BRENDA KISCHKEL

Explorando as vias de inflamação em infecções fúngicas endêmicas e potenciais novas estratégias de tratamento

Tese apresentada ao Programa de Pós-graduação em Microbiologia do Instituto de Ciências biomédicas da Universidade de São Paulo, para obtenção do título de doutor em Ciências

São Paulo

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BRENDA KISCHKEL

Exploring inflammation pathways in endemic fungal infections and potential novel treatment strategies

Thesis presented to the Postgraduate Program in Microbiology of the Institute of Biomedical Sciences of the University of São Paulo, to obtain the title of Doctor in Sciences

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Advisor: Carlos Pelleschi Taborda

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ATA DE DEFESA

Ata de defesa de Tese do(a) Senhor(a) Brenda Kischkel no Programa: Ciências Biológicas (Microbiologia), do(a) Instituto de Ciências Biomédicas da Universidade de São Paulo.

Aos 24 dias do mês de junho de 2022, no(a) via remota realizou-se a Defesa da Tese do(a) Senhor(a) Brenda Kischkel, apresentada para a obtenção do título de Doutora intitulada:

"Explorando as vias de inflamação em infecções fúngicas endêmicas e potenciais novas estratégias de tratamento"

Após declarada aberta a sessão, o(a) Sr(a) Presidente passa a palavra ao candidato para exposição e a seguir aos examinadores para as devidas arguições que se desenvolvem nos termos regimentais. Em seguida, a Comissão Julgadora proclama o resultado:

Nome dos Participantes da Banca	Função	Sigla da CPG	Resultado
Carlos Pelleschi Taborda	Presidente	ICB - USP	Não Votante
Sandro Rogerio de Almeida	Titular	FCF - USP	APROVADA
André Luis Souza dos Santos	Titular	UFRJ - Externo	APROVADA
Mário Henrique de Barros	Suplente	ICB - USP	APROVADA

Resultado Final: APROVADA

Parecer da Comissão Julgadora *

Eu, Lucianna Vicente da Silva _____, lavrei a presente ata, que assino juntamente com os(as) Senhores(as). São Paulo, aos 24 dias do mês de junho de 2022.

Sandro Rogerio de Almeida

André Luis Souza dos Santos

Mário Henrique de Barros

Carlos Pelleschi Taborda
Presidente da Comissão Julgadora

* Obs: Se o candidato for reprovado por algum dos membros, o preenchimento do parecer é obrigatório.

A defesa foi homologada pela Comissão de Pós-Graduação em 12/07/2022 e, portanto, o(a) aluno(a) _____ jus ao título de Doutora em Ciências obtido no Programa Ciências Biológicas (Microbiologia) - Área de concentração: Microbiologia.

Presidente da Comissão de Pós-Graduação

Profa. Dra. Ana Paula Lepique
Presidente da CPG/ICB

Instituto de Ciências Biomédicas
ICB USP Excelência em Ensino e Pesquisa

Universidade de São Paulo
Comissão de Ética no Uso de Animais

CERTIFICADO

Certificamos que a proposta intitulada "Prospecção de novos epitopos com potencial vacinal no controle da infecção experimental por Histoplasma capsulatum", protocolada sob o CEUA nº 1169061218, sob a responsabilidade de **Carlos Pelleschi Taborda** *e equipe; Brenda Kischkel* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **aprovada** pela Comissão de Ética no Uso de Animais da Instituto de Ciências Biomédicas (Universidade de São Paulo) (CEUA-ICB/USP) na reunião de 20/03/2019.

We certify that the proposal "Prospection of new epitopes with vaccine potential in the control of experimental infection by Histoplasma capsulatum", utilizing 315 Isogenics mice (315 males), protocol number CEUA 1169061218, under the responsibility of **Carlos Pelleschi Taborda** *and team; Brenda Kischkel* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **approved** by the Ethic Committee on Animal Use of the Biomedical Sciences Institute (University of São Paulo) (CEUA-ICB/USP) in the meeting of 03/20/2019.

Finalidade da Proposta: Pesquisa (Acadêmica)

Vigência da Proposta: 48 meses Depto/Setor: Microbiologia

Origem:	Biotério de matrizes de Camundongos do ICB				
Espécie:	Camundongos isogênicos	sexo:	Machos	Idade ou peso:	6 a 8 semanas
Linhagem:	BALB/c e C57BL/6			**N amostral:**	315

São Paulo, 21 de março de 2019

Profa. Dra. Luciane Valéria Sita
Coordenadora da Comissão de Ética no Uso de Animais
Instituto de Ciências Biomédicas (Universidade de São Paulo)

Dr. Alexandre Ceroni
Vice-Coordenador da Comissão de Ética no Uso de Animais
Instituto de Ciências Biomédicas (Universidade de São Paulo)

São Paulo, 22 de junho de 2022
CEUA N 1169061218

Ilmo(a). Sr(a).
Responsável: Carlos Pelleschi Taborda
Área: Microbiologia

Título da proposta: "Explorando as vias de inflamação em infecções fúngicas endêmicas e potenciais novas estratégias de tratamento Título anterior (Prospecção de novos epitopos com potencial vacinal no controle da infecção experimental por Histoplasma capsulatum)".

Parecer Consubstanciado da Comissão de Ética no Uso de Animais ICB (ID 002960)

A Comissão de Ética no Uso de Animais da Instituto de Ciências Biomédicas (Universidade de São Paulo), no cumprimento das suas atribuições, analisou e **APROVOU** a Alteração do cadastro (versão de 25/maio/2022) da proposta acima referenciada.

Resumo apresentado pelo pesquisador: "Prezada Comissão, Solicitamos a mudança do título do projeto. O título anterior da Tese era: Prospecção de novos epitopos com potencial vacinal no controle da infecção experimental por Histoplasma capsulatum O novo título da Tese é: Explorando as vias de inflamação em infecções fúngicas endêmicas e potenciais novas estratégias de tratamento Ressalto que não houve mudança na metodologia empregada no projeto. O motivo da mudança de título é porque tese está dividida em 7 capítulos, no qual cada capítulo corresponde a um artigo diferente. O artigo referente ao comitê de ética no qual houve o uso de animais se refere apenas ao capítulo 4 da tese. ".

Comentário da CEUA: "".

Profa. Dra. Luciane Valéria Sita
Coordenadora da Comissão de Ética no Uso de Animais
Instituto de Ciências Biomédicas (Universidade de São Paulo)

Prof. Dr. Francemilson Goulart da Silva
Vice-Coordenador da Comissão de Ética no Uso de Animais
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628

Prof. dr. Netea
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Ons Kenmerk
DS/CMO 009

Datum
03 januari 2017

Titel: Donatie van bloed door gezonde vrijwilligers voor experimenteel in-vitro onderzoek
Dossiernummer: 2010-104
NL-nummer: NL32357.091.10

Geachte heer Netea,

Bijgevoegd treft u aan het positieve oordeel van de CMO Regio Arnhem-Nijmegen over het amendement ingediend d.d. 17 oktober 2016 behorend bij bovengenoemd onderzoek.

Bij correspondentie over het onderzoek gelieve titel en dossiernummer te vermelden.

Ik vertrouw erop u met dit schrijven van dienst te zijn en namens de commissie wens ik u succes met de verdere uitvoering van het onderzoek.

Met vriendelijke groet,
Namens de CMO Regio Arnhem-Nijmegen

Drs. R.B. Keus, vicevoorzitter

Radboudumc

BESLUIT
Beoordeling amendement

NL nummer:	**NL32357.091.10**	**METC nr.**	**2010-104**
Titel onderzoek:	**Donatie van bloed door gezonde vrijwilligers voor experimenteel in-vitro onderzoek**		

Contactgegevens: Prof. dr. Netea, 463 Afdeling Interne Geneeskunde, Radboudumc
Verrichter: Radboudumc te Nijmegen

Besluit
De medisch-ethische toetsingscommissie CMO Regio Arnhem-Nijmegen heeft zich op grond van artikel 2, tweede lid, sub a van de *Wet medisch wetenschappelijk onderzoek met mensen* (WMO), beraden over het amendement behorend bij bovengenoemd onderzoeksdossier.

De commissie oordeelt positief over het amendement.

Documenten
Het besluit is gebaseerd op de documenten die in bijlage 1 zijn vermeld.

Achtergrond
Op 17 oktober 2016 is het amendement ter beoordeling bij de commissie ingediend. Daarna heeft de commissie u vragen gesteld over het amendement waarop naar tevredenheid is geantwoord.
Het amendement is buiten de vergadering besproken door/onder leiding van de voorzitter.

Overwegingen
De commissie is van oordeel dat aan alle voorwaarden in artikel 3 van de WMO is voldaan.
Naar de mening van de commissie heeft het amendement geen directe consequenties voor lokale uitvoerbaarheidsaspecten.

Ten slotte wijst de commissie u op de verplichtingen die bij het oorspronkelijke positieve besluit zijn vermeld.

Hoogachtend,
Namens de CMO Regio Arnhem-Nijmegen

Drs. R.B. Keus, vicevoorzitter

Nijmegen, 03 januari 2017

Beroepsprocedure
Tegen dit besluit kan een belanghebbende op grond van artikel 23 van de WMO binnen zes weken na de dag waarop het besluit is bekend gemaakt, administratief beroep instellen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO). Het beroepschrift dient u te adresseren aan CCMO, Postbus 16302, 2500 BH Den Haag.

Radboudumc

Bijlage 1

Documenten

A	Aanbiedingsbrief van mw. M. Doppenberg-Oosting d.d. 17 oktober 2016 Aanbiedingsbrief van mw. M. Doppenberg-Oosting d.d. 22 november 2016, in reactie op commissiemail d.d. 07 november 2016 Aanbiedingsbrief van mw. M. Doppenberg-Oosting d.d. 20 december 2016, in reactie op commissiemail d.d. 19 december 2016
C	Protocol, versie 3 d.d. 24 mei 2011, ontvangen d.d. 17 oktober 2016
M	Formulier voortgangsrapportage, versie 1 mei 2015, ontvangen d.d. 20 december 2016

I dedicate this thesis to my family (including my dog, Jack) and friends, who together have always renewed my strength throughout this journey.

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"*However strong you become, never seek to bear everything alone. If you do, failure is certain*"

Masaki Kishimoto.

RESUMO

Kischkel, B. Explorando as vias de inflamação em infecções fúngicas endêmicas e potenciais novas estratégias de tratamento. [Tese (Doutorado-direto em Microbiologia)] Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2022.

Nos últimos anos o aumento do número de indivíduos imunocomprometidos contribuiu para as altas taxas globais de incidência de infecções fúngicas. O tratamento para micoses sistêmicas ainda é limitado devido a toxicidade das drogas e os longos períodos para tratamento que não protegem contra recidivas da doença. Uma alternativa para solucionar esses problemas é o desenvolvimento de vacinas e imunoterapias que podem estimular o sistema imune na resolução da doença e serem liadas a terapias antifúngicas em baixas doses (Capítulo 3). Através de ferramentas bioinformáticas, selecionamos epitopos com maiores afinidades pelas moléculas de antígeno leucocitário humano classe I (HLA-I) e classe II (HLA-II) e conservados entre diferentes espécies de fungos. Experimentos *ex vivo* demonstraram que esses epitopos tem potencial antigênico e podem se tornar possíveis candidatos no desenvolvimento de uma vacina peptídica pan-fúngica (Capítulo 4). Além disso, nós também identificamos importantes vias de sinalização de citocinas em resposta a esporotricose e ao peptidoramnomanano da parede celular do fungo. Nós demonstramos que a via de IL-1 é crucial para a resposta imune contra esporotricose e pode ser alvo para imunoterapias personalizadas que visam amenizar e controlar a resposta inflamatória e destruição do tecido (Capítulo 5 e 7). Por fim, nós discutimos a reposta imune da pele a infecções fúngicas e sugerimos que a patogenicidade de doenças infecciosas de pele como a esporotricose também podem estar relacionada com a imunidade treinada (Capítulo 6). Em conclusão, o conjunto de dados compilados neste trabalho contribui para o desenvovimento de novas estratégias vacinais e terapêuticas contra micoses endêmicas.

Palavras-chave: Histoplasmose. Esporotricose. Vacina. Citocina. Peptidoramnomanano.

ABSTRACT

Kischkel, B. Exploring inflammation pathways in endemic fungal infections and potential novel treatment strategies. [Thesis (Ph.D thesis in Microbiology)] Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2022.

In recent years the increase in the number of immunocompromised individuals has contributed to the high global incidence rates of fungal infections. Treatment for systemic mycoses is still limited due to drug toxicity and long treatment periods that do not protect against disease recurrence. An alternative to solve these problems is the development of vaccines and immunotherapies that can stimulate the immune system to resolve the disease and be linked to low-dose antifungal therapies (Chapter 3). Using bioinformatics tools, we selected epitopes with greater affinities for human leukocyte antigen class I (HLA-I) and class II (HLA-II) molecules and conserved among different fungal species. Ex vivo experiments have demonstrated that these epitopes have antigenic potential and may become possible candidates in the development of a pan-fungal peptide vaccine (Chapter 4). In addition, we also identified important cytokine signalling pathways in response to sporotrichosis and the peptidorhamnomannan from the fungal cell wall. We demonstrate that the IL-1 pathway is crucial for the immune response against sporotrichosis and can be targeted for personalized immunotherapies that aim to ameliorate and control the inflammatory response and tissue destruction (Chapter 5 and 7). Finally, we discuss the skin's immune response to fungal infections and suggest that the pathogenicity of infectious skin diseases such as sporotrichosis may also be related to trained immunity (Chapter 6). In conclusion, the set of data compiled in this work contributes to the development of new vaccine and therapeutic strategies against endemic mycoses.

Keywords: Histoplasmosis. sporotrichosis. Vaccine. cytokine. Peptidoramnomannan.

SUMMARY

1 GENERAL INTRODUCTION

1.1. Endemic Fungal Infections

Invasive fungal infections can be caused by opportunistic and / or endemic species of pathogenic fungi. Opportunistic fungal infections usually occur in immunocompromised individuals as a result of subjacent infection or the treatment itself (1). Species of *Aspergillus*, *Candida* and *Cryptococcus* are the main agents of opportunistic mycoses. Endemic fungal infections are usually caused by dimorphic fungi that occupy specific climatic zones such as tropical, subtropical and temperate regions. Host acquisition occurs by inhalation of infectious spores/infective propagules present in the soil or in animal faeces (2). The main species that cause endemic mycoses are *Blastomyces dermatitidis, Coccidioides immitis* and *C. posadasii, Histoplasma capsulatum, Paracoccidioides brasiliensis* and *P. lutzii, Sporothrix*, particularly *S. brasiliensis* and *S. schenckii,* and *Talaromyces marneffei* (3).

In this thesis, we focus on the study of the immune response and potential new treatment strategies for two endemic mycoses that occur in Brazil, histoplasmosis and sporotrichosis. *H. capsulatum* and *Sporothrix* spp. are considered primary pathogens as they are capable of causing disease in immunocompromised and immunocompetent individuals (4,5).

Histoplasmosis is a fungal infection endemic in the American continent caused by the thermo dimorphic fungus *H. capsulatum* (5). It is also the most common respiratory fungal infection having a worldwide distribution. The histoplasmosis may vary from asymptomatic infection to deep mycosis pulmonary and/or systemic (6). The yeast form of *H. capsulatum* has mechanisms to prevent intracellular death by phagocytes, through the degradation of reactive oxygen species, regulation of the pH of lysosomes and expression of several mechanisms for the acquisition of nutrients such as iron under limited conditions (7). After replication, the yeasts lead to the destruction of the macrophage and spread to the neighbouring phagocytes. Furthermore, the intracellular position of the fungus is challenging for the infection treatment, since phagocytes may act as a barrier, preventing the antifungal from interacting with its target in the cell (7).

Sporotrichosis is a deep mycosis caused by the dimorphic fungi S. *Schenckii*, *S. brasiliensis* and *S. globosa.* The disease usually manifests as subcutaneous, extracutaneous and disseminated clinical forms after traumatic inoculation of materials contaminated with infectious propagules of *Sporothrix* species in the skin, mucous membranes and lymphatic

vessels (8). In particular, *S. brasiliensis* has drawn attention due to its greater virulence and its association with abnormal clinical cases of the disease, affecting lung and central nervous system (9,10). *S. brasiliensis* is currently responsible for the biggest outbreak of sporotrichosis ever documented in Brazil and it continues to expand to other countries in Latin America (11). Furthermore, recent studies have begun to detect the emergence of *Sporothrix* species resistant to antifungals (12,13).

1.2. Immune response against fungal infections

Innate immune cells such as macrophages, monocytes and dendritic cells have molecules called Pattern Recognition Receptors (PRRs) on their surface. The PRRs are responsible for the identification of specific and conserved molecules present on the surface of pathogens, the Pathogen-Associated Molecular Patterns (PAMPs). PRRs involved in recognizing fungal pathogens include, C-type lectin-like (CLR), Toll-like (TLR) and NOD-like (NLR) receptors (14). Among them, Dectin-1, CR3, TLR2 and TRL4 play a crucial role in the recognition of *H. capsulatum* and *Sporothrix* sp.

Components from fungi cell wall, such as chitin, mannans and glucans, are important PAMPs. Dectin-1 receptor is required in the recognition of β-glucans. However, *H. Capsulatum* is able to mask β-glucans by expressing α-glucans in the cell wall (15). Thus, the recognition of *H. capsulatum* by cells of the immune system as macrophages occurs through the interaction of the CD11/CD18 integrin (CR3 receptor) with the heat shock protein 60 from *H. Capsulatum*. On the other hand, dendritic cells use the fibronectin receptor (VLA-5) to recognize cyclophilin A from *H. Capsulatum* (16).

Although Dectin-1 is extremely important for the activation of the immune response against fungi, triggering it alone was not sufficient for the production of cytokines by murine macrophages (17). Dectin-1 co-stimulation with two or more different receptors may render synergistic effects. This fact can be observed for *H. capsulatum*, in which Dectin-1 interacts with CR3 on macrophages and triggers tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) mediated inflammatory response through activation of Syk-JNK-AP-1 pathway (18).

TLR receptors have been the most studied in the context of sporotrichosis (19). The recognition of *S. schenckii* by TLR2 promotes the production of pro-inflammatory cytokines TNF-α, IL-1β, IL-12 and anti-inflammatory such as IL-10 (20). Dectin-1 was described as essential for cytokine production by human PBMCs after stimulation with *S. brasiliensis* and *S. schenckii*

yeasts (21). Recently, peptidorhamnomannan (PRM) has been described for *S. brasiliensis* and *S. schenckii* as the major cell wall component present on the outer layer of both fungi and responsible for the recognition of the fungi by human macrophages via CR3. The same authors also observed cooperation between CR3 and TLR4 in IL-1β induction and secretion of pentraxin-3 (22).

The Th1 and Th17 response are crucial for host protection during histoplasmosis and sporotrichosis (4,16). Differentiation of T $CD4^+$ cells into the Th1 subset requires IL-12 and IFN-γ, while Th17 subset requires TGF-β, IL-6, IL-21 and IL-23, which are cytokines produced after CLR or TLR activation (14). The Th1 cytokines (e.g. IFN-γ) induces cell-mediated immunity through stimulating phagocytes. Th17 cells produce IL-17 and IL-22 and induce the secretion of proinflammatory factors, including IL-6, IL-8, GM-CSF and chemokines CXCL1 and CCL20 responsible for macrophage and neutrophil recruitment to the site of infection (23).

1.3. Challenges and opportunities in the treatment of fungal infections

Fungal infections are often defined as difficult to treat, including the toxicity of antifungals and their interaction with other drugs. There is broad consensus that currently available antifungal therapy is limited and far from ideal and it does not exclude the possibility of disease relapses (24,25). The most of those affected by fungal infections are immunocompromised individuals, this fact limits the development of safe and at the same time effective antifungal vaccines for this fraction of the population (26). A promising strategy in the treatment of fungal infections may be the combination of immunotherapeutic agents (e.g. therapeutic vaccines, monoclonal antibodies) with antifungal chemotherapy to improve the effectiveness of treatment by reducing the dose of antifungal needed throughout the course of treatment (27). Other beneficial factors to be considered would be a possible reduction in the treatment period and a decrease in the chances of disease recurrence due to optimized treatment. However, more studies need to be carried out in this regard to establish such benefits.

According to Hole *et al*., (28) preventive and immunotherapeutic vaccines can be designed to program innate immune cells to respond specifically to antigens in a protective or suppressive manner. Thus, for the development of an effective vaccine for the therapy of certain pathogens, it is necessary to incorporate fungal antigens with immunogenic potential for administration. Researchers have recently proposed that an efficient design of a vaccine should consider including an antigen, an adjuvant, and an amplifier (29).

Regarding antigens, conventional vaccines usually use the whole microorganisms or large proteins. However, these antigens can elicit allergenic and / or reactogenic responses by presenting an unnecessary antigenic load. A promising option are the peptide-based vaccines containing only the epitope recognized by B and T cells, capable of inducing highly targeted immune response (30). Of note, the use of only peptides can be weakly immunogenic, unstable and degraded or modified after injection, therefore, the peptide carrier system and amplifier are essential to ensure successful vaccination (29).

β-glucans can also be considered a promising candidate for use as an immunostimulant agent (or amplifier for vaccines), also in immunocompromised patients. The β-glucans are polysaccharides present abundantly in the wall of yeasts and fungi, being recognized by cell-specific surface receptors such as macrophages, dendritic cells, neutrophils and natural killer, stimulating the host immune response (31). β-glucans are recognized by specific transmembrane pattern recognition receptors (PRRs) such as Dectin-1 or complement receptor 3 (CR3), leading to a cascade of signalling events that result in faster release of phagocytosis of β-glucans particles, release of proinflammatory cytokines, chemokines, antimicrobial proteins (e.g. lysozyme and defensins) and increased oxidative burst (32,33).

It has been reported in recent years that innate immune cells through infection or vaccination can be trained to induce a nonspecific, protective and increased immune response to reinfection or secondary stimulus by pathogens (34). This immune memory is called trained innate immunity (TII), and β-glucans are able to induce TII through stable epigenetic reprogramming in macrophages and monocytes, altering the metabolic state of the cell, in this case, induction of aerobic glycolysis by Akt-mTOR-HIF-1α pathway (35). In this case, TII-based vaccines for preventive purposes can be applied in states of immunodeficiency, in which the individual's innate immunity is preserved (36). In addition, we suggest that it can help ensure the protection of susceptible individuals living in endemic areas.

CHAPTER 2

GENERAL OUTLINE OF THE THESIS AND RELATION BETWEEN THE CHAPTERS

This thesis aims to identify novel treatment strategies for fungal infections in two different ways: (I) based on the selection of pan-fungal peptides from *H. capsultum* with potential to be used for therapeutic vaccination against different mycoses and (II) identification of treatment strategies based on the cytokine immune response against *Sporothrix* spp. Compared to other fungi, knowledge about immunity against sporotrichosis is scarce, therefore, the identification and characterization of pathways involved in the host immune response and its relations with disease susceptibility and clinical outcome is primarily needed in order to identify personalized treatment strategies.

Chapter 3 we discuss the use of nanoparticles as adjuvants for the development of new vaccination and therapy strategies against systemic mycosis caused by Candida sp., *Cryptococcus* sp., *Paracoccidioides* sp., *Histoplasma* sp., *Coccidioides* sp., and *Aspergillus* sp. The use of different types of nanoparticles, nanocarriers for the targeted or sustained delivery of antigens for vaccination or drugs for therapy was explored. In addition, we provide important information about their corresponding mechanisms of action.

Chapter 4 identifies pan-fungal peptides without similarity to human proteins. Using bioinformatics tools, we selected conserved and antigenic epitopes with greater affinities for class I (HLA-I) and class II (HLA-II) human leukocyte antigen molecules. Some of these epitopes are present in other species of pathogenic fungi such as *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Coccidioides immitis* and *Aspergillus fumigatus*. The selected epitopes came from the following proteins: heat shock protein 60, enolase, and the ATP-dependent molecular chaperone HSC82 and were able to induce the proliferation of CD4+ and CD8+ T cells and produced a Th1 and Th17 response. The results presented in this chapter constitute an advance in the identification of T cell epitopes that can be explored individually or together for the development of a multi-epitope peptide vaccine to combat *H. capsulatum* and other fungi.

In **Chapter 5** we have identified IL-1β as a key cytokine for inducing an inflammatory response caused by *S. brasiliensis*. Moreover, we identified that *S. schenckii* induces higher

concentrations of interleukin-1 antagonist receptor (IL-1Ra) than S. *brasiliensis*. Inhibition of IL-1 receptor, inflammasome or caspase-1 were able to decrease the production of proinflammatory cytokines by *S. brasiliensis*. Since one of the main characteristics of the disease is the exacerbation of the inflammatory response that leads to the destruction of the host's skin, our findings contribute to the understanding of the pathogenesis of *Sporothrix* spp. and offer possibilities for improved treatment of sporotrichosis.

In **Chapter 6** we provide a short review of the skin's immune response to fungal infections. We address the types of immune (macrophages, Langerhans cells, neutrophils, natural killer cells) and non-immune (keratinocytes and fibroblasts) cell types and the role they play in the immune response against fungal infections. Furthermore, we discuss the possible involvement of trained immunity in the pathogenesis of fungal skin infections such as sporotrichosis.

Chapter 7 we explore the IL-36 pathway in the context of sporotrichosis. We demonstrate for the first time that *S. schenckii* and *S. brasiliensis* are able to induce IL-36 expression in PBMCs and keratinocytes. Especially, IL-36γ plays a crucial role in the pathogenesis of sporotrichosis. We identified IL-17, TNF, IL-1β and IL-1α as cytokines related to IL-36γ production by *Sporothrix*-stimulated keratinocytes and demonstrated genetic variations in the *IL36* gene that influence the production of these same cytokines. Our findings demonstrate that IL-36 signalling pathway modulates the inflammatory response in sporotrichosis and may be a promising therapeutic target.

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