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KNOWLEDGE HUB · ACNE SCIENCE SERIES — CHAPTER 4

The Biofilm–Inflammation Connection

Why the fortress is the real enemy

How *C. acnes* biofilm — not bacterial count — drives the inflammatory cascade of acne, and what that means for treatment design.

PUBLIC EDITION · FREE TO SHARE

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Singapore · Brussels

A NOTE BEFORE YOU READ

A chain reaction below the surface

Inflammatory acne does not begin with a bacterium behaving badly in open space. It begins with a microenvironment that rewards a change of behaviour — one that turns a harmless skin resident into the engine of a lesion.

Inside the pilosebaceous unit — the follicle-and-sebaceous-gland complex of facial skin — sebum accumulates, the duct plugs, oxygen is consumed and not replaced, and *C. acnes* shifts from a solitary, free-swimming lifestyle into a matrix-protected **biofilm**. That shift is the hinge on which the entire inflammatory cascade turns.

WHAT THIS CHAPTER EXPLAINS

The mechanism, step by step

How the biofilm forms, the seven molecular weapons it deploys, why it resists treatment, and the open question that should shape how we dismantle it.

HOW TO READ THE EVIDENCE

Confident where proven; honest where not

The mechanistic case is strong and convergent. Where human proof is still incomplete — notably post-treatment kinetics — we say so plainly.

THE ONE IDEA TO CARRY THROUGH

The fortress, not the bacterium, is the enemy.

Acne is not a story of *how many* bacteria are present, but of how they are *organised*. The biofilm is simultaneously a structural plug, a chemical reactor, and an immunological alarm — and that is what we have to defeat.

7

INTERLOCKING MOLECULAR WEAPONS

32×

BIOFILM ANTIBIOTIC TOLERANCE (CLINDAMYCIN)

~6wk

TO FIRST MEASURABLE IMPROVEMENT ON DISRUPTION

01

HOW THE FORTRESS IS BUILT

The biofilm switch

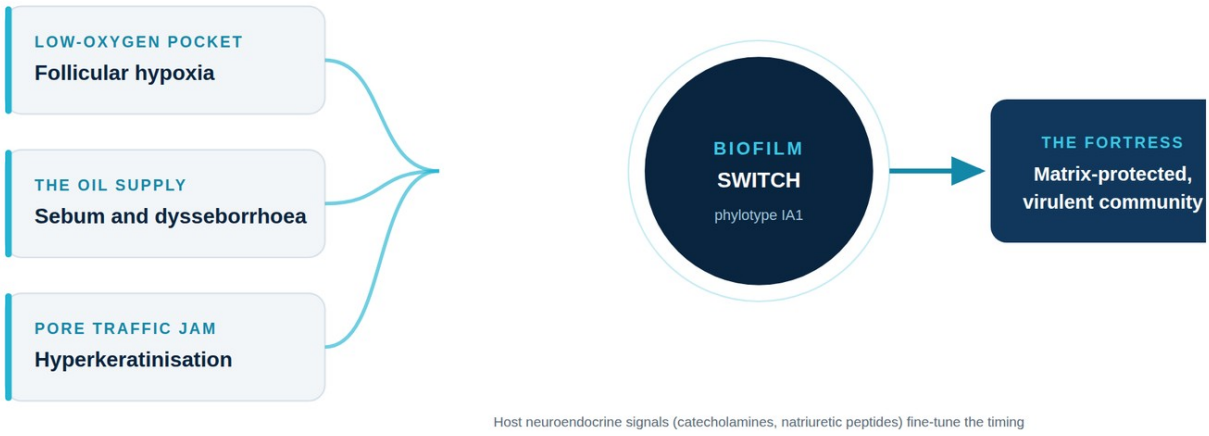
Three converging conditions inside the follicle flip *C. acnes* from free-swimming to fortified — and select for its most virulent lineage.

SECTION 1 · THE BIOFILM SWITCH

How *C. acnes* builds its fortress

The transition from planktonic to biofilm life is not random. It is induced by three converging conditions, with host signals fine-tuning the timing.

THE PLANKTONIC-TO-BIOFILM SWITCH



Host neuroendocrine signals (catecholamines, natriuretic peptides) fine-tune the timing

LOW-OXYGEN POCKET

Follicular hypoxia

A plugged follicle turns anoxic. Hypoxia favours *C. acnes* over aerobes and reprograms it toward porphyrin synthesis — priming the molecules that later trip the inflammasome.

THE OIL SUPPLY

Sebum chemistry

Acne-type sebum — high triglyceride, oxidised squalene, low linoleic acid, high palmitic acid — selects the lipid-adapted, virulent **IA1** phylotype.

PORE TRAFFIC JAM

Hyperkeratinisation

Adhesive corneocytes and trapped sebum form the microcomedo; biofilm matrix then acts as a glue that compacts the plug — occlusion begets biofilm.

REMEMBER THIS

The switch is a dialogue, not a whim.

Stress catecholamines and host natriuretic peptides actively push the follicular community toward biofilm — so the bacterium's lifestyle is shaped by the host environment, not bacterial chance alone.

Sources: O'Neill & Gallo 2018, *Microbiome*; Mayslich et al. 2021, *Microorganisms*; Borrel et al. 2019, *Front. Med.*; Coenye et al. 2021, *Biofilm.*

02

THE ARSENAL

Seven molecular weapons

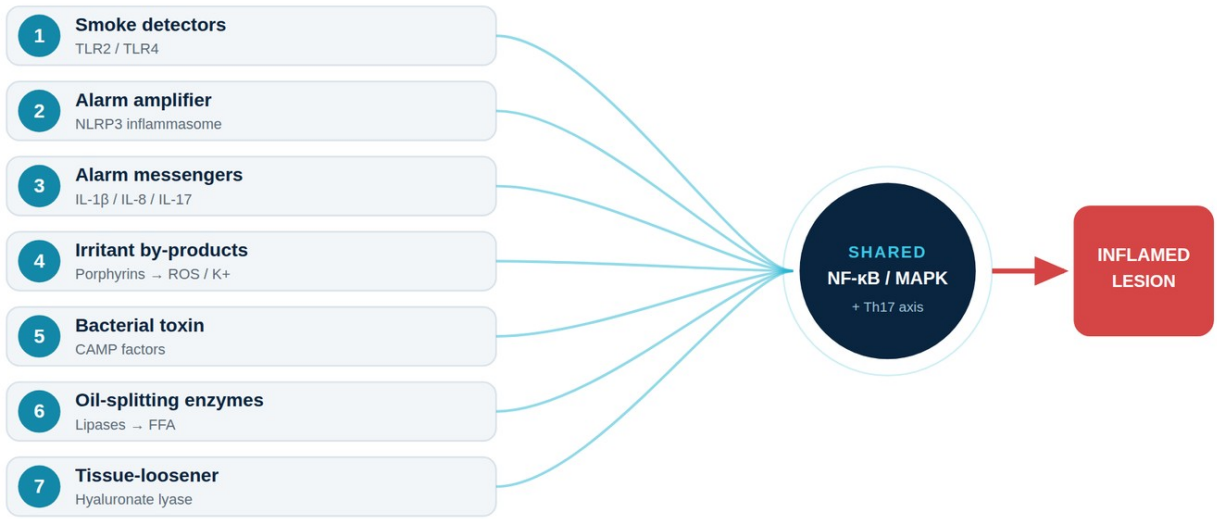
Once built, the fortress deploys a convergent arsenal — seven effectors that map onto the same handful of inflammatory nodes.

SECTION 2 · THE ARSENAL

How biofilm drives inflammation

Independent studies repeatedly map these weapons onto the same nodes — TLR2/4, NF-κB/MAPK, the NLRP3 inflammasome, and the Th17 axis. They interlock rather than fire alone.

SEVEN WEAPONS, SHARED INFLAMMATORY NODES



WHY IT MATTERS

An integrated platform

Porphyrins and CAMP pores both drive the potassium efflux that powers the inflammasome; lipase-derived fatty acids both occlude and inflame; hyaluronate fragments and CAMP both feed TLR2.

THE DECISIVE NUANCE

Biofilm pulls the trigger

Biofilm-derived *C. acnes* activates the keratinocyte TLR2 axis robustly; planktonic cells under identical conditions largely do not. State, not census, determines pathogenicity.

Sources: Zeng et al. 2019, *J. Invest. Dermatol.*; Spittaels et al. 2021, *iScience*; Chen et al. 2025, *Microb. Genom.*; Mayslich et al. 2021, *Microorganisms*.

SECTION 2 · THE SEVEN WEAPONS IN DETAIL

Each weapon, in plain language

1 · SMOKE DETECTORS

TLR2 / TLR4

Cell-wall ligands trip Toll-like receptors, firing NF-κB and MAPK and the IL-6 / IL-8 / TNF-α programme.

2 · ALARM AMPLIFIER

NLRP3 inflammasome

A potassium-efflux trigger assembles NLRP3, activating caspase-1 and maturing **IL-1β** — seen in lesion macrophages.

3 · ALARM MESSENGERS

IL-1β / IL-8 / IL-17

IL-1β drives hyperkeratosis, IL-8 recruits neutrophils, and IA1 dominance skews the response toward Th17.

4 · IRRITANT BY-PRODUCTS

Porphyrins

Coproporphyrin III drives membrane K^+ leakage (the inflammasome trigger) and photogenerates reactive oxygen species.

5 · BACTERIAL TOXIN

CAMP factors

Pore-forming effectors injure keratinocytes and drive IL-8 — in a feedback loop that further raises CAMP expression.

6 · OIL-SPLITTING ENZYMES

Lipases → FFA

GehA hydrolyses sebum to free fatty acids; palmitic acid acts as a TLR2 danger signal and inflammasome activator.

7 · TISSUE-LOOSENER

Hyaluronate lyase

Degrades dermal matrix, releases pro-inflammatory HA fragments, and opens a route toward nodules and scarring.

THE PATTERN

Convergence

Seven inputs, a few shared outputs. That redundancy is exactly why the biofilm is so reliably inflammatory.

Sources: Coenye et al. 2021, *Biofilm*; Kistowska et al. 2014, *J. Invest. Dermatol.*; Agak et al. 2014, *J. Invest. Dermatol.*; Spittaels et al. 2021, *iScience.*

SECTION 3 · A DIFFERENT BEAST

Fortified and ferocious

Why does the same species behave so differently in biofilm form? Three properties make the biofilm state categorically more dangerous than the lone swimmer.

PLANKTONIC

The lone swimmer

- Free-floating, solitary
- Antibiotic-susceptible
- Does NOT trigger keratinocyte
- TLR2 / cytokine response

vs

BIOFILM

The fortress

- Matrix-encased community
- Tolerant: up to 32× (clindamycin)
- Immune-evading
- **DRIVES the inflammatory cascade**

>6log
KILL WHEN MATRIX IS STRIPPED FIRST (DISPERSIN B → BPO)

32×
BIOFILM ERADICATION-TO-INHIBITION RATIO, CLINDAMYCIN

PNAG
MATRIX POLYMER BEHIND BENZOYL-PEROXIDE TOLERANCE

Crucially, biofilm **tolerance is distinct from genetic resistance**: clinical isolates can be genetically resistant yet weak biofilm formers, so the two phenomena do not track together. The fortress protects through structure — a diffusion barrier, dormant metabolism, and an immune-evading matrix — which is why dismantling the matrix re-sensitises the community.

ANTIBIOTIC TOLERANCE

The matrix is a diffusion barrier and its dormant cells resist drugs that target active division — tolerance that returns the moment the community disperses.

IMMUNE EVASION

The extracellular-DNA scaffold shields surface antigens from complement and phagocytes, letting IA1 strains build thicker, more biomass-rich fortresses than commensals.

"The relevant pro-inflammatory entity is the organised community — not the individual cell. State and strain, not census, determine pathogenicity."

Sources: Kaplan et al. 2024/2025, *Front. Microbiol. / PLOS ONE*; Cavallo et al. 2022, *Sci. Rep.*; Paul et al. 2025, *Indian J. Dermatol. Venereol. Leprol.*; Zeng et al. 2019, *J. Invest. Dermatol.*

SECTION 4 · IT'S NOT ABOUT THE COUNT

The biofilm is the problem

The single most important fact in modern acne microbiology is a negative result: total *C. acnes* abundance does not reliably separate acne-prone from healthy skin. Organisation does.

ACNE IS A DISORDER OF QUALITY, NOT QUANTITY

THE SIGNAL

Diversity collapses; IA1 dominates

In inflammatory lesions, microbiome diversity falls and the virulent IA1 phylotype predominates — even as species-level counts stay comparable to healthy skin.

THE HONEST NUANCE

Dynamics may matter more than mass

Some evidence suggests biofilm first *stabilises* the comedone; the decisive event may be the transition from stable biofilm to ruptured follicle.

Sources: Platsidaki & Dessinioti 2018, *F1000Research*; Cavallo et al. 2022, *Sci. Rep.*; Loss et al. 2021, *Int. J. Dermatol.*

SECTION 5 · BREAK IT, AND WHAT HAPPENS

Break it and the inflammation subsides

If the biofilm is the problem, dismantling it should resolve inflammation — and the available evidence is encouraging, if still thinner than the mechanistic case deserves.

CLINICAL TIMELINE AFTER SUSTAINED BIOFILM DISRUPTION

STATED PLAINLY

The molecular proof is still incomplete.

Clinical studies measure lesion counts and severity grades — not cytokines. No verified human study has tracked IL-1β, IL-8 or TNF-α resolution at defined timepoints after a biofilm-targeted intervention. Improvement on a scale of weeks is consistent with the hypothesis; the cytokine kinetics that would close the loop remain an open, fundable question.

Sources: Kaplan et al. 2025, *PLOS ONE*; Marshall-Hudson et al. 2023, *J. Clin. Aesthet. Dermatol.*; Bae et al. 2023, *J. Cosmet. Dermatol.*

SECTION 6 · THE LYSIS-RELEASE PROBLEM

Why killing isn't enough

Killing bacteria and dissolving a matrix are not clean events — they liberate cargo. The acne biofilm matrix is an inventory of immunologically active material.

MATRIX CARGO, AND THE TREATMENT-DESIGN QUESTION IT RAISES

- Polysaccharides 63%
- Proteins ~10%
- eDNA ~4% (DAMP)
- Porphyrins, hydrolases ~24%

TWO TREATMENT PATHS

Kill & abandon
Lysate left in place may sustain inflammation

Disperse & remove
Theoretically preferable — but untested in acne

THE CRITICAL EVIDENCE GAP

No acne study has compared lysate-left-in-place versus rinsed away.

The lysis-release concern is biologically credible — grounded in matrix composition and bactericidal-lysis principles — but it remains a hypothesis. Indirect evidence cuts both ways: a leave-on biofilm-disrupting cream improved, not worsened, outcomes. The defensible position is to treat *disperse-and-remove* as theoretically preferable to *kill-and-abandon*, and to call for the head-to-head trial, with cytokine readouts, that would settle it.

Sources: Gannesen et al. 2019, *Front. Microbiol.*; Coenye et al. 2021, *Biofilm*; Nau & Eiffert 2002, *Clin. Microbiol. Rev.*

THE BOTTOM LINE

Defeat the fortress, not the census

FOUR THINGS TO REMEMBER

01 **The unit is the biofilm**
Biofilm-derived *C. acnes* triggers the inflammatory cascade; planktonic cells do not.

02 **Quality over quantity**
Biofilm burden and IA1 dominance — not total count — track with inflammation.

03 **Tolerance is structural**
Matrix and PNAG confer tolerance distinct from genetic resistance — reversible by disruption.

04 **How you kill matters**
Lysis-and-leave may sustain inflammation — a credible, still-untested hypothesis.

> ***"The therapeutic question is no longer how many bacteria to kill, but how to dismantle the fortress — cleanly."***
>
> ArrowBiome Knowledge Hub · Acne Science Series · Chapter 4

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KNOWLEDGE HUB · ACNE SCIENCE SERIES — CHAPTER 4

The Biofilm–Inflammation Connection

A public science explainer for a technically literate reader. Grounded in a synthesis of peer-reviewed literature (2015–2026) on *C. acnes* biofilm and the inflammatory cascade of acne. Free to read and share.

SELECTED REFERENCES

Coenye et al. The role of biofilm formation in *C. acnes*. *Biofilm* 2021;4.

Mayslich et al. *C. acnes* as an opportunistic pathogen. *Microorganisms* 2021;9.

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