sialidases that could potentially be harnessed or formulated if needed. Alternatively, a competitive inhibitor that saturates Siglec receptors (preventing *Pythium* from engaging them) might be applied – though this is quite experimental.[62] Immunotherapy (as already practiced in some settings for *Pythium*, where patients receive injections of *Pythium* antigen to stimulate immunity) would also benefit from understanding of evasion.

Table 3 Proposed Experimental Approaches to Investigate *Pythium insidiosum* Immune Evasion via Cellulose Masking, Siglec-Mediated Inhibition, and PRR Circumvention, with Anticipated Outcomes to Validate These Mechanisms

S. No	Experiment	Hypothesis	Expected Positive Result	Interpretation
1	**Cellulase treatment + macrophage assay**	Cellulose masks β-glucan	Increased IL-1β and TNF-α secretion vs untreated	Confirms physical PAMP unmasking
2	**Siglec-9 blockade assay**	Pythium uses sialic acid for Siglec-mediated inhibition	↑ pro-inflammatory cytokines upon Siglec-9 blockade vs control	Demonstrates functional molecular mimicry
3	**Infection in Dectin-1 vs WT mice**	Pythium evades Dectin-1	Similar disease severity in both mouse strains	Shows Dectin-1 is not primary defense against Pythium
4	**PRR global activation (imiquimod) adjunct**	TLR agonist overcomes evasion	Reduced Pythium burden in treated vs untreated mice	Suggests immunopotentiation can unmask Pythium to immune system

For instance, knowing that a Th1 response is protective, clinicians could monitor cytokine profiles after immunotherapy doses and ensure patients are mounting the right type of response. In the future, a more refined *Pythium* vaccine could be developed that not only exposes the immune system to *Pythium* antigens but also includes an adjuvant that blocks the organism's inhibitory tricks (perhaps a conjugate that ties up inhibitory receptors) (Table 3).[63]

Rationale for Combination Therapy

If immune evasion is key, then successful treatment likely requires both killing the organism *and* engaging the immune system. This might explain why combinations of antibiotics (like azithromycin or linezolid) with surgery have had partial success, some antibiotics like azithromycin have immunomodulatory properties (azithromycin is known to dampen neutrophil responses in other contexts, but perhaps its inhibition of protein synthesis in *Pythium* also stresses it and exposes PAMPs).[64] The hypothesis encourages combination therapy where one component targets the pathogen and another "enables" the immune system. For example, a combination of linezolid (to inhibit Pythium's protein synthesis) + interferon-gamma eye drops (to activate macrophages) could be envisioned. While speculative, if *Pythium* often infects individuals with suboptimal immune function (like those with thalassemia or even local immune deviation in the eye), providing immune stimulants externally could tip the balance.[65]

Rethinking Pathogenesis in Other Contexts

Validating immune camouflage in *Pythium* might prompt a re-examination of other "atypical" infections. For instance, *Acanthamoeba* keratitis is another difficult corneal infection, caused by a protozoan that also has a cyst form with cellulose in the wall – does it similarly evade immune detection? Some evidence in animal models shows *Acanthamoeba* cysts induce less inflammation, and like *Pythium*, it often requires vigorous immune activation (eg via miltefosine or PHMB that might also act on host immune cells). The parallels suggest that immune evasion might be a broader theme among organisms that are not classical bacteria or fungi. Studying *Pythium* could thus shed light on a spectrum of "stealth" pathogens.

Rethinking Host Damage

The hypothesis also reframes the cause of tissue damage in *Pythium* keratitis. Rather than simply attributing it to the organism's invasiveness or toxins, it suggests a two-phase damage model: early damage is due to the organism digesting tissue unchecked (since immune cells are not stopping it), and late damage is due to an overzealous immune response (once the immune cells finally engage, they release a storm of enzymes and radicals that harm tissue).[4] This aligns with the observation that *Pythium* can cause a cornea to melt rapidly – likely a combination of proteolytic enzymes from the pathogen and matrix metalloproteinases from neutrophils once they arrive. Therefore, therapies might need to protect the cornea in two ways: by bringing in immune help earlier, and by controlling excessive inflammation later. For the latter,

adding collagen cross-linking or anti-proteinase therapy could be beneficial. Indeed, one could speculate that early immune evasion followed by late inflammation means an ideal therapy might oddly include both an immune stimulant (early) and an anti-inflammatory (later) in a timed sequence.[66] This is complicated to implement, but worth investigating (eg in animal models, give an immune booster at inoculation and a steroid 4 days later once treatment has started, to see if outcome improves). Traditionally steroids are contraindicated in infectious keratitis, but in *Pythium*, if the immune response is tardy and then destructive, a carefully timed anti-inflammatory might preserve vision once adequate antimicrobial action is in place. This is conjectural but follows logically from the hypothesis.

Rationale for Early Surgical Intervention

Currently, early therapeutic keratoplasty is often done in *Pythium* keratitis because medical therapy is unreliable. Our hypothesis lends immunological justification to this practice: by removing the bulk of the *camouflaged* pathogen, surgery essentially removes the source of immune evasion. The wound from surgery will trigger a classic wound-healing immune response, which can then clean up any remaining *Pythium* (especially if combined with immunotherapy).[67] Surgeons have noted that even after therapeutic keratoplasty, recurrence at the graft margin can happen, presumably from residual organism – one might interpret that as *Pythium* trying to reinvade, but now in the presence of a lot of post-surgical inflammation it sometimes fails to take hold. Ensuring the immune system is activated (perhaps by debriding edges, etc.) is likely one reason that large excisions with a good rim of clear tissue have better outcomes. In this context, surgery is an immune-restoring measure (in addition to pathogen debulking). If immune-based therapies improve, perhaps surgery could be less extensive or avoided. Still, until then, it remains a mainstay partly because it sidesteps the need for the immune system to do the initial heavy lifting.[31]

Rethinking Epidemiology and Prevention

Emerging evidence indicates that P.insidiosum keratitis is not limited to a single geographic region but has a truly global footprint. Although initially described in Thailand, subsequent case reports and case series have detailed infections in India, Australia, China, Israel, and the USA.[3] A recent systematic review noted that Pythiosis—including its ocular form—has been documented in more than 23 tropical, subtropical and temperate countries, with mean incidence increasing over the past decade.[4] In South India, for example, a prevalence of approximately 5.9% of microbial keratitis cases was attributed to *P. insidiosum* in one series.[2] These data emphasise that *P. insidiosum* should be considered a globally relevant ocular pathogen, particularly in water-related and agrarian exposures, and highlight the need for heightened awareness, region-adapted diagnostic pathways, and surveillance systems in both endemic and non-endemic regions. If *Pythium* mainly causes disease in those whose immune system does not react properly, identifying those at risk (like individuals with subtle immunosuppression or genetic predispositions in PRRs) could be important. Perhaps in the future, genetic screening or immune profiling could identify people who might need prophylactic measures when in endemic areas (for example, avid swimmers with diabetes or iron overload could avoid stagnant water exposure). Also, understanding that *Pythium* is an environmental organism that our immune system is not "trained" to recognize might encourage development of prophylactic measures for high-risk groups, maybe even an experimental vaccine for veterinarians or others who frequently encounter it. In the broader sense, confirming immune camouflage in *Pythium* would underscore the importance of looking at host-pathogen interactions in infections that are atypical. It would remind clinicians that a pathogen's "virulence" is often a two-way street – sometimes the most dangerous pathogens are those that *do not* immediately send our immune system into battle mode. This has analogies in other fields (for instance, certain cancers escape immune detection in similar ways; chronic infections like hepatitis B have phases of immune tolerance). *Pythium* keratitis could become a model for studying immune tolerance in acute infection (Table 4).

While the hypothesis integrates existing evidence on immune evasion mechanisms, several uncertainties remain regarding the specific molecular interactions between *P. insidiosum* and host immune receptors. Future research should focus on validating these proposed pathways through in vitro PRR-binding studies, cytokine response assays, and in vivo infection models. Addressing these questions will be essential to confirm whether *Pythium* employs immune camouflage as a dominant survival strategy and to identify potential therapeutic targets for intervention.

Table 4 Potential Immunotherapeutic Targets and Candidate Agents for *Pythium insidiosum*, Highlighting Mechanisms to Unmask Pathogen Antigens, Boost Innate and Adaptive Immunity, and Counteract Immune Evasion

S. No	Target	Mechanism	Candidate Agent	Rationale
1	**Cellulose layer**	Degrade cellulose cloak	Topical cellulase	Unmasks β-glucan, exposing PAMPs for PRR detection
2	**Siglec inhibitory**	Block inhibitory signalling via sialic acid	Siglec-9 Fc decoy or antibody	Prevents Pythium engagement of macrophage Siglecs
3	**Inflammasome activation**	Promote IL-1β release	NOD-Like Receptor Pyrin domain-containing protein (NLRP)3 agonist (eg, imiquimod analog)	Drives early IL-1β production to initiate robust innate response
4	**Th1 polarization**	Skew adaptive immunity to Th1	Recombinant IFN-γ	Enhances macrophage killing and supports protective antibody response
5	**Checkpoint inhibition**	Block PD-1/PD-L1–like evasion (speculative)	Anti– programmed cell death protein (PD)-1 topical peptide	Could counteract local T cell or macrophage inhibitory pathways

The current hypothesis lays a conceptual foundation for understanding immune evasion by *Pythium insidiosum* in the cornea, and further empirical validation is essential to substantiate the proposed mechanisms. To strengthen the translational potential of this hypothesis, it is acknowledged that the proposed experimental design remains conceptual and requires validation in controlled corneal infection models. Future studies will focus on minimizing confounding factors that may influence immune escape, including host immune variability, corneal epithelial integrity, microbial load, and environmental factors. Standardized ex vivo human corneal models and in vivo animal models will be employed to simulate physiological immune responses within the ocular microenvironment. Appropriate experimental controls, reproducible inoculum preparation, and temporal cytokine profiling will be integrated to distinguish pathogen-driven immune modulation from secondary host effects. These approaches will enable precise delineation of the structural and molecular components of *P. insidiosum*—including its cellulose-rich wall and hydroxyproline-rich glycoproteins—that contribute to altered recognition by pattern recognition receptors and dampened inflammatory signalling. Such refined validation strategies will help substantiate the immune-camouflage hypothesis and deepen understanding of corneal immune evasion mechanisms.

Challenges and Future Directions

While the present work is conceptual, translating the immune-camouflage hypothesis into experimental validation poses particular challenges. *Pythium insidiosum* is a fastidious organism, and standard fungal immunoassays may not adequately capture its cellulose-rich, β-glucan–deficient wall interactions. Future studies could focus on Pattern Recognition Receptor (PRR) activation assays, particularly those targeting the TLR2, TLR4, and Dectin-1 pathways, to elucidate innate immune signalling in response to Pythium antigens. In vitro cytokine profiling of corneal epithelial and stromal cells, along with cell wall unmasking experiments using β-glucan- or cellulose-targeted enzymes, may provide insights into how the pathogen modulates host recognition. Establishing reproducible infection models in corneal tissue or organoids could further strengthen mechanistic understanding. Acknowledging these limitations and defining potential experimental frameworks not only reinforces the hypothesis's plausibility but also provides a roadmap for future translational studies exploring immunomodulatory or enzyme-assisted therapies for Pythium keratitis.

Conclusion

The hypothesis that *Pythium insidiosum* keratitis is driven by immuno-camouflage provides a coherent explanation for many perplexing aspects of this disease – from the subtle clinical onset and diagnostic difficulty, to the failure of typical antifungals and the dramatic tissue destruction. While some molecular details remain to be established, the pieces of the

puzzle (cellulose shielding, delayed cytokine responses, survival in macrophages, etc.) fit a narrative in which the host is initially "fooled" and then retaliates too late. Validating this theory would not only help tailor more effective therapies (e.g., by combining unmasking agents with targeted drugs and immunotherapy) but also shift the paradigm for managing recalcitrant infections: sometimes, helping the immune system recognize the pathogen is as essential as directly attacking the microbe. Ultimately, the interplay of *Pythium* and the host immune system is a battle of disguise and discovery. By uncovering the strategies Pythium employs, we can tip the balance in the host's favour, potentially transforming an almost always blinding infection into one that can be detected early, treated effectively, and even prevented in those at risk. The story of *Pythium insidiosum* may well exemplify that in the contest between pathogens and the immune system, it's not always brute force that wins the day – sometimes, it's stealth. And knowing that, we can respond in kind: by finding ways to illuminate the infiltrator and call the immune system to arms at the right place and time.

In conclusion, this hypothesis proposes that *Pythium insidiosum* employs immune camouflage to evade early host recognition, representing a novel conceptual advance in understanding its corneal pathogenicity. Future validation of this hypothesis will require targeted experimental approaches, including PRR activation assays, cytokine profiling, and cell wall–unmasking studies to confirm the pathogen's immune-modulatory behaviour. These experiments, coupled with molecular and immunohistochemical analyses, could provide definitive insights into the mechanisms of immune evasion and guide the development of effective immunotherapeutic strategies.

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