Review

Role of *Cutibacterium acnes* in the Aetiopathogenesis of Sarcoidosis: Current Insights and Future Study Directions

Angela Maria Di Francesco , Giuliana Pasciuto , Elena Verrecchia , Ludovico Luca Sicignano , Laura Gerardino , Donato Rigante , Raffaele Manna *

Posted Date: 25 June 2025

doi: 10.20944/preprints202506.2059.v1

Keywords: *Cutibacterium acnes*; sarcoidosis; granulomatous inflammation; innovative biotechnologies; personalized medicine

 doi:10.20944/preprints202506.2059.v1

Review

Role of *Cutibacterium acnes* in the Aetiopathogenesis of Sarcoidosis: Current Insights and Future Study Directions

Angela Maria Di Francesco [1], Giuliana Pasciuto [2], Elena Verrecchia [3], Ludovico Luca Sicignano [3], Laura Gerardino [3], Donato Rigante [4,5] and Raffaele Manna [1,5,*]

[1] Periodic Fever and Rare Diseases Research Centre, Catholic University of Sacred Heart, Rome (Italy)
[2] Complex Pneumology Operational Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3] Department of Aging, Orthopaedic and Rheumatological Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[4] Department of Life Sciences and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[5] Catholic University of Sacred Heart, Rome (Italy)
* Correspondence: raffaele.manna@unicatt.it; Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli, 8 - 00168 Rome, Italy; Tel.+39 06 30155173

Abstract

Cutibacterium acnes (*C. acnes*) is a commensal bacterium of the skin microbiota which can transform itself into a pathogen depending on the peculiar susceptibility and permissivity of the host: *C. acnes* is the sole microorganism so far to be found in the specific organ lesions of sarcoidosis, and *C. acnes*-induced activation of T helper type 1 (Th1) immune responses is generally higher in patients with sarcoidosis than in healthy individuals. This bacterium acts as an opportunistic agent in several inflammatory conditions other than sarcoidosis, such as prostate cancer (PCa) and prosthetic joint infections. Both innate and adaptive immunity appear involved in the pathogenesis of *C. acnes*-mediated sarcoid lesions and a key-role is played by host toll-like receptors (TLR)-2, -4, and -6, NOD-like receptors (NLR), and monocytes/macrophages cytoplasmic receptors. This review aims at summarizing the updated knowledge about the potential cause-effect relationship existing between *C. acnes* and sarcoidosis, addressing issues of future research directions and novel therapeutic strategies in the management of a complex disease as sarcoidosis.

Keywords: *Cutibacterium acnes*; sarcoidosis; granulomatous inflammation; innovative biotechnologies; personalized medicine

1. Introduction

Sarcoidosis is a complex systemic disease characterized by the formation of granulomas in various organs, predominantly affecting the lungs, lymph nodes, skin, eyes, central nervous system and heart: it remains an insidious disease, since etiology is not fully elucidated yet and because the standard corticosteroid therapy may cause severe collateral effects [1]. The immune system is engaged in the *incipit* of an inflammatory response to different environmental triggers, leading to the formation of granulomas as sarcoidosis histologic hallmark; therefore, understanding its pathogenesis remains an important task to achieve in order to explore alternative therapeutic strategies [1].

Specifically, this minireview deals with the relationship between *Cutibacterium acnes* (*C. acnes*) and sarcoidosis: the medical literature has been screened with the keywords "*C. acnes*", "sarcoidosis",

 doi:10.20944/preprints202506.2059.v1

"pathogenesis of sarcoidosis", and the most significant papers have been selected as the main sources to highlight and review the updated know-how on this topic.

The aim is to summarize the present knowledge about the potential cause-effect relationship existing between *C. acnes* and sarcoidosis, clarifying the role of specific molecular patterns of *C. acnes* able to activate immunological pathways relevant in the pathogenesis of sarcoidosis. That will allow the future research and novel therapeutic strategies in the management of a complex disease as sarcoidosis.

2. *Cutibacterium acnes*: Commensal Bacterium and Opportunistic Pathogen

The genus *Cutibacterium* is a cutaneous group of microorganisms previously designated as *Propionibacterium*, which has been reclassified into four genera [2], and is a Gram-positive bacterium considered as commensal, representing the major component of microbiota in human skin and eyes, though also well-represented in the anaerobic component of both intestinal tract and human gingival plaques (Table 1).

Table 1. Some of the major identity characteristics of the microorganism *Cutibacterium acnes* [3].

Cutibacterium acnes
Aerotolerant anaerobe
Non-Spore Forming
Gram-positive
Rod bacterium, diphtheroid or coryneform (slightly curved, 0.4 - 0.7 μm width and 3 - 5 μm length) [4]
Cell wall consists of phosphatidylinositol, triacylglycerol, other lipids and peptidoglycan with L-acid L-diaminopelic acid and D-alanine in the peptide chain
It expresses the following proteins (oxidative phosphorylation apparatus): NAPDH dehydrogenase/complex I, cytochrome c reductase, cytochrome c oxidase, and FoF1-type ATP synthase
Indigenous to skin and mucosal surfaces: it predominantly resides in the pilosebaceous follicle of the skin, but normally resides also in the oral cavity, conjunctiva, external ear canal, and gut
Slow growing (5-to-7 days with a division time of about five hours) [5]
The genus comprises five species (*Cutibacterium acnes*, *Cutibacterium avidum*, *Cutibacterium granulosum*, *Cutibacterium namnetense*, and *Cutibacterium modestum* [2].

In particular, *C. acnes* is an ubiquitous Gram-positive anaerobe slow-growing microorganism present in the sebaceous sites (on the face, back, and pre-thoracic region), with individual-specific rather than site-specific distribution [6]. *C. acnes* is usually considered a commensal, i.e. a member of the skin microbiota, established through adaptive immune tolerance mechanisms put in action since the early neonatal period [7]. Epidermis has a complex structure with many functions, such as to protect and defend the body from external hazards by acting as a physical and immunological barrier modulating the microbiota [8]. The healthy skin harbors microorganisms from multiple kingdoms: bacteria, fungi, and viruses; in particular *Cutibacterium* biofilm formation is significantly enhanced in the presence of staphylococcal strains, enabling robust growth under both anaerobic and aerobic conditions [9].

C. acnes strains can be divided into the major types IA, IB, II, and III, according to sequence comparison of the *recA* or *tly* genes [10]. More recently, further discrimination has been provided by various multilocus sequence typing (MLST) schemes and repetitive-sequence-based PCR protocols [11–14]. *C. acnes* subtype I, more specifically termed I-1a, is predominantly associated with moderate-to-severe acne [12,13]. In contrast, *C. acnes* type II is reported as the most prevalent type by previous studies of prostatic specimens from patients with prostate cancer (PCa) [15]. *C. acnes* is believed to play a remarkable role in maintaining skin health via occupation of ecological niches that could be colonised by more pathogenic microbes; it produces short chain fatty acids, thiopeptides,

 doi:10.20944/preprints202506.2059.v1

bacteriocins, and other molecules with inhibitory properties against such organisms [16]. Moreover, it plays a role in the balance between healthy and inflamed skin (as in the case of acne disease), acting also as an opportunistic pathogen in other various inflammatory conditions, including sarcoidosis, PCa and prosthetic joint infections (Figure 1).

There is evidence of certain disease-associated phylotypes of the bacterium persisting on body implants and causing postoperative inflammation such as endocarditis, endophthalmitis and intravascular nervous system infections [17]. Tissue invasion and deposition of *C. acnes* have also been reported in glandular epithelial cells and circulating macrophages contributing to benign prostate hyperplasia [18]. Moreover, the prevalence of the phylotypes IA-1 over the others, rather than a change in the abundance of *C. acnes*, is responsible for the development of acne [19,20].

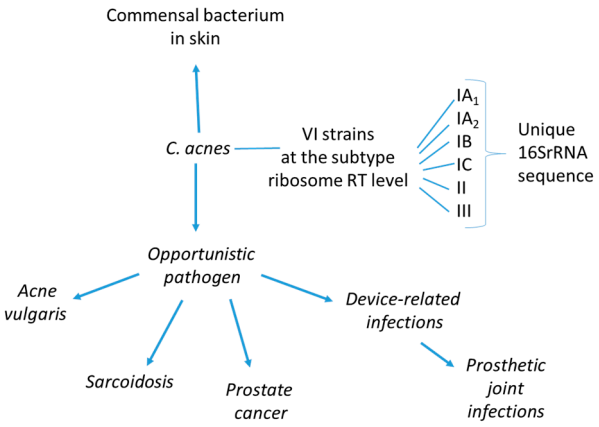

Figure 1. *Cutibacterium acnes* is considered an opportunistic microorganism, with the potential to switch from being a commensal to a pathogen causing different diseases. The *C. acnes* different phylotypes recognised by MALDI-MS prototyping [21] are shown.

However, beyond the evidence that analysis of these infections has shown an involvement of different phylotypes of the bacterium, it remains important to ascertain whether the isolation of *C. acnes* strains in different tissues should be considered as a true infection or a contamination [3]. To date, it is not clear which are the underlying mechanisms set in motion by *C. acnes* strains to result in infection, inflammation and/or localization in distant parts of the body. However, it is known that bacteria-infected cells secrete pro-inflammatory cytokines and chemokines and also anti-microbial factors, all playing a role in the delicate balance between functional and dysfunctional (disease) conditions [22].

2.1. Molecular Markers of Cutibacterium acnes

C. acnes strains show both high- and low-inflammatory potential, but the individual colonization by a microorganism sequence does not predict the host susceptibility to the disease [23]. It is largely accepted that almost all *C. acnes* subspecies and phylotypes share a similar invasiveness ability [24]. Several molecular markers exist, which can lead to *C. acnes* identification, typing and different pathogenic roles in many clinical conditions. For instance, lipidomic analysis helped identifying specific lipid markers of *C. acnes* species such as phosphatidylcholine (PC) 30:0, sphingomyelins (SM) 33:1 and 35:1, derived phosphatidylglycerol (PG) with an alkyl ether substituent PG O-32, and cardiolipins/fatty acid amides, specific of different phylotypes with potential diagnostic value [23,25].

Indeed, each *C. acnes* type (IA1, IB, II, and III) exhibits pathogenic or commensal potential. Type I strains abundantly produce lipases, proteinases, and hyaluronidases, and type IA1 has previously been isolated from acne-prone skin; hence, it is considered a particularly virulent and prevalent strain in conditions such as acne vulgaris [26]. Analyzing the lipidome of each *C. acnes* strain, individual lipid compounds are considered markers for a given phylotype; i.e. *C. acnes* DSM 16379 (type IB), has

 doi:10.20944/preprints202506.2059.v1

a significant amount of PC 30:0. In addition to their obvious structural role, these PCs presumably play an active role in virulence determination, confirming the pathogenic potential of type I strains [27]. Type II and III *C. acnes* are considered to represent "healthy skin" microbiota species [28]. While some bacterial strains are capable of producing sphingolipids, they can also acquire them from a mammalian host: the acquired sphingolipids can then be modified by bacterial enzymes to produce new sphingolipids, which help to conceal microorganisms from the host immune system [29]. Particularly noteworthy is sphingomyelin SM 35:1, whose distinct amounts are observed only in *C. acnes* strains PCM 2334 and DSM 13655, which are type II and III, respectively. This finding supports the hypothesis that the acquisition and modification of host sphingolipids may lead to commensalism or hostile interactions (tissue damage/disease) [29].

C. acnes produces two variants of hyaluronate lyase (HYL). The HYL-IB/II variant has a high level of activity and can completely degrade the hyaluronic acid (HA) present in type IB and II strains; the HYL-IA variant has a lower level of activity and can only partially degrade the HA present only in type IA strains [30]. This difference in expression between *C. acnes* strains may account for differences in tissue invasion capability between phylotypes. Indeed, type AI strains are found mostly on the surface of the skin in inflammatory acne, whereas type IB/II strains are more frequently associated with deep soft tissue infections [31]. HYL is considered to act as a virulence factor by facilitating the bacterial invasion of tissues and degrading the compounds of the upper layers of skin and its extracellular matrix, thereby promoting the spread of inflammation. In addition, the products of HA degradation by HYL may be used as nutrients by the bacterium, but may also variably contribute to inflammation [32,33].

T helper type 1 (Th1) immune responses to catalase (KAT) *C. acnes* were measured by interferon (IFN)-γ assay in peripheral blood mononuclear cells from 12 sarcoidosis patients, 13 other pneumonitis patients, and 11 healthy volunteers; the KAT protein provoked a significantly higher response in sarcoidosis patients [34].

The *C. acnes*-related inflammation produces matrix metalloproteinase (MMP) activation, contributing to tissue remodeling; other markers are adhesion factors and pore forming toxins, CMP1 to CMP5 [35], lipase-mediated free fatty acids and coproporphyrin III. The latter one contributes to the perifollicular inflammatory reaction by stimulating the expression of pro-inflammatory molecules, such as CXCL8/IL-8 and prostaglandin PGE2 [4] of keratinocytes, inducing the aggregation of *Staphylococcus aureus* and formation of biofilms in the nose [4].

2.2. Innate and Acquired Immunity in the Pathogenicity of Cutibacterium acnes

The causal relationship between dysfunctional microbiome and disease states requires a careful analysis taking into account bacterial strain heterogeneity, host genetics as well as host's environments. Many factors contribute to the development of *C. acnes* infection, first of all the role played by host immunity. As commensal, *C. acnes* stays latent in the body until a mixture and overlapping of triggering insults activate it towards the switching to be pathogenic. In this process, *C. acnes* can elicit many different responses from the host: after the initial recognition process of the bacterium danger- or pathogen-associated molecular patterns (D/PAMP) by the host patterns recognition receptors (PRR), a cascade of chemokines is produced by innate immune response followed by the host modulation of adaptive immune response. *C. acnes* final effects on the host are the complex result of a fine balance between evasion and stimulation mechanisms. *C. acnes* also represents a priming agent enhancing the efficacy of the host anti pathogenic response [36]. The first step in the switching process from commensal into pathogenic implies the recognition process by the host. *C. acnes* has many arrows to its bow for being recognized by the host as a prostimulatory agent by its cell-wall components (peptidoglycan, lipoteichoic acid, muramyl dipeptide, etc) or through metabolite production such as porphyrins [37] and antimicrobial peptides (AMP)[38]. (Figure 2). The recognition of *C. acnes* PAMPs is mediated by host toll-like receptors (TLR) (TLR-2, -4, -6, and the intracellular TLR-9, [35,39]), NOD-like receptors (NLR), and monocytes/macrophages cytoplasmic

 doi:10.20944/preprints202506.2059.v1

receptors. NLR can be also activated via reactive-oxygen species (ROS) released by *C. acnes*-stimulated cellular stress, as shown in *C. acnes*-mediated skin inflammation [40].

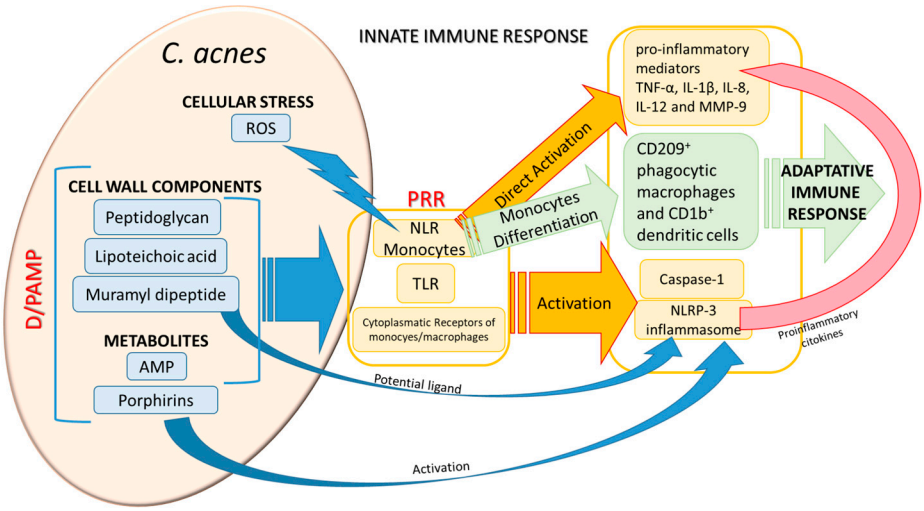

Figure 2. Major host recognition processes of *Cutibacterium acnes* and its principal innate immunity-mediated responses. Reactive-oxygen species can activate NLR of monocytes, whereas muramyl dipeptide and porphyrins act directly on the NLRP3 inflammasome. D/PAMP (danger- or pathogen-associated molecular patterns); PRR (patterns recognition receptors); NLR (NOD-like receptors); TLR (toll-like receptors); ROS (reactive-oxygen species); AMP (antimicrobial peptides); Tumor Necrosis Factor (TNF).

The PRR-mediated response results in NLRP3 inflammasome, caspase-1 activation and finally in adaptive immune response. Inflammasome can be also directly activated by either muramyl dipeptide [41] or porphyrins [37], potentiating the *C. acne*s recognition process by the host. PRR activation elicits different signaling pathways leading to the production of pro-inflammatory mediators; activation of TLR of monocytes produces Tumor Necrosis Factor (TNF), IL-1β, IL-8, IL-12 and MMP-9 [42] and a further differentiation of these monocytes into different subsets which in turn trigger the immune adaptive response [43]. Cytokine production stimulation by keratinocytes was mediated either by viable bacteria [44] or by *C. acnes* extracellular vesicles [45].

C. acnes can also evade the host response engaged to eliminate the pathogen attack, such as granuloma formation, extracellular traps, phagocytosis, autophagy and pyroptosis, although little is known about the evasion mechanisms set in motion by the bacterium [46].

2.3. Association of Cutibacterium acnes with Sarcoidosis

In a Japanese study the isolation frequency of *C. acnes* was 78% in a group of 40 sarcoidosis cases, and it increased to 92% when using high osmolarity culture media [47,48], and almost all *C. acnes* cultures from patients with active sarcoidosis were successful. Compared with sarcoidosis patients, the isolation frequency of *C. acnes* in biopsied lymph nodes from control patients without sarcoidosis was significantly lower (25% of 150 cases), and fewer isolated colonies were obtained.

In the bronchoalveolar (BAL) lavage the *C. acnes* can be found in approximately 70% of patients with sarcoidosis, being associated with disease activity, though it can also be found in 23% of controls [49,50]. Moreover, the immunohistochemistry approach has been used to detect *C. acnes* within the granuloma formation [51] by commercially available *P. acnes*-specific monoclonal antibody (PAB antibody). Formalin-fixed paraffin-embedded tissue samples from 94 sarcoidosis patients and 30 control patients with other granulomatous diseases were examined by the original manual IHC method: *C. acnes* was detected in sarcoid granulomas of samples obtained by transbronchial lung biopsy (64%), video-associated thoracic surgery (67%), endobronchial-ultrasound-guided transbronchial-needle aspiration (32%), lymph node biopsy (80%), and skin biopsy (80%) from sarcoidosis patients, but not in any non-sarcoid granulomas of samples obtained from control

 doi:10.20944/preprints202506.2059.v1

subjects (with other granulomatous diseases). *C. acnes* signals were observed more frequently in immature granulomas compared to mature granulomas [52], suggesting that *C. acnes* may be degraded and abolished during maturation of the granuloma. Therefore, sarcoidosis should be suspected when *C. acnes* is detected in granulomas, but sarcoidosis cannot be ruled out when *C. acnes* is not detected in granulomas.

Nowadays, molecular methods (Sanger sequencing of the 16S rRNA gene) in the mediastinal lymph node of patients with sarcoidosis have shown the presence of strains of *Streptococcus gordonii* (52 of 71 clones) and *C. acnes* (19 of 71 clones) [53]. Microorganisms usually trigger the sarcoid reaction either because they act as antigens producing the immunological response, or by representing a non-degradable product [54] (Figure 3).

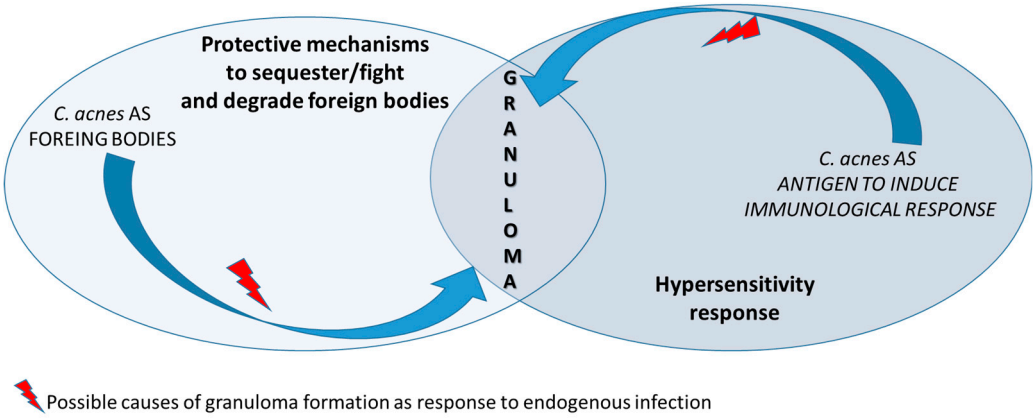

Figure 3. Granuloma represents a response to infectious microorganisms such as *Cutibacterium acnes* through the overlapping of different responses. Sarcoid granulomas raise as a protective mechanism to contrast the spread of the infectious agent at sites of proliferating activated bacteria. In patients with hypersensitive immune responses to the antigen presented by *Cutibacterium acnes*, granuloma represents the expression of the innate immunity response of the organism.

3. Sarcoidosis

Sarcoidosis is an intriguing disease studied for decades and whose exact aetiology remains elusive [55]. It would be useful to consider sarcoidosis as a syndrome comprising multiple genetic predisposing factors and many types of triggers. Recent hypotheses converge on the idea that different environmental triggers (infectious, occupational, etc) may induce a dysregulated inflammatory response in a genetically predisposed individual [25,56,57].

3.1. Genetics

The heritability of sarcoidosis may vary according to ethnicity. About 20% of African Americans with sarcoidosis have a family member with this condition, whereas for European Americans it is about 5%; additionally, in African Americans, who seem to experience a more severe and chronic disease, siblings and parents of sarcoidosis cases have about a 2.5-fold increased risk for developing the disease [58]. In Swedish individuals heritability was found to be 39% [59]. In this group, if a first-degree member was affected, a person has a four-fold greater risk of becoming affected [59].

Investigations of a genetic susceptibility yielded many candidate genes, but only few were confirmed by further investigations and no reliable genetic markers are currently known. The most interesting candidate gene is *BTNL2*, [60] coding for Butyrophilins which inhibit T cell activation and act as negative costimulatory molecules in several conditions such as sarcoidosis, autoimmune diseases, and cancer. Several HLA-DR risk alleles are also being investigated. In persistent sarcoidosis, the HLA haplotype HLA-B7-DR15 is associated with the disease, either directly cooperating in disease development or via another gene between the two loci. In nonpersistent disease, a strong genetic association exists with HLA DR3-DQ2 [61]. Cardiac sarcoidosis (CS) has

 doi:10.20944/preprints202506.2059.v1

been connected to TNF variants, particularly in the promoter region of the TNFA, increasing susceptibility to and the severity of CS. Specifically, certain haplotypes including the A allele at position -308 and the T allele at position -857 have been found to be more prevalent in patients with CS [62]. There is an individual predisposition to develop *C. acnes* infection following a genetic pathway involving genes coding for innate immunity e.g. TLR2 and 4, MAPK, NF-kB, IL-1, IL-6, and IL-8, TNF, and granulocyte-macrophage colony-stimulating factor (GM-CSF) from keratinocytes, and other inflammatory signalling pathways in the host [22,63]. As NF-κB-dependent response to *C. acnes*, toll-like receptor 2 (TLR2) was shown to represent a critical receptor mediating the selective activation of innate immunity genes [35]. Therefore, the susceptibility of the host to the latent infection of the bacterium plays an important role in deciding the final fate of the infectious process.

3.2. Sarcoidosis: Immune Pathways

The hypothetical infectious triggers do not make sarcoidosis a simple infectious disease. Among the different microorganisms investigated, the only one that received confirmation was *C. acnes*, which has been isolated from sarcoid lesions by bacterial culture [47].

Invasive *C. acnes* can act as bacterial ligands to cause aberrant NOD receptor activation in certain individuals with long-lasting susceptibility to sarcoidosis [64,65]. NOD1 and NOD2 are intracellular pattern recognition receptors that can sense bacterial molecules such as peptidoglycan moieties [66–68]. *C. acnes*-mediated aberrant NF-κB activation may induce granuloma formation in a NOD1/NOD2-dependent manner [22].

In recent years, evidence has suggested a role of T helper 17 (Th17) cells in sarcoidosis. Researchers have found that IL-17A-expressing CD4+ T lymphocytes or IL-17A+IFN-γ+ memory T cells and RORγt, a nuclear receptor crucial for the differentiation of Th17 cells, are increased in both BAL and peripheral blood of patients with sarcoidosis [69,70]. IL-17A+ cells are also suggested to be persistently present in patients with sarcoidosis relapses [71](Figure 4).

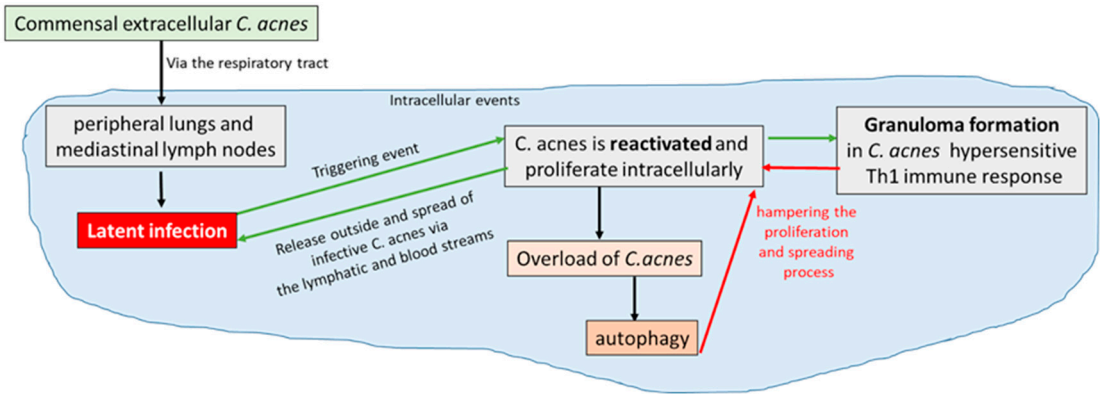

Figure 4. Proposed pathogenesis of sarcoidosis from a *Cutibacterium acnes* infection: intracellular events from latent infection to reactivation of the bacterium towards the formation of granuloma. Green arrows show pro-proliferation events, promoting spread of active infection around the body; red arrows show the potential mechanisms of *Cutibacterium acnes* containment and fighting that, in the absence of evasion mechanisms, can lead to infection resolution [54].

In the model of IL-17A-knockout C57BL/6 mice, the heat-killed *C. acnes* is able to induce sarcoidosis-like granulomas and pulmonary fibrosis. Wild-type mice with granulomatosis were treated with anti-IL-17A antibody and the administration of *C. acnes* enhanced the expression of IL-17A, granulomatosis and fibrosis in mouse lungs after boost stimulation. Neither granuloma, nor fibrosis were observed in IL-17A-knockout mice, even in the presence of IFN-γ enhancement. Neutralizing IL-17A antibody reduced inflammatory cells in BAL fluid and ameliorated both granulomatosis and fibrosis in sarcoidosis mice. Then, IL-17A plays a critical role in *C. acnes*-induced

 doi:10.20944/preprints202506.2059.v1

sarcoidosis-like inflammation in both granulomatosis inflammation and disease progression to pulmonary fibrosis [72].

Immunologic mediated Th1 response produces non-necrotizing granulomas which can localize anywhere in the body, making sarcoidosis a systemic disease [1]. The term "*C. acnes*-associated sarcoidosis" is applied to cases in which *C. acnes* is detected in granulomas via immunohistochemistry using the anti-*Propionibacterium acnes* monoclonal antibody (PAB antibody). This antibody reacts with a species-specific lipoteichoic acid (LTA) of *C. acnes* in sarcoid granulomas and it has been developed by mice immunization with the whole bacterial lysate followed by immunohistochemical screening of *C. acnes*-specific antibody-producing hybridoma clones using FFPE sarcoid lymph nodes [52]. PAB-antibody-positive Hamazaki-Wesenberg (HW) bodies (hypothesised to be cell-wall deficient forms of *C. acnes*) were detected by these *C. acnes*-specific antibodies which are mainly located in sinus macrophages of the lymph nodes; although they are not specific for sarcoid subjects, they are detected at a higher frequency in sarcoid *versus* non-sarcoid lesions (50% of 119 subjects *versus* 15% of 165 cases, respectively [52]. Furthermore, the sarcoid specimen were shown to contain *C. acnes* DNA in different studies [73,74] and even in lymph node samples from European subjects in an international study [67], supporting the hypothesis of a causative connection between the two conditions. Overall, sarcoidosis can be considered an endogenous hypersensitivity infection, which develop only after the following three factors are established: 1) a latent infection by *C. acnes*; 2) a reactivation of latent *C. acnes* triggered by environmental factors; 3) a hypersensitive Th1 immune response against the intracellular *C. acnes* as host factors.

The *C. acnes* is the sole microorganism ever isolated from sarcoid lesions and activation of Th1 immune responses by *C. acnes* is generally higher in sarcoidosis patients than in healthy individuals [34,75]. Some sarcoidosis subjects have increased amounts of *C. acnes*-derived circulating immune complexes, which suggest proliferation of this bacterium in multiple affected organs [76] (Figure 3). Indeed, current trials in subjects with cardiac sarcoidosis are evaluating combined treatment with corticosteroids and antimicrobials during active disease with continued antimicrobial therapy while tapering off steroids after the disease subsides [77].

3.3. Aetiopathogenesis of Sarcoidosis: Which Role for Cutibacterium acnes?

C. acnes can be assumed to be one potential trigger of sarcoidosis. The pathogenesis of the process implies a first passage from being extracellular commensal to an intracellular latent infectious agent in peripheral lungs and mediastinal lymph nodes [54]. The *in vitro* model of persistence of *C. acnes* in human blood cell phagocytes in a cellular and physiological environment can mimic the *in vivo* situation [78] in order to investigate the cellular processes during granuloma formation. In particular, the *C. acnes* strain isolated from prosthetic joint infection (PJI) induced a higher recruitment of CD8+ lymphocytes inside the granuloma. In patients suffering from *C. acnes* PJI, these lymphocytes, through their cytotoxic activity, may cause tissue damage leading to osteoclast activation and thereafter aseptic loosening of the prosthesis [79], frequently observed during chronic and low-grade infections due to *C. acnes* [80]. In contrast, in acne-related sarcoidosis, a high recruitment of CD4+ lymphocytes is in accordance with previous studies, demonstrating the main role played by this specific lymphocyte subset [81,82]. Interestingly, S8 *C. acnes* strain recovered from the lymph node of a sarcoidosis subject was particularly able to produce the highest number of granulomas. Moreover, the bacterial burden inside the granulomas was significantly higher with this strain. Based on its clinical origin, it has been supposed that strain S8 harbored several antigens leading to the formation of granulomatous structures [83].

Indeed, the granuloma formation can be affected by *C. acnes* catalase expression as this enzyme induces hypersensitive Th1 immune responses in sarcoidosis [34,84]. It has been reported that granuloma formation takes place only in predisposed individuals hypersensitive to *C. acnes* through a Th1 immune response. *C acnes* proliferating intracellularly can therefore be confined by the growing granuloma triggered by the bacterium and hampered by local autophagy processes, leading to a final

 doi:10.20944/preprints202506.2059.v1

resolution of the granulomatous inflammation and of the sarcoidosis process. The alternative fate occurs when *C. acnes* escapes either the granulomatous confinement or the other host defence strategies, leading to the spreading of intracellular latent infection from the respiratory tract to other organs of the body through bloodstream, where reactivation by triggering events can cause systemic sarcoidosis [54](Figure 5).

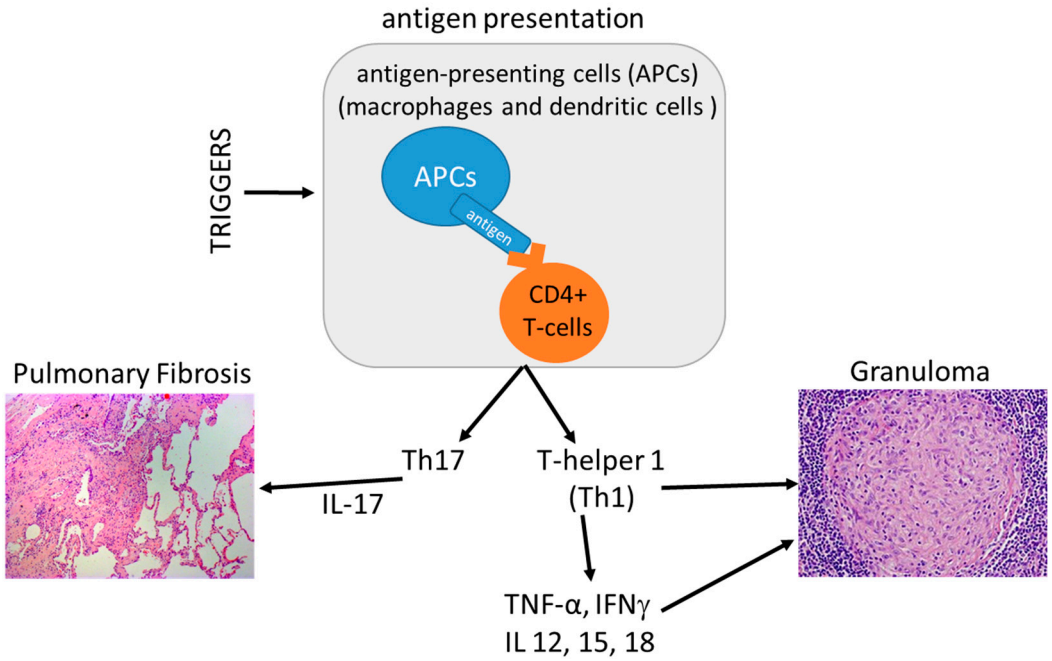

Figure 5. A synthetic schematic view of main immunopathogenesis pathways of sarcoidosis [85]. APC: antigen presenting cells; CD4+ T cell: cluster of differentiation 4 T cell; Th: helper T; INF-γ: interferon-gamma; TNF: tumor necrosis factor. .

4. Novel Therapeutic Options

C. acnes-related sarcoidosis has been treated with antimicrobial agents. There are several reports or small case-studies in which antibiotic treatment resulted in improved clinical symptoms [86,87]. When minocycline therapy was used, treatment discontinuation resulted in symptoms relapse; as tetracyclines have anti-inflammatory properties, these results have been interpreted as a consequence of an immunomodulatory effect rather than a true antimicrobial effect of the treatment [86,88]. In the same direction is the case-report of cutaneous sarcoidosis in a tattooed subject, showing improving symptoms after minocycline treatment [89]. However, the immunohistochemistry detection of *C. acnes* with PAB antibody on cutaneous sarcoidosis in a subject undergoing permanent makeup [90], opens to the hypothesis that the antimicrobial action might play an important role in treating these *C.acnes*-related sarcoidosis subjects.

The Japanese Antibacterial Drug Management for Cardiac Sarcoidosis (CS) (J-ACNES) trial showed interesting results of antimicrobial therapy *plus* corticosteroid therapy compared to corticosteroid therapy alone in CS [77]. The standard treatment of CS is lifelong corticosteroid therapy with the need to dose escalation in order to control inflammation worsening, with dose-dependent adverse effects. The use of corticosteroid sparing drugs such as methotrexate to contain adverse effects produced limited data so far [91], making the use of antimicrobial an interesting option to be evaluated in these subjects.

The rationale for the J-ACNES trial was the identification of *C. acnes* in sarcoid granulomas of myocardial tissues of CS subjects [92] suggesting an etiologic role for *C. acnes* in CS. The use of antimicrobial monotherapy was not effective against CS [93]. In the J-ACNES trial a combination of antimicrobial drugs (clarithromycin 200-400 mg/day and doxycycline hydrochloride 100-200 mg/day)

 doi:10.20944/preprints202506.2059.v1

in addition to corticosteroid therapy was used for 6 months with a good safety profile, mimicking the clinical strategy of long-lasting drugs combination successfully used in other granulomatous diseases, such as tuberculosis and leprosy [94]. The results of this trial are still under investigation and it will be interesting to evaluate them in the light of sarcoidosis pathogenesis. The PHENOSAR trial (use of antibiotics in treatment of sarcoidosis, NCT05291468) [95] was initiated in the Netherlands during 2022 but the study has passed its completion date and study status has not been updated after two years. This trial represented the first based on a targeted therapy rationale in sarcoidosis, i.e. the presence of *C. acnes* in the granulomatous tissues of sarcoidosis subjects. Two antibiotics were administered for 13-weeks, azithromycin and doxycycline, and the results were expected to be compared between placebo and treated groups; inflammation status was expected to be monitored by PET/CT-scan and serum biomarkers ACE and IL-2R. Unfortunately, nothing is known so far from this study and therefore the question whether the presence of *C. acnes* in sarcoidosis patients might represent a successful strategy awaits further investigation.

5. *Cutibacterium acnes*, Sarcoidosis and Malignant Tumours

Chintalapati et al [96] proposed that *C. acnes can be* isolated from tumors, since the host-response to the microorganism resulted in an "immunologic hub" at the infected niches responsible for anti tumoral activity. *C. acnes* has been used as immunostimulant adjuvant therapy for malignant tumors since the 70/80s; indeed, when injected as a heat- or formol-inactivated suspension, this bacterium induced immunomodulatory effects on both innate and adaptive immune responses. Its antitumoral activity has been demonstrated in murine models [97]; *C. acnes* has also been used as a priming agent to enable host cells to respond efficiently to a pathogen attack [98]. McCaskill et al. [98] established an *in vivo* model of *C. acnes*-induced pulmonary inflammation, in which mice were intraperitoneally sensitized and intratracheally challenged with heat-killed *C. acnes*. The study revealed a significant increase in leukocyte recruitment to the lung and cytokine production in comparison with both control and no sensitized but challenged mice. This anti-tumor activity appears to be strain-specific, with certain *C. acnes* types exhibiting stronger effects than others. For example, *C. acnes* type I showed a higher survival rate in mice than type II [99]. Differences in the carbohydrate composition of the cell walls of different *C. acnes* strains may contribute to their varying immunological and biological activities, potentially influencing their anti-tumor properties [100]. Some *C. acnes* strains not only inhibit tumor growth but also inhibit the spread and growth of metastasized tumor cells [101]. Moreover, clinical trials have reported the use of *C. acnes* in the treatment of various cancers (ovarian carcinoma, malignant melanoma, lung cancer, breast cancer), and the disease-free survival was shown to be significantly increased in patients who received this adjuvant therapy [102]. Additionally, a recent study showed that tumor-isolated *C. acnes* activated the immune system, and the immune cells effectively penetrated through the tumor tissue and formed an immunologic hub inside, explicitly targeting the tumor and destroying its cells [103]. The anti-tumor activity was mainly attributed to a local stimulation of lymphokine production (IL-12, IFN-γ, TNF) resulting in T cells recruitment, proliferation, and their orientation toward a Th1 profile [103,104] as well as non-specific macrophage activation [105] leading to tumor size regression.

These data are consistent with a recent investigation [106] on 287 sarcoidosis outpatients assessed between 2000 and 2024; in this retrospective study the diagnosis of cancer was recorded in 36 subjects (12.5%). The cancer preceded sarcoidosis or sarcoid-like reactions in 63.8%, and the sarcoidosis accompanying the onset of malignancy was 27.8%, whereas the cancer arising after sarcoidosis diagnosis was only 8.3%. Only 2/36 subjects with sarcoidosis and cancer showed metastasis, and one of them was affected by lymphoma. These data suggest that granulomatous inflammation due to sarcoidosis represents a protective shield, preventing the formation of metastasis through the induction of immune surveillance against cancer, while, on the other hand, it can be a risk factor for lymphomagenesis due to the persistence of a chronic active inflammatory status [106].

 doi:10.20944/preprints202506.2059.v1

6. Future Directions of the Research and Treatment

A rational approach to treatment should include precision in etiologic and microbiological investigations with the ancillary aim of avoiding infectious complications of either corticosteroids or immunosuppressors; therefore, the use of a combination of antimicrobial agents and immune regulators in *C. acnes*-related sarcoidosis subjects seems promising because of the clinical effects in limiting the use of corticosteroids. Indeed, as it is already a common practice in rheumatology to investigate the pre-existence of latent tuberculosis or persistent viral infections before steroid treatment or immunosuppression. Therefore, the coexistence or presence of *C. acnes* as a trigger for sarcoidosis should recommend a preventive treatment before steroid treatment or immunosuppression. Since the nonspecific or multidrug therapy induces development of resistant strains (as rifampicin-resistant strains in leprosy treatment) [107], according to personalized medicine, the typing of acne strains and the use of specific antibiograms should be used. This procedure has not yet become routinary, but reasonably it should be considered as a potentially fruitful clinical practice. Therefore, a combination of strategies that also take into account the etiology and pathogenesis could be the best approach to brake and restrain the granulomatous manifestations observed in subjects with sarcoidosis.

Author Contributions: Conceptualization, R.M. and A.M.D.F.; methodology, A.M.D.F.; software, A.M.D.F.; validation, A.M.D.F,; formal analysis, A.M.D.F.; investigation, G.P., E.V., L.L.S., L.G.; resources, R.M.; writing—original draft preparation, R.M. and A.M.D.F.; writing—review and editing, A.M.D.F.; visualization and supervision, D.R..; project administration, R.M.; funding acquisition, R.M.. All authors have read and agreed to the published version of the manuscript. Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work **reported**.

Funding: This research was funded by Fondazione Policlinico A. Gemelli IRCCS, grant number 5502162 and by the Research Center of Periodic Fevers of the Catholic University.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors thank prof. A. Urbani and prof. L. Richeldi for their support.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AMP	Antimicrobial peptides
APC	Antigen-presenting cell
CNS	Central nervous system
D/PAMP	Danger- or pathogen-associated molecular patterns
HA	Hyaluronic acid
HYL	Hyaluronate lyase
HW	Hamazaki-Wesenberg
INF-γ	Interferon-gamma
KAT	Catalase
LTA	Lipoteichoic acid
NLR	NOD-like receptors
PAB	P. acnes-specific monoclonal antibody
PRR	Patterns recognition receptors
PCa	Prostate cancer
PC	Phosphatidylcholine
PG	Prostaglandine

 doi:10.20944/preprints202506.2059.v1

ROS	Reactive oxygen species
SM	Sphingomyelin
TLR	Toll-like receptors
TNF	Tumor necrosis factor

References

1. Brito-Zerón, P.; Pérez-Álvarez, R.; Ramos-Casals, M. Sarcoidosis. *Med Clin* **2022**, 159, 195-204.
2. Dekio, I.; Sugiura, Y.; Hamada-Tsutsumi, S.; Murakami, Y.; Tamura, H.; Suematsu, M. What Do We See in Spectra?: Assignment of High-Intensity Peaks of Cutibacterium and Staphylococcus Spectra of MALDI-TOF Mass Spectrometry by Interspecies Comparative Proteogenomics. *Microorganisms* **2021**, 9, 1243.
3. Gajdács, M.; Spengler, G.; Urbán, E. Identification and Antimicrobial Susceptibility Testing of Anaerobic Bacteria: Rubik's Cube of Clinical Microbiology? *Antibiotics* **2017**, 6, 25.
4. Mayslich, C.; Grange, P.A.; Dupin, N. Cutibacterium acnes as an Opportunistic Pathogen: An Update of Its Virulence-Associated Factors. *Microorganisms* **2021**, 9, 303.
5. Hall, G.S.; Pratt-Rippin, K.; Meisler, D.M.; Washington, J.A.; Roussel, T.J.; Miller, D. Growth Curve for Propionibacterium acnes. *Curr Eye Res* **1994**, 13, 465–466.
6. Oh, J.; Byrd, A. L.; Deming, C.; Conlan, S.; NISC Comparative Sequencing, Program; Kong, H.H.; Segre, J.A. Biogeography and individuality shape function in the human skin metagenome. *Nature* **2014**, 514, 59–64.
7. Scharschmidt, T. C.; Vasquez, K. S.; Truong, H. A.; Gearty, S. V.; Pauli, M. L.; Nosbaum, A.; Gratz, I.K.; Otto, M.; Moon, J.J.; Liese, J.; Abbas, A.K.; Fischbach, M.A.; Rosenblum, M.D. A wave of regulatory t cells into neonatal skin mediates tolerance to commensal microbes. *Immunity* **2015**, 43, 1011–1021.
8. Borkowski, A.W.; Gallo, R.L. The Coordinated Response of the Physical and Antimicrobial Peptide Barriers of the Skin. *J Investig Dermatol* **2011**, 131, 285–287.
9. Kaplan, J.B.; Assa, M.; Mruwat, N.; Sailer, M.; Regmi, S.; Kridin, K. Facultatively Anaerobic Staphylococci Enable Anaerobic *Cutibacterium* Species to Grow and Form Biofilms Under Aerobic Conditions. *Microorganisms* **2024,** 12, 2601.
10. McDowell, A.; Valanne, S.; Ramage, G.; Tunney, M.M.; Glenn, J.V.; McLorinan, G.C.; Bhatia, A.; Maisonneuve, J.F.; Lodes, M.; Persing, D.H.; Patrick, S. Propionibacterium acnes types I and II represent phylogenetically distinct groups. *J Clin Microbiol* **2005,** 43, 326-34.
11. Davidsson, S.; Soderquist, B.; Elgh, F.; Olsson, J.; Andren, O.; Unemo, M.; Mölling, P. Multilocus sequence typing and repetitive-sequence-based PCR (DiversiLab) for molecular epidemiological characterization of Propionibacterium acnes isolates of heterogeneous origin. *Anaerobe* **2012**, 18, 392–9.
12. Lomholt, H.B.; Kilian, M. Population genetic analysis of Propionibacterium acnes identifies a subpopulation and epidemic clones associated with acne. *PLoS One* **2010**, 5, e12277.
13. McDowell, A.; Gao, A.; Barnard, E.; Fink, C.; Murray, P.I.; Dowson, C.G.; Nagy, I.; Lambert, P.A.; Patrick, S. A novel multilocus sequence typing scheme for the opportunistic pathogen Propionibacterium acnes and characterization of type I cell surface- associated antigens. *Microbiology* **2011**, 157, 1990–2003.
14. Mak, T.N.; Yu, S.H.; De Marzo, A.M.; Bruggemann, H.; Sfanos, K.S. Multilocus sequence typing (MLST) analysis of Propionibacterium acnes isolates from radical prostatectomy specimens. *Prostate* **2013**, 73, 770–7.
15. Fassi Fehri, L.; Mak, T.N.; Laube, B,; Brinkmann, V.; Ogilvie, L.A.; Mollenkopf, H.; Lein, M.; Schmidt, T.; Meyer, T.F.; Brüggemann, H. Prevalence of Propionibacterium acnes in diseased prostates and its inflammatory and transforming activity on prostate epithelial cells. *Int J Med Microbiol* **2011**, 301, 69–7.
16. Shu, M.; Wang, Y.; Yu, J.; Kuo, S.; Coda, A.; Jiang, Y.; Gallo, R.L.; Huang, C.M. Fermentation of Propionibacterium acnes, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant Staphylococcus aureus. *PLoS One* **2013**, 8, e55380.
17. Portillo, M. E.; Corvec, S.; Borens, O.; Trampuz, A. Propionibacterium acnes: an underestimated pathogen in implant-associated infections. *Biomed Res Int* **2013**, 804391.

 doi:10.20944/preprints202506.2059.v1

18. Davidsson, S.; Molling, P.; Rider, J.R.; Unemo, M.; Karlsson, M.G.; Carlsson, J.; Andersson, S.O.; Elgh, F.; Söderquis, B.; Andrén, O. Frequency and typing of Propionibacterium acnes in prostate tissue obtained from men with and without prostate cancer. *Infect Agent Cancer* **2016**, 11, 26.
19. Dréno, B.; Pécastaings, S.; Corvec, S.; Veraldi, S.; Khammari, A.; Roques, C. Cutibacterium acnes (Propionibacterium acnes) and Acne Vulgaris: A Brief Look at the Latest Updates. *J Eur Acad Dermatol Venereol* **2018**, 32, 5–14.
20. Renz, N.; Mudrovcic, S.; Perka, C.;Trampuz, A. Orthopedic Implant-Associated Infections Caused by Cutibacterium spp.—A Remaining Diagnostic Challenge. *PLoS ONE* **2018**, 13, e0202639.
21. Teramoto, K.; Okubo, T.; Yamada, Y.; Sekiya, S.; Iwamoto, S.; Tanaka, K. Classification of Cutibacterium acnes at phylotype level by MALDI-MS proteotyping. *Proc Jpn Acad Ser B Phys Biol Sci* **2019**, 95: 612-623.
22. Leheste, J.R.; Ruvolo, K.E.; Chrostowski, J.E.; Rivera, K.; Husko, C.; Miceli, A.; Selig, M.K.; Brüggemann, H.; Torres G. P. acnes-driven disease pathology: current knowledge and future directions. *Front Cell Infect Microbiol* **2017**, 7, 81.
23. Chudzik, A.; Bromke, M.A.; Gamian, A.; Paściak, M. Comprehensive lipidomic analysis of the genus *Cutibacterium*. mSphere. **2024**, 9:e0005424
24. Both, A.; Huang, J.; Hentschke, M.; Tobys, D.; Christner, M.; Klatte, T.O.; Seifert, H.; Aepfelbacher, M.; Rohde, H. Genomics of Invasive Cutibacterium acnes Isolates from Deep-Seated Infections. *Microbiol Spectr* **2023**, 11, e0474022.
25. Petersson, F.; Kilsgård, O.; Shannon, O.; Lood, R. Platelet activation and aggregation by the opportunistic pathogen Cutibacterium (Propionibacterium) acnes. ***PLoS One*** **2018**, 13, e0192051.
26. McDowell, A.; Perry, A.L.; Lambert, P.A.; Patrick, S. A new phylogenetic group of Propionibacterium acnes. *J Med Microbiol* **2008**, 57, 218-224.
27. Geiger, O.; López-Lara, I.M; Sohlenkamp, C. Phosphatidylcholine biosynthesis and function in bacteria, Biochimica et Biophysica Acta (BBA) *Molecular and Cell Biology of Lipids* **2013**, 1831, 503-513,
28. Rozas, M.; Hart de Ruijter, A.; Fabrega, M.J.; Zorgani, A.; Guell, M.; Paetzold, B.; Brillet, F. From Dysbiosis to Healthy Skin: Major Contributions of *Cutibacterium acnes* to Skin Homeostasis. *Microorganisms* **2021**, *9*, 628.
29. Heung, L.J.; Luberto, C.; Del Poeta, M. Role of Sphingolipids in Microbial Pathogenesis. *Infect Immun* **2006**, 74
30. Nazipi, S.; Stødkilde, K.; Scavenius, C.; Brüggemann, H. The Skin Bacterium *Propionibacterium acnes* Employs Two Variants of Hyaluronate Lyase with Distinct Properties. *Microorganisms* **2017**, *5*, 57.
31. McDowell, A.; Nagy, I.; Magyari, M.; Barnard, E.; Patrick S. The Opportunistic Pathogen *Propionibacterium acnes*: Insights into Typing, Human Disease, Clonal Diversification and CAMP Factor Evolution. *PLoS ONE,* **2013**, 8, e70897.
32. Marion CStewart, J.M.; Tazi, M.F.; Burnaugh, A.M.; Linke, C.M.; Woodiga, S.A.; King, S.J. Streptococcus pneumoniae Can Utilize Multiple Sources of Hyaluronic Acid for Growth. *Infect Immun* **2012**, 80, 1390-8.
33. Schommer, N.N.; Muto, J.; Nizet, V.; Gallo, R.L. Hyaluronan Breakdown Contributes to Immune Defense against Group A Streptococcus. *Journal of Biological Chemistry* **2014**, 289, 26914-26921.
34. Yorozu, P.; Furukawa, A.; Uchida, K.; Akashi, T.; Kakegawa,T.; Ogawa, T.; Minami, J.; Suzuki, Y.; Awano, N.; Furusawa, H.; Miyazaki, Y.; Inase,N.; Eishi,Y. Propionibacterium acnes catalase induces increased Th1 immune response in sarcoidosis patients. *Respir Investig* **2015,** 3, 161-9.
35. Mayslich, C.; Grange, P.A.; Castela, M.; Marcelin, A.G.; Calvez, V.; Dupin, N. Characterization of a *Cutibacterium acnes* Camp Factor 1-Related Peptide as a New TLR-2 Modulator in In Vitro and Ex Vivo Models of Inflammation. *Int J Mol Sci* **2022**, 23, 5065.
36. McCaskill, J.G.; Chason, K.D.; Hua, X.; Neuringer, I.P.; Ghio, A.J.; Funkhouser, W.K.; Tilley, S.L. Pulmonary immune responses to propionibacterium acnes in C57bl/6 and BALB/ c mice. *Am J Respir Cell Mol Biol* **2006**, 35, 347–56.
37. Spittaels, K-J.; Van Uytfanghe, K.; Zouboulis, C.C.; Stove, C.; Crabb´e, A.; Coenye, T. Porphyrins produced by acneic Cutibacterium acnes strains activate the inflammasome by inducing K+ leakage. *iScience* **2021**, 24, 102575.

 doi:10.20944/preprints202506.2059.v1

38. Chronnell, C.M.; Ghali, L.R.; Ali, R.S.; Quinn, A.G.; Holland, D.B.; Bull, J.J.; Cunliffe, W.J.; McKay, I.A.; Philpott, M.P.; Müller-Röver, S. Human beta defensin-1 and -2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. *J Invest Dermatol* **2001**, 117, 1120–5.
39. Kalis, C.; Gumenscheimer, M.; Freudenberg, N.; Tchaptchet, S.; Fejer, G.; Heit, A.; Akira, S.; Galanos, C. Freudenberg MA.Requirement for TLR9 in the immunomodulatory activity of Propionibacterium acnes. *J Immunol* **2005**, 174, 4295–300.
40. Grange, P.A.; Chéreau, C.; Raingeaud, J.; Nicco, C.; Weill, B.; Dupin, N.; Batteux, F. Production of superoxide anions by keratinocytes initiates P. acnes-induced inflammation of the skin. *PLoS Pathog* **2009**, 5, e1000527.
41. Girvan, R.C.; Knight, D.A.; O'loughlin, C.J.; Hayman, C.M.; Hermans, I.F.; Webster, G.A. MIS416, a non-toxic microparticle adjuvant derived from Propionibacterium acnes comprising immunostimulatory muramyl dipeptide and bacterial DNA promotes cross-priming and Th1 immunity. *Vaccine* **2011**, 29, 545–57.
42. Kim, J.; Ochoa, M-T.; Krutzik, S.R.; Takeuchi, O.; Uematsu, S.; Legaspi, A.J.; Brightbill, H.D.; Holland, D.; Cunliffe, W.J.; Akira, S.; Sieling, P.A.; Godowski, P.J.; Modlin, R.L. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002, 169, 1535–41.
43. Krutzik, S.R.; Tan, B.; Li, H.; Ochoa, M.T.; Liu, P.T.; Sharfstein, S.E.; Graeber, T.G.; Sieling, P.A.; Liu, Y.J.; Rea, T.H.; Bloom, B.R.; Modlin, R.L. TLR activation triggers the rapid differentiation of monocytes into macrophages and dendritic cells. *Nat Med* **2005**, 11, 653–60.
44. Graham, G.M.; Farrar, M.D.; Cruse-Sawyer, J.E.; Holland, K.T.; Ingham, E. Proinflammatory cytokine production by human keratinocytes stimulated with Propionibacterium acnes and P. acnes GroEL. *Br J Dermatol* **2004**, 150, 421–8.
45. Choi, E-J.; Lee, H.G.; Bae, I-H.; Kim, W.; Park, J.; Lee, T.R.; Cho, E.G. Propionibacterium acnes-derived extracellular vesicles promote acne-like phenotypes in human epidermis. *J Invest Dermatol* **2018**, 138, 1371–9.
46. Thoraval L, Varin-Simon J, Ohl X, Velard F, Reffuveille F, Tang-Fichaux M. Cutibacterium acnes and its complex host interaction in prosthetic joint infection: Current insights and future directions. *Res Microbiol* **2025**, 17,104265.
47. Abe, C.; Iwai, K.; Mikami, R.; Hosoda, Y. Frequent isolation of Propionibacterium acnes from sarcoidosis lymph nodes. Zentralbl Bakteriol Mikrobiol Hyg A 1984, 256, 541-7.
48. Homma, J.Y.; Abe, C.; Chosa, H.; Ueda, K.; Saegusa, J.; Nakayama, M.; Homma, H.; Washizaki M, Okano H. Bacteriological investigation on biopsy specimens from patients with sarcoidosis. *Jpn J Exp Med* **1978**, 48, 251-5.
49. Hiramatsu, J.; Kataoka, M.; Nakata, Y.; Okazaki, K.; Tada, S.; Tanimoto, M.; Eishi, Y. Propionibacterium acnes DNA detected in bronchoalveolar lavage cells from patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* **2003**, 20, 197-203.
50. Inoue, Y.; Suga, M. Granulomatous diseases and pathogenic microorganism. Kekkaku. 2008, 83, 115-30. Japanese.
51. Isshiki, T.; Homma, S.; Eishi, Y.; Yabe, M.; Koyama, K.; Nishioka, Y.; Yamaguchi, T.; Uchida, K.; Yamamoto, K.; Ohashi, K.; Arakawa, A.; Shibuya, K.; Sakamoto, S.; Kishi, K. Immunohistochemical Detection of Propionibacterium acnes in Granulomas for Differentiating Sarcoidosis from Other Granulomatous Diseases Utilizing an Automated System with a Commercially Available PAB Antibody. *Microorganisms* **2021**, 9, 1668.
52. Negi, M.; Takemura, T.; Guzman, J.; Uchida, K.; Furukawa, A.; Suzuki, Y.; Iida, T.; Ishige, I.; Minami, J.; Yamada, T.; Kawachi, H.; Costabel, U.; Eishi, Y. Localization of propionibacterium acnes in granulomas supports a possible etiologic link between sarcoidosis and the bacterium. *Mod Pathol* **2012**, 25, 1284-97.
53. Akata, K.; Yamasaki, K.; Nemoto, K.; Ikegami, H.; Kawaguchi, T.; Noguchi, S.; Kawanami, T.; Fukuda, K.; Mukae, H.; Yatera, K. Sarcoidosis Associated with Enlarged Mediastinal Lymph Nodes with the Detection of Streptococcus gordonii and Cutibacterium acnes Using a Clone Library Method. Intern Med 2024, 63, 299-304.

 doi:10.20944/preprints202506.2059.v1

54. Eishi, Y. Potential Association of Cutibacterium Acnes with Sarcoidosis as an Endogenous Hypersensitivity Infection. *Microorganisms* **2023**, 11, 289.
55. Ungprasert, P.; Ryu, J.H.; Matteson, E.L. Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis. *Mayo Clin Proc Innov Qual Outcomes* **2019**, 3, 358-375.
56. Inaoka, P.T.; Shono, M.; Kamada, M.; Espinoza, J.L. Host-microbe interactions in the pathogenesis and clinical course of sarcoidosis. *J Biomed Sci* **2019**, 26, 45.
57. Grunewald, J.; Grutters,J.C.; Arkema, E.V.; Saketkoo, L.A.; Moller, D.R. Müller-Quernheim, J. Sarcoidosis. *Nat Rev Dis Primers* **2019**, 5, 45.
58. Rybicki, B.A.; Iannuzzi, M.C.; Frederick, M.M.; Thompson, B.W.; Rossman, M.D.; Bresnitz, E.A.; Terrin, M.L.; Moller, D.R.; Barnard, J.; Baughman, R.P.; DePalo, L.; Hunninghake, G.; Johns, C.; Judson, M.A.; Knatterud, G.L.; McLennan, G.; Newman, L.S.; Rabin, D.L.; Rose, C.; Teirstein, A.S.; Weinberger, S.E.; Yeager, H.; Cherniack, R. ACCESS Research Group. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). *Am J Respir Crit Care Med* **2001**, 164, 2085-91.
59. Rossides, M.; Grunewald, J.; Eklund, A. Familial aggregation and heritability of sarcoidosis: a Swedish nested case–control study. *Eur Respir J* **2018**, 52, 1800385.
60. Wijnen, P.A.; Voorter, C.E.; Nelemans, P.J.; Verschakelen, J.A.; Bekers, O.; Drent, M. Butyrophilin-like 2 in pulmonary sarcoidosis: a factor for susceptibility and progression? *Hum Immunol* **2011**, 72, 342-7.
61. Wolin, A.; Lahtela, E.L.; Anttila, V.; Petrek, M.; Grunewald, J.; van Moorsel, C.H.M.; Eklund, A.; Grutters, J.C.; Kolek, V.; Mrazek, F.; Kishore, A.; Padyukov, L.; Pietinalho, A.; Ronninger, M.; Seppänen, M.; Selroos, O.; Lokki, M.L. SNP Variants in Major Histocompatibility Complex Are Associated with Sarcoidosis Susceptibility-A Joint Analysis in Four European Populations. *Front Immunol* **2017**, 8, 422.
62. Jamilloux, Y.; Cohen-Aubart, F.; Chapelon-Abric, C.; Maucort-Boulch, D.; Marquet, A.; Pérard, L.; Bouillet, L.; Deroux, A.; Abad, S.; Bielefeld, P.; Bouvry, D.; André, M.; Noel, N.; Bienvenu, B.; Proux, A.; Vukusic, S.; Bodaghi, B.; Sarrot-Reynauld, F.; Iwaz, J.; Amoura, Z.; Broussolle, C.; Cacoub, P.; Saadoun, D.; Valeyre, D.; Sève, P. Groupe Sarcoïdose Francophone. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. *Semin Arthritis Rheum* **2017**, 47, 288-294.
63. Lee, Y.B.; Byun, E.J.; Kim, H.S. Potential role of the microbiome in acne: a comprehensive review. *J Clin Med* **2019**, 8, 987.
64. Inohara, N.; Nuñez, G. The NOD: a signaling module that regulates apoptosis and host defense against pathogens. *Oncogene* **2001**, 20, 6473-81.
65. Moreira, L.O.; Zamboni, D.S. NOD1 and NOD2 Signaling in Infection and Inflammation. *Front Immunol* **2012**, 3, 328.
66. Moller, D.R.; Rybicki, B.A.; Hamzeh, N.Y.; Montgomery, C.G.; Chen, E.S.; Drake, W.; Fontenot, A.P. Genetic, immunologic, and environmental basis of sarcoidosis. Ann Am Thorac Soc **2017**, 14, S429–36.
67. Eishi, Y.; Suga, M.; Ishige, I.; Kobayashi, D.; Yamada, T.; Takemura, T.; Takizawa, T.; Koike, M.; Kudoh, S.; Costabel, U.; Guzman, J.; Rizzato, G.; Gambacorta, M.; du Bois, R.; Nicholson, A.G.; Sharma, O.P.; Ando, M. Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. *J Clin Microbiol* **2002**, 40, 198–204
68. Tanabe, T.; Ishige, I.; Suzuki, Y.; Aita, Y.; Furukawa, A.; Ishige, Y.; Uchida, K.; Suzuki, T.; Takemura, T.; Ikushima, S.; Oritsu, M.; Yokoyama, T.; Fujimoto, Y.; Fukase, K.; Inohara, N.; Nunez, G.; Eishi, Y. Sarcoidosis and NOD1 variation with impaired recognition of intracellular Propionibacterium acnes. *Biochim Biophys Acta* **2006**, 1762, 794–801.
69. Ragusa F. Sarcoidosis and Th1 chemokines. *Clin Ter* **2015**, 166, e72–6.
70. Georas, S.N.; Chapman, T.J.; Crouser, E.D. Sarcoidosis and T-helper cells. Th1, Th17, or Th17.1? *Am J Respir Crit Care Med* **2016**, 193, 1198–200.
71. Liu, Y.; Qiu, L.; Wang, Y.; Aimurola, H.; Zhao, Y.; Li, S.; Xu, Z. The Circulating Treg/Th17 Cell Ratio Is Correlated with Relapse and Treatment Response in Pulmonary Sarcoidosis Patients after Corticosteroid Withdrawal. *PLoS One* **2016**,11.
72. Song, J.; Zhao, M.; Li, Q.; Lu, L.; Zhou, Y.; Zhang, Y.; Chen, T.; Tang, D.; Zhou, N.; Yin, C.; Weng, D.; Li H. IL-17A Can Promote Propionibacterium acnes-Induced Sarcoidosis-Like Granulomatosis in Mice. *Front Immunol* **2019**, 10, 1923.

 doi:10.20944/preprints202506.2059.v1

73. Ishige, I.; Usui, Y.; Takemura, T.; Eishi, Y. Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. *Lancet* **1999**, 354, 120-3.
74. Zhou, Y.; Wei, Y.R.; Zhang, Y.; Du, S.S.; Baughman, R.P.; Li, H.P. Real-time quantitative reverse transcription-polymerase chain reaction to detect propionibacterial ribosomal RNA in the lymph nodes of Chinese patients with sarcoidosis. *Clin Exp Immunol* **2015**, 181,511-7.
75. Furusawa, H.; Suzuki, Y.; Miyazaki, Y.; Inase, N.; Eishi, Y. Th1 and Th17 immune responses to viable Propionibacterium acnes in patients with sarcoidosis. *Respir Investig* **2012**, 50, 104–9.
76. Uchida, K.; Furukawa, A.; Yoneyama, A.; Furusawa, H.; Kobayashi, D.; Ito, T.; Yamamoto, K.; Sekine, M.; Miura, K.; Akashi, T.; Eishi, Y.; Ohashi, K. Propionibacterium acnes-Derived Circulating Immune Complexes in Sarcoidosis Patients. *Microorganisms* **2021**, 9, 2194.
77. Ishibashi, K.; Eishi, Y.; Tahara, N.; Asakura, M.; Sakamoto, N.; Nakamura, K.; Takaya, Y.; Nakamura, T.; Yazaki, Y.; Yamaguchi, T.; Asakura, K.; Anzai, T.; Noguchi, T.; Yasuda, S.; Terasaki, F.; Hamasaki, T.; Kusano, K. Japanese antibacterial drug management for cardiac sarcoidosis (J-ACNES): A multicenter, open-label, randomized, controlled study. *J Arrhythmia* **2018**, 34, 520–526.
78. Deknuydt,F.; Roquilly, A.; Cinotti, R.; Altare,F.; Asehnoune, K. An in vitro model of mycobacterial granuloma to investigate the immune response in brain- injured patients. *Crit. Care Med* **2013,** 41,245e254.
79. Landgraeber, S.; von Knoch, M.; Löer, F.; Brankamp. J.; Tsokos, M.; Grabellus, F.; Schmid, K.W.; Totsch, M. Association between apoptosis and CD4(+)/CD8(+) T-lymphocyte ratio in aseptic loosening after total hip replacement. *Int J Biol Sci* **2009**, 5, 182-91.
80. Portillo, M.E.; Salvadó, M.; Alier, A.; Sorli, L.; Martínez, S.; Horcajada, J.P.; Puig, L. Prosthesis failure within 2 years of implantation is highly predictive of infection. Clin *Orthop Relat Res* **2013**, 471, 3672-8.
81. Loke, W.S.; Herbert, C.; Thomas, P.S. Sarcoidosis: Immunopathogenesis and Immunological Markers. *Int J Chronic Dis* **2013**, 2013, 928601.
82. Kistowska, M.; Meier, B.; Proust, T.; Feldmeyer, L.; Cozzio, A.; Kuendig, T.; Contassot, E.; French, L.E. Propionibacterium acnes promotes Th17 and Th17/Th1 responses in acne patients. *J Invest Dermatol* **2015**, 135, 110-118.
83. Aubin, G.G.; Ada Da Silva, G.; Eishi, Y.; Jacqueline, C.; Altare, F.; Corvec, S.; Asehnoune, K. Immune discrepancies during in vitro granuloma formation in response to Cutibacterium (formerly Propionibacterium) acnes infection. *Anaerobe* **2017** Dec;48:172-176.
84. Yamamoto, K.; Uchida, K.; Furukawa, A.; Tamura, T.; Ishige, Y.; Negi, M.; Kobayashi, D.; Ito, T.; Kakegawa, T.; Hebisawa, A.; Awano, N.; Takemura, T.; Amano, T.; Akashi, T.; Eishi, Y. Catalase expression of Propionibacterium acnes may contribute to intracellular persistence of the bacterium in sinus macrophages of lymph nodes affected by sarcoidosis. *Immunol Res* **2019**, 67, 182–193.
85. Sakhamuru, S.; Kambampati, S.; Wasim, S.; Kukkar, V.; Malik, B.H. The Role of Propionibacterium acnes in the Pathogenesis of Sarcoidosis and Ulcerative Colitis: How This Connection May Inspire Novel Management of These Conditions. *Cureus* **2020** 12, e10812.
86. Miyazaki, E.; Ando, M.; Fukami, T.; Nureki, S.I.; Eishi, Y.; Kumamoto, T. Minocycline for the treatment of sarcoidosis: Is the mechanism of action immunomodulating or antimicrobial effect? *Clin Rheumatol* **2008**, 27, 1195–1197.
87. Takemori, N.; Nakamura, M.; Kojima, M.; Eishi, Y. Successful treatment in a case of Propionibacterium acnes-associated sarcoidosis with clarithromycin administration: A case report. *J Med Case Rep* **2014**, 8, 15.
88. Bachelez, H.; Senet, P.; Candranel, J.; Kaoukhov, A.; Dubertret, L. The use of tetracyclines for the treatment of sarcoidosis. *Arch Dermatol* **2001**, 137, 69–73.
89. Sheu, J.; Saavedra, A.P.; Mostaghimi, A. Rapid response of tattoo-associated cutaneous sarcoidosis to minocycline: case report and review of the literature. *Dermatol Online* J **2014**, 20, 13030/qt6dd1m2j9.
90. Hirai, Y.; Hamada, Y.; Sasaki, S.; Suzuki, M.; Ito, Y.; Katayama, K.; Uno, H.; Nakada, T.; Kitami, Y.; Uchida, K.; Eishi, Y.; Sueki, H. Sarcoidosis and sarcoidal foreign body reaction after permanent eye makeup application: Analysis by immunohistochemistry with commercially available antibodies specific to Cutibacterium acnes and Mycobacteria. *J Cutan Pathol* **2022**, 49, 651-657.

 doi:10.20944/preprints202506.2059.v1

91. Nagai, S.; Yokomatsu, T.; Tanizawa, K.; Ikezoe, K.; Handa, T.; Ito, Y.; Ogino, S.; Izumi, T. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. *Intern Med* **2014**, 53, 427–33.
92. Asakawa, N.; Uchida, K.; Sakakibara, M.; Omote, K.; Noguchi, K.; Tokuda, Y.; Kamiya, K.; Hatanaka, K.C.; Matsuno, Y.; Yamada, S.; Asakawa, K.; Fukasawa, Y.; Nagai, T.; Anzai, T.; Ikeda, Y.; Ishibashi-Ueda, H.; Hirota, M.; Orii, M.; Akasaka, T.; Uto, K.; Shingu, Y.; Matsui, Y.; Morimoto, S.I.; Tsutsui, H.; Eishi, Y. Immunohistochemical identification of Propionibacterium acnes in granuloma and inflammatory cells of myocardial tissues obtained from cardiac sarcoidosis patients. *PLoS ONE* **2017**, 12, e0179980.
93. Hiraga, Y.; Omichi, M.; Yamada, G. The effect of antibacterial drug for sarcoidosis. *Ministry of Health and Welfare specific disease diffuse lung disease research team research report*. **1995**, 174–5.
94. Smith, C.S.; Aerts, A.; Saunderson, P.; Kawuma, J.; Kita, E.; Virmond, M. Multidrug therapy for leprosy: a game changer on the path to elimination. *Lancet Infect Dis* **2017**, 17, e293-e297.
95. Kraaijvanger, R.; Veltkamp, M. The Role of Cutibacterium acnes in Sarcoidosis: From Antigen to Treatable Trait? *Microorganisms* **2022**, 10, 1649.
96. Chintalapati, S.S.V.V.; Iwata, S.; Miyahara, M.; Miyako, E. Tumor-isolated Cutibacterium acnes as an effective tumor suppressive living drug. *Biomed Pharmacother* **2024**, 170, 116041.
97. Kennedy, J.D.; Sutton, R.C.; Conley, F.K. Effect of intracerebrally injected Corynebacterium parvum on the development and growth of metastatic brain tumor in mice. *Neurosurgery* **1989**, 25, 709–14.
98. McCaskill, J.G.; Chason, K.D.; Hua, X.; Neuringer, I.P.; Ghio, A.J.; Funkhouser, W.K.; Tilley, S.L. Pulmonary immune responses to propionibacterium acnes in C57bl/6 and BALB/ c mice. *Am J Respir Cell Mol Biol* **2006**, 35, 347–56.
99. Berek, J.S.; Cantrell, J.L.; Lichtenstein, A.K.; Hacker, N.F.; Knox, R.M.; Nieberg, R.K.; Poth, T.; Elashoff, R.M.; Lagasse, L.D.;Zighelboim, J. Immunotherapy with biochemically dissociated fractions of Propionibacterium acnes in a murine ovarian cancer model. *Cancer Res* **1984**, 44, 1871–1875.
100. Roszkowski, W.; Ko, H.L.; Szmigielski, S.; Jeljaszewicz, J.; Pulverer, G. The correlation of susceptibility of different Propionibacterium strains to macrophage killing and antitumor activity. *Med. Microbiol. Immunol* **1980**, 169, 1–8.
101. Fujiwara, H.; Tsuchida, T.; Tsuji, Y.; Hamaoka, T. Preventive effect of Propionibacterium acnes on metastasis in mice rendered tolerant to tumor-associated transplantation antigens. GANN Jpn. J. *Cancer Res* **1980**, 71, 692–698)
102. Chintalapati, S.S.V.V.; Iwata, S.; Miyahara, M.; Miyako, E. Tumor-isolated Cutibacterium acnes as an effective tumor suppressive living drug. *Biomed Pharmacother* **2024**, 170,116041.
103. Tsuda, K.; Yamanaka, K.; Linan, W.; Miyahara, Y.; Akeda, T.; Nakanishi, T.; Kitagawa, H.; Kakeda, M.; Kurokawa, I.; Shiku, H.; Gabazza, E.C., Mizutani, H. Intratumoral injection of Propionibacterium acnes suppresses malignant melanoma by enhancing Th1 immune responses. *PLoS One* **2011**, 6, e29020.
104. Talib, W.H.; Saleh, S. Propionibacterium acnes Augments Antitumor, Anti-Angiogenesis and Immunomodulatory Effects of Melatonin on Breast Cancer Implanted in Mice. *PLoS One* **2015,** 10, e0124384.
105. Fanning, M.M.; Kazura, J.W. Lack of biological significance of in vitro Brugia malayi microfilarial cytotoxicity mediated by Propionibacterium acnes ("Corynebacterium parvum")-and Mycobacterium bovis BCG-activated macrophages. *Infect Immun* **1986**, 52, 534-7.
106. Di Francesco, A.M.; Pasciuto, G.; Verrecchia, E.; Sicignano, L.L.; Gerardino, L.; Massaro, M.G.; Urbani, A.; Manna, R. Sarcoidosis and Cancer: The Role of the Granulomatous Reaction as a Double-Edged Sword. *J Clin Med* **2024**, 13, 5232.
107. Li, X.; Ma, Y.; Li, G.; Jin, G.; Xu, L.; Li, Y.; Wei, P.; Zhang, L. Leprosy: treatment, prevention, immune response and gene function. *Front Immunol* **2024**, 15, 1298749.