

9. Bibliography

- (1) De Gregorio, E.; Rappuoli, R. From Empiricism to Rational Design: A Personal Perspective of the Evolution of Vaccine Development. *Nat. Rev. Immunol.* **2014**, *14* (7), 505–514. <https://doi.org/10.1038/nri3694>.
- (2) Lahariya, C. A Brief History of Vaccines & Vaccination in India. *Indian J. Med. Res.* **2014**, *139* (4), 491–511.
- (3) Thucydides. The History of the Peloponnesian War Done into English by Richard Crawley. *Creative Media Partners, LLC*. **2015**.
- (4) Tognotti, E. The Eradication of Smallpox, a Success Story for Modern Medicine and Public Health: What Lessons for the Future? *J Infect Dev Ctries.* **2010**, *5* (6) 264–266.
- (5) Plotkin, S. Vaccines : Past , Present and Future Early Successes. *Nat. Med.* **2005**, *11* (4), 5–11. <https://doi.org/10.1038/nm1209>.
- (6) Smith, K. A. Louis Pasteur, the Father of Immunology? *Front. Immunol.* **2012**, *3*, 68. <https://doi.org/10.3389/fimmu.2012.00068>.
- (7) Doherty, M.; Robertson, M. J. Some Early Trends in Immunology. *Trends Immunol.* **2004**, *5* (12), 623–631. <https://doi.org/10.1016/j.it.2004.10.008>.
- (8) Bordon, Y. The Many Sides of Paul Ehrlich. *Nat. Immunol.* **2016**, *17* (1), S6–S6. <https://doi.org/10.1038/ni.3601>.
- (9) Gordon, S. Elie Metchnikoff: Father of Natural Immunity. *Eur. J. Immunol.* **2008**, *38* (12), 3257–3264. <https://doi.org/10.1002/eji.200838855>.

- (10) Zepp, F. Principles of Vaccine Design-Lessons from Nature. *Vaccine*. **2010**, *28 Suppl 3*, C14-24. <https://doi.org/10.1016/j.vaccine.2010.07.020>.
- (11) Moser, M.; Leo, O. Key Concepts in Immunology. *Vaccine*. **2010**, *28 Suppl 3*, C2-13. <https://doi.org/10.1016/j.vaccine.2010.07.022>.
- (12) Di Pasquale, A.; Preiss, S.; Tavares Da Silva, F.; Garcon, N. Vaccine Adjuvants: From 1920 to 2015 and Beyond. *Vaccines*. **2015**, *3* (2), 320–343. <https://doi.org/10.3390/vaccines3020320>.
- (13) Decade of Vaccines Collaboration. Global Vaccine Action Plan 2011-2020 https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/.
- (14) Burza, S.; Croft, S. L.; Boelaert, M. Leishmaniasis. *Lancet*. **2018**, *392* (10151), 951–970. [https://doi.org/10.1016/S0140-6736\(18\)31204-2](https://doi.org/10.1016/S0140-6736(18)31204-2).
- (15) Colmenares, M.; Kar, S.; Goldsmith-Pestana, K.; McMahon-Pratt, D. Mechanisms of Pathogenesis: Differences amongst Leishmania Species. *Trans. R. Soc. Trop. Med. Hyg.* **2002**, *96 Suppl 1*, S3-7. [https://doi.org/10.1016/s0035-9203\(02\)90044-1](https://doi.org/10.1016/s0035-9203(02)90044-1).
- (16) Kedzierski, L. Leishmaniasis. *Hum. Vaccin.* **2011**, *7* (11), 1204–1214. <https://doi.org/10.4161/hv.7.11.17752>.
- (17) Bern, C.; Maguire, J. H.; Alvar, J. Complexities of Assessing the Disease Burden Attributable to Leishmaniasis. *PLoS Negl. Trop. Dis.* **2008**, *2* (10), e313. <https://doi.org/10.1371/journal.pntd.0000313>.
- (18) Okwor, I.; Uzonna, J. Vaccines and Vaccination Strategies against Human Cutaneous Leishmaniasis. *Hum. Vaccin.* **2009**, *5* (5), 291–301.

- https://doi.org/10.4161/hv.5.5.7607.
- (19) Alvar, J.; Velez, I. D.; Bern, C.; Herrero, M.; Desjeux, P.; Cano, J.; Jannin, J.; den Boer, M. Leishmaniasis Worldwide and Global Estimates of Its Incidence. *PLoS One* **2012**, *7* (5), e35671. https://doi.org/10.1371/journal.pone.0035671.
- (20) Cobo, F. 16 - Leishmaniasis. Imported Infectious Diseases - The impact in developing countries, *Woodhead Publishing*, **2014**, 227–242. https://doi.org/10.1533/9781908818737.227.
- (21) Pavli, A.; Maltezou, H. C. Leishmaniasis, an Emerging Infection in Travelers. *Int. J. Infect. Dis.* **2010**, *14* (12), e1032–e1039. https://doi.org/10.1016/j.ijid.2010.06.019.
- (22) Buckner, F. S.; Schwartz, E. Chapter 39 - Leishmaniasis. Travel and Tropical Medicine manual - Fifth Edition, *Elsevier*, **2017**, 501–512. https://doi.org/10.1016/B978-0-323-37506-1.00039-8.
- (23) Fenwick, A. SECTION 6 International Medicine: Major Tropical Syndromes: Systemic Infections. 118 - Schistosomiasis. Infectious Diseases - Fourth edition. *Elsevier*. **2017**, 2, 1026–1031.e1. https://doi.org/10.1016/B978-0-7020-6285-8.00118-0.
- (24) Guerra, J. A. de O.; Prestes, S. R.; Silveira, H.; Coelho, L. I. de A. R. C.; Gama, P.; Moura, A.; Amato, V.; Barbosa, M. das G. V.; Ferreira, L. C. de L. Mucosal Leishmaniasis Caused by Leishmania (Viannia) braziliensis and Leishmania (Viannia) guyanensis in the Brazilian Amazon. *PLoS Negl. Trop. Dis.* **2011**, *5* (3), e980. https://doi.org/10.1371/journal.pntd.0000980.
- (25) Amato, V. S.; Tuon, F. F.; Imamura, R.; Abegao de Camargo, R.; Duarte, M. I;

- Neto, V. A. Mucosal Leishmaniasis: Description of Case Management Approaches and Analysis of Risk Factors for Treatment Failure in a Cohort of 140 Patients in Brazil. *J. Eur. Acad. Dermatol. Venereol.* **2009**, *23* (9), 1026–1034. <https://doi.org/10.1111/j.1468-3083.2009.03238.x>.
- (26) Pace, D. Leishmaniasis. *J. Infect.* **2014**, *69 Suppl 1*, S10-8. <https://doi.org/10.1016/j.jinf.2014.07.016>.
- (27) Leishmaniasis in Sudan. *Lancet* **1993**, *341* (8843), 488. [https://doi.org/10.1016/0140-6736\(93\)90236-A](https://doi.org/10.1016/0140-6736(93)90236-A).
- (28) Zijlstra, E. E.; Musa, A. M.; Khalil, E. A. G.; el-Hassan, I. M.; el-Hassan, A. M. Post-Kala-Azar Dermal Leishmaniasis. *Lancet. Infect. Dis.* **2003**, *3* (2), 87–98.
- (29) Aleman, C. Finestructure of Cultured Leishmania Brasiliensis. *Exp. Parasitol.* **1969**, *24* (2), 259–264. [https://doi.org/10.1016/0014-4894\(69\)90163-5](https://doi.org/10.1016/0014-4894(69)90163-5).
- (30) Rudzinska, M. A.; D'Alesandro, P. A.; Trager, W. The Fine Structure of Leishmania donovani and the role of the Kinetoplast in the Leishmania-leptomonad transformation. *J. Protozool.* **1964**, *11*, 166–191. <https://doi.org/10.1111/j.1550-7408.1964.tb01739.x>.
- (31) Gluenz, E.; Hoog, J. L.; Smith, A. E.; Dawe, H. R.; Shaw, M. K.; Gull, K. Beyond 9+0: Noncanonical Axoneme Structures Characterize Sensory Cilia from Protists to Humans. *FASEB J.* **2010**, *24* (9), 3117–3121. <https://doi.org/10.1096/fj.09-151381>.
- (32) Silverman, J. M.; Clos, J.; Horakova, E.; Wang, A. Y.; Wiesigl, M.; Kelly, I.; Lynn, M. A.; McMaster, W. R.; Foster, L. J.; Levings, M. K.; et al. Leishmania Exosomes Modulate Innate and Adaptive Immune Responses through Effects on

- Monocytes and Dendritic Cells. *J. Immunol.* **2010**, *185* (9), 5011–5022.
<https://doi.org/10.4049/jimmunol.1000541>.
- (33) Field, M. C.; Carrington, M. The Trypanosome Flagellar Pocket. *Nat. Rev. Microbiol.* **2009**, *7* (11), 775–786. <https://doi.org/10.1038/nrmicro2221>.
- (34) Sunter, J.; Gull, K. Shape, Form, Function and Leishmania Pathogenicity: From Textbook Descriptions to Biological Understanding. *Open Biol.* **2017**, *7* (9), pii: 170165. <https://doi.org/10.1098/rsob.170165>.
- (35) Kamhawi, S. Phlebotomine Sand Flies and Leishmania Parasites: Friends or Foes? *Trends Parasitol.* **2006**, *22* (9), 439–445. <https://doi.org/10.1016/j.pt.2006.06.012>.
- (36) Pimenta, P. F.; Modi, G. B.; Pereira, S. T.; Shahabuddin, M.; Sacks, D. L. A Novel Role for the Peritrophic Matrix in Protecting Leishmania from the Hydrolytic Activities of the Sand Fly Midgut. *Parasitology*. **1997**, *115* (Pt 4), 359–369. <https://doi.org/10.1017/s0031182097001510>.
- (37) Pruzinova, K.; Sadlova, J.; Seblova, V.; Homola, M.; Votypka, J.; Wolf, P. Comparison of Bloodmeal Digestion and the Peritrophic Matrix in Four Sand Fly Species Differing in Susceptibility to Leishmania Donovanii. *PLoS One*. **2015**, *10* (6), e0128203. <https://doi.org/10.1371/journal.pone.0128203>.
- (38) Dostalova, A.; Wolf, P. Leishmania Development in Sand Flies: Parasite-Vector Interactions Overview. *Parasit. Vectors*. **2012**, *5*, 276. <https://doi.org/10.1186/1756-3305-5-276>.
- (39) Wilson, R.; Bates, M. D.; Dostalova, A.; Jecna, L.; Dillon, R. J.; Wolf, P.; Bates, P. A. Stage-Specific Adhesion of Leishmania Promastigotes to Sand Fly Midguts

- Assessed Using an Improved Comparative Binding Assay. *PLoS Negl. Trop. Dis.* **2010**, *4* (9), pii: e816. <https://doi.org/10.1371/journal.pntd.0000816>.
- (40) Bates, P. A. Transmission of Leishmania Metacyclic Promastigotes by Phlebotomine Sand Flies. *Int. J. Parasitol.* **2007**, *37* (10), 1097–1106. <https://doi.org/10.1016/j.ijpara.2007.04.003>.
- (41) Wakid, M. H.; Bates, P. A. Flagellar Attachment of Leishmania Promastigotes to Plastic Film in Vitro. *Exp. Parasitol.* **2004**, *106* (3–4), 173–178. <https://doi.org/10.1016/j.exppara.2004.03.001>.
- (42) Gossage, S. M.; Rogers, M. E.; Bates, P. A. Two Separate Growth Phases during the Development of Leishmania in Sand Flies: Implications for Understanding the Life Cycle. *Int. J. Parasitol.* **2003**, *33* (10), 1027–1034. [https://doi.org/10.1016/s0020-7519\(03\)00142-5](https://doi.org/10.1016/s0020-7519(03)00142-5).
- (43) Rogers, M. E.; Chance, M. L.; Bates, P. A. The Role of Promastigote Secretory Gel in the Origin and Transmission of the Infective Stage of Leishmania Mexicana by the Sandfly Lutzomyia Longipalpis. *Parasitology*. **2002**, *124* (Pt 5), 495–507. <https://doi.org/10.1017/s0031182002001439>.
- (44) Ready, P. D. Biology of Phlebotomine Sand Flies as Vectors of Disease Agents. *Annu. Rev. Entomol.* **2013**, *58*, 227–250. <https://doi.org/10.1146/annurev-ento-120811-153557>.
- (45) de Almeida, M. C.; Vilhena, V.; Barral, A.; Barral-Netto, M. Leishmanial Infection: Analysis of Its First Steps. A Review. *Mem. Inst. Oswaldo Cruz*. **2003**, *98* (7), 861–870. <https://doi.org/10.1590/s0074-02762003000700001>.

- (46) Schlein, Y.; Warburg, A. The Effect of Post-Bloodmeal Nutrition of Phlebotomus Papatasi on the Transmission of Leishmania Major. *Am. J. Trop. Med. Hyg.* **1986**, *35* (5), 926–930. <https://doi.org/10.4269/ajtmh.1986.35.926>.
- (47) Puentes, S. M.; Da Silva, R. P.; Sacks, D. L.; Hammer, C. H.; Joiner, K. A. Serum Resistance of Metacyclic Stage Leishmania Major Promastigotes Is Due to Release of C5b-9. *J. Immunol.* **1990**, *145* (12), 4311-4316.
- (48) McConville, M. J.; Turco, S. J.; Ferguson, M. A.; Sacks, D. L. Developmental Modification of Lipophosphoglycan during the Differentiation of Leishmania Major Promastigotes to an Infectious Stage. *EMBO J.* **1992**, *11* (10), 3593–3600. <https://doi.org/10.1002/j.1460-2075.1992.tb05443.x>.
- (49) Dey, R.; Joshi, A. B.; Oliveira, F.; Pereira, L.; Guimaraes-Costa, A. B.; Serafim, T. D.; de Castro, W.; Coutinho-Abreu, I. V; Bhattacharya, P.; Townsend, S.; et al. Gut Microbes Egested during Bites of Infected Sand Flies Augment Severity of Leishmaniasis via Inflammasome-Derived IL-1beta. *Cell Host Microbe.* **2018**, *23* (1), 134-143.e6. <https://doi.org/10.1016/j.chom.2017.12.002>.
- (50) Peters, N. C.; Egen, J. G.; Secundino, N.; Debrabant, A.; Kimblin, N.; Kamhawi, S.; Lawyer, P.; Fay, M. P.; Germain, R. N.; Sacks, D. In Vivo Imaging Reveals an Essential Role for Neutrophils in Leishmaniasis Transmitted by Sand Flies. *Science.* **2008**, *321* (5891), 970-974. <https://doi.org/10.1126/science.1159194>.
- (51) John, B.; Hunter, C. A. Immunology. Neutrophil Soldiers or Trojan Horses? *Science.* **2008**, *321* (5891), 917–918. <https://doi.org/10.1126/science.1162914>.
- (52) Carlsen, E. D.; Liang, Y.; Shelite, T. R.; Walker, D. H.; Melby, P. C.; Soong, L.

- Permissive and Protective Roles for Neutrophils in Leishmaniasis. *Clin. Exp. Immunol.* **2015**, *182* (2), 109–118. <https://doi.org/10.1111/cei.12674>.
- (53) Gabriel, C.; McMaster, W. R.; Girard, D.; Descoteaux, A. Leishmania Donovanii Promastigotes Evade the Antimicrobial Activity of Neutrophil Extracellular Traps. *J. Immunol.* **2010**, *185* (7), 4319–4327. <https://doi.org/10.4049/jimmunol.1000893>.
- (54) Lira, R.; Rosales-Encina, J. L.; Arguello, C. Leishmania Mexicana: Binding of Promastigotes to Type I Collagen. *Exp. Parasitol.* **1997**, *85* (2), 149–157. <https://doi.org/10.1006/expr.1996.4127>.
- (55) Petropolis, D. B.; Rodrigues, J. C. F.; Viana, N. B.; Pontes, B.; Pereira, C. F. A.; Silva-Filho, F. C. Leishmania Amazonensis Promastigotes in 3D Collagen I Culture: An in Vitro Physiological Environment for the Study of Extracellular Matrix and Host Cell Interactions. *PeerJ* **2014**, *2*, e317. <https://doi.org/10.7717/peerj.317>.
- (56) Vannier-Santos, M. A.; Saraiva, E. M.; Martiny, A.; Neves, A.; de Souza, W. Fibronectin Shedding by Leishmania May Influence the Parasite-Macrophage Interaction. *Eur. J. Cell Biol.* **1992**, *59* (2), 389–397.
- (57) Kulkarni, M. M.; Jones, E. A.; McMaster, W. R.; McGwire, B. S. Fibronectin Binding and Proteolytic Degradation by Leishmania and Effects on Macrophage Activation. *Infect. Immun.* **2008**, *76* (4), 1738–1747. <https://doi.org/10.1128/IAI.01274-07>.
- (58) Figuera, L.; Acosta, H.; Gomez-Arreaza, A.; Davila-Vera, D.; Balza-Quintero, A.; Quinones, W.; Mendoza-Briceno, R. V.; Concepcion, J. L.; Avilan, L. Plasminogen Binding Proteins in Secreted Membrane Vesicles of Leishmania Mexicana. *Mol.*

- Biochem. Parasitol.* **2013**, *187* (1), 14–20.
<https://doi.org/10.1016/j.molbiopara.2012.11.002>.
- (59) Bandyopadhyay, K.; Karmakar, S.; Ghosh, A.; Das, P. K. Role of 67 KDa Cell Surface Laminin Binding Protein of *Leishmania Donovanii* in Pathogenesis. *J. Biochem.* **2001**, *130* (1), 141–148.
<https://doi.org/10.1093/oxfordjournals.jbchem.a002953>.
- (60) Fatoux-Ardore, M.; Peysselon, F.; Weiss, A.; Bastien, P.; Pratlong, F.; Ricard-Blum, S. Large-Scale Investigation of *Leishmania* Interaction Networks with Host Extracellular Matrix by Surface Plasmon Resonance Imaging. *Infect. Immun.* **2014**, *82* (2), 594–606. <https://doi.org/10.1128/IAI.01146-13>.
- (61) de Menezes, J. P.; Saraiva, E. M.; da Rocha-Azevedo, B. The Site of the Bite: *Leishmania* Interaction with Macrophages, Neutrophils and the Extracellular Matrix in the Dermis. *Parasit. Vectors* **2016**, *9*, 264. <https://doi.org/10.1186/s13071-016-1540-3>.
- (62) de Moura, T. R.; Oliveira, F.; Rodrigues, G. C.; Carneiro, M. W.; Fukutani, K. F.; Novais, F. O.; Miranda, J. C.; Barral-Netto, M.; Brodskyn, C.; Barral, A.; et al. Immunity to Lutzomyia Intermedia Saliva Modulates the Inflammatory Environment Induced by *Leishmania braziliensis*. *PLoS Negl. Trop. Dis.* **2010**, *4* (6), e712. <https://doi.org/10.1371/journal.pntd.0000712>.
- (63) Ueno, N.; Wilson, M. E. Receptor-Mediated Phagocytosis of *Leishmania*: Implications for Intracellular Survival. *Trends Parasitol.* **2012**, *28* (8), 335–344.
- (64) Ueno, N.; Bratt, C. L.; Rodriguez, N. E.; Wilson, M. E. Differences in Human

- Macrophage Receptor Usage , Lysosomal Fusion Kinetics and Survival between Logarithmic and Metacyclic *Leishmania infantum Chagasi* Promastigotes. *Cell Microbiol.* **2009**, *11* (12), 1827–1841. <https://doi.org/10.1111/j.1462-5822.2009.01374.x>.
- (65) Gagnon, E.; Duclos, S.; Rondeau, C.; Chevet, E.; Cameron, P. H.; Steele-Mortimer, O.; Paiement, J.; Bergeron, J. J. M.; Desjardins, M. Endoplasmic Reticulum-Mediated Phagocytosis Is a Mechanism of Entry into Macrophages. *Cell* **2002**, *110* (1), 119–131. [https://doi.org/10.1016/s0092-8674\(02\)00797-3](https://doi.org/10.1016/s0092-8674(02)00797-3).
- (66) Rodriguez, N. E.; Gaur Dixit, U.; Allen, L.-A. H.; Wilson, M. E. Stage-Specific Pathways of *Leishmania infantum Chagasi* Entry and Phagosome Maturation in Macrophages. *PLoS One* **2011**, *6* (4), e19000. <https://doi.org/10.1371/journal.pone.0019000>.
- (67) Forestier, C.-L.; Machu, C.; Loussert, C.; Pescher, P.; Spath, G. F. Imaging Host Cell-*Leishmania* Interaction Dynamics Implicates Parasite Motility, Lysosome Recruitment, and Host Cell Wounding in the Infection Process. *Cell Host Microbe* **2011**, *9* (4), 319–330. <https://doi.org/10.1016/j.chom.2011.03.011>.
- (68) Desjardins, M.; Descoteaux, A. Inhibition of Phagolysosomal Biogenesis by the *Leishmania* Lipophosphoglycan. *J. Exp. Med.* **1997**, *185* (12), 2061–2068. <https://doi.org/10.1084/jem.185.12.2061>.
- (69) Holm, É.; Tejle, K.; Magnusson, K. *Leishmania donovani* Lipophosphoglycan Causes Periphagosomal Actin Accumulation: Correlation with Impaired Translocation of PKC α and Defective Phagosome Maturation. *Cell Microbiol.*

- 2001**, 3 (7), 339-347.
- (70) Vinet, A. F.; Fukuda, M.; Turco, S. J.; Descoteaux, A. The Leishmania Donovanii Lipophosphoglycan Excludes the Vesicular Proton-ATPase from Phagosomes by Impairing the Recruitment of Synaptotagmin V. *PLoS Pathog.* **2009**, 5 (10), e1000628.
- (71) Srivastav, S.; Kar, S.; Chande, A. G.; Mukhopadhyaya, R.; Das, P. K. Leishmania Donovanii Exploits Host Deubiquitinating Enzyme A20, a Negative Regulator of TLR Signaling, to Subvert Host Immune Response. *J. Immunol.* **2012**, 189 (2), 924–934. <https://doi.org/10.4049/jimmunol.1102845>.
- (72) de Veer, M. J.; Curtis, J. M.; Baldwin, T. M.; DiDonato, J. A.; Sexton, A.; McConville, M. J.; Handman, E.; Schofield, L. MyD88 Is Essential for Clearance of Leishmania Major: Possible Role for Lipophosphoglycan and Toll-like Receptor 2 Signaling. *Eur. J. Immunol.* **2003**, 33 (10), 2822–2831. <https://doi.org/10.1002/eji.200324128>.
- (73) Srivastava, S.; Pandey, S. P.; Jha, M. K. Leishmania Expressed Lipophosphoglycan Interacts with Toll-like Receptor (TLR)-2 to Decrease TLR-9 Expression and Reduce Anti-Leishmanial Responses. *Clin. Exp. Immunol.* **2013**, 172 (3), 403–409. <https://doi.org/10.1111/cei.12074>.
- (74) Vivarini, A. de C.; Pereira, R. de M. S.; Teixeira, K. L. D.; Calegari-Silva, T. C.; Bellio, M.; Laurenti, M. D.; Corbett, C. E. P.; Gomes, C. M. de C.; Soares, R. P.; Silva, A. M.; et al. Human Cutaneous Leishmaniasis: Interferon-Dependent Expression of Double-Stranded RNA-Dependent Protein Kinase (PKR) via TLR2.

- FASEB J.* **2011**, 25 (12), 4162–4173. <https://doi.org/10.1096/fj.11-185165>.
- (75) Vargas-inchaustegui, D. A.; Tai, W.; Xin, L.; Hogg, A. E.; Corry, D. B.; Soong, L. Distinct Roles for MyD88 and Toll-Like Receptor 2 during Leishmania Braziliensis Infection in Mice. *Infect. Immun.* **2009**, 77 (7), 2948–2956. <https://doi.org/10.1128/IAI.00154-09>.
- (76) Galdino, H. J.; Saar Gomes, R.; Dos Santos, J. C.; Pessoni, L. L.; Maldaner, A. E.; Marques, S. M.; Gomes, C. M.; Dorta, M. L.; de Oliveira, M. A. P.; Joosten, L. A. B.; et al. Leishmania (Viannia) Braziliensis Amastigotes Induces the Expression of TNF α and IL-10 by Human Peripheral Blood Mononuclear Cells in Vitro in a TLR4-Dependent Manner. *Cytokine* **2016**, 88, 184–192. <https://doi.org/10.1016/j.cyto.2016.09.009>.
- (77) Tolouei, S.; Hejazi, S. H.; Ghaedi, K.; Khamesipour, A.; Hasheminia, S. J. TLR2 and TLR4 in Cutaneous Leishmaniasis Caused by Leishmania Major. *Scand. J. Immunol.* **2013**, 78 (5), 478–484. <https://doi.org/10.1111/sji.12105>.
- (78) Gupta, P.; Giri, J.; Srivastav, S.; Chande, A. G.; Mukhopadhyaya, R.; Das, P. K.; Ukil, A. Leishmania Donovani Targets Tumor Necrosis Factor Receptor-Associated Factor (TRAF) 3 for Impairing TLR4-Mediated Host Response. *FASEB J.* **2014**, 28 (4), 1756–1768. <https://doi.org/10.1096/fj.13-238428>.
- (79) Franco, L. H.; Fleuri, A. K. A.; Pellison, N. C.; Quirino, G. F. S.; Horta, C. V; Carvalho, R. V. H. De; Oliveira, S. C.; Zamboni, X. D. S. Autophagy Downstream of Endosomal Toll-like Receptor Signaling in Macrophages Is a Key Mechanism for Resistance to Leishmania Major Infection. *J. Biol. Chem.* **2017**, 292 (32), 13087–

13096. <https://doi.org/10.1074/jbc.M117.780981>.
- (80) Ives, A.; Ronet, C.; Prevel, F.; Ruzzante, G.; Fuertes-Marraco, S.; Schutz, F.; Zangerer, H.; Revaz-Breton, M.; Lye, L.-F.; Hickerson, S. M.; et al. Leishmania RNA Virus Controls the Severity of Mucocutaneous Leishmaniasis. *Science* **2011**, *331* (6018), 775–778. <https://doi.org/10.1126/science.1199326>.
- (81) Mathur, R. K.; Awasthi, A.; Wadhone, P.; Ramanamurthy, B.; Saha, B. Reciprocal CD40 Signals through P38MAPK and ERK-1 / 2 Induce Counteracting Immune Responses. *Nat. Med.* **2004**, *10* (5), 1–6. <https://doi.org/10.1038/nm1045>.
- (82) Rub, A.; Dey, R.; Jadhav, M.; Kamat, R.; Chakkaramakkil, S.; Majumdar, S.; Mukhopadhyaya, R.; Saha, B. Cholesterol Depletion Associated with Leishmania Major Infection Alters Macrophage CD40 Signalosome Composition and Effector Function. *Nat. Immunol.* **2009**, *10* (3), 273–280. <https://doi.org/10.1038/ni.1705>.
- (83) Chandel, H. S.; Pandey, S. P.; Shukla, D. Toll-like Receptors and CD40 Modulate Each Other’s Expression Affecting Leishmania Major Infection. *Clin. Exp. Immunol.* **2014**, *176* (2), 283–290. <https://doi.org/10.1111/cei.12264>.
- (84) Bhattacharyya, S.; Ghosh, S.; Sen, P.; Roy, S.; Majumdar, S. Selective Impairment of Protein Kinase C Isotypes in Murine Macrophage by Leishmania Donovani. *Mol. Cell. Biochem.* **2001**, *216* (1–2), 47–57. <https://doi.org/10.1023/a:1011048210691>.
- (85) Sudan, R.; Srivastava, N.; Pandey, S. P.; Majumdar, S.; Saha, B. Reciprocal Regulation of Protein Kinase C Isoforms Results in Differential Cellular Responsiveness. *J. Immunol.* **2012**, *188* (5), 2328–2337. <https://doi.org/10.4049/jimmunol.1101678>.

- (86) Srivastava, N.; Sudan, R.; Saha, B. CD40-Modulated Dual-Specificity Phosphatases MAPK Phosphatase (MKP)-1 and MKP-3 Reciprocally Regulate Leishmania Major Infection. *J. Immunol.* **2011**, *186* (10), 5863–5872. <https://doi.org/10.4049/jimmunol.1003957>.
- (87) Khan, T. H.; Srivastava, N.; Srivastava, A.; Sareen, A.; Mathur, R. K.; Chande, A. G.; Musti, K. V; Roy, S.; Mukhopadhyaya, R.; Saha, B. SHP-1 Plays a Crucial Role in CD40 Signaling Reciprocity. *J. Immunol.* **2014**, *193* (7), 3644–3653. <https://doi.org/10.4049/jimmunol.1400620>.
- (88) Silverman, J. M.; Clos, J.; De’Oliveira, C. C.; Shirvani, O.; Fang, Y.; Wang, C.; Foster, L. J.; Reiner, N. E. An Exosome-Based Secretion Pathway Is Responsible for Protein Export from Leishmania and Communication with Macrophages. *J. Cell Sci.* **2010**, *123* (6), 842–852. <https://doi.org/10.1242/jcs.056465>.
- (89) Lambertz, U.; Silverman, J. M.; Nandan, D.; Mcmaster, W. R.; Clos, J.; Foster, L. J.; Reiner, N. E. Secreted Virulence Factors and Immune Evasion in Visceral Leishmaniasis. *J. Leukoc. Biol.* **2012**, *91* (6), 887–899. <https://doi.org/10.1189/jlb.0611326>.
- (90) Forget, G.; Gregory, D. J.; Olivier, M. Proteasome-Mediated Degradation of STAT1alpha Following Infection of Macrophages with Leishmania Donovani. *J. Biol. Chem.* **2005**, *280* (34), 30542–30549. <https://doi.org/10.1074/jbc.M414126200>.
- (91) Courret, N.; Prina, E.; Mougneau, E.; Saraiva, E. M.; David, L.; Glaichenhaus, N.; Antoine, J. Presentation of the Leishmania Antigen LACK by Infected Macrophages

- Is Dependent upon the Virulence of the Phagocytosed Parasites. *Eur. J. Immunol.* **1999**, *29* (3), 762–773.
- (92) De Souza Leao, S.; Lang, T.; Prina, E.; Hellio, R.; Antoine, J. C. Intracellular Leishmania Amazonensis Amastigotes Internalize and Degrade MHC Class II Molecules of Their Host Cells. *J. Cell Sci.* **1995**, *108* (Pt 10), 3219–3231.
- (93) Roy, K.; Mandloi, S.; Chakrabarti, S.; Roy, S. Cholesterol Corrects Altered Conformation of MHC-II Protein in Leishmania Donovani Infected Macrophages : Implication in Therapy. *PLoS Negl. Trop. Dis.* **2016**, *10* (5), e0004710. <https://doi.org/10.1371/journal.pntd.0004710>.
- (94) Antoine, J. C.; Lang, T.; Prina, E.; Courret, N.; Hellio, R. H-2M Molecules, like MHC Class II Molecules, Are Targeted to Parasitophorous Vacuoles of Leishmania-Infected Macrophages and Internalized by Amastigotes of L. Amazonensis and L. Mexicana. *J. Cell Sci.* **1999**, *112* (15), 2559–2570.
- (95) Saha, B.; Das, G.; Vohra, H.; Ganguly, N. K.; Mishra, G. C. Macrophage-T Cell Interaction in Experimental Visceral Leishmaniasis: Failure to Express Costimulatory Molecules on Leishmania-infected Macrophages and Its Implication in the Suppression of Cell-mediated Immunity. *Eur. J. Immunol.* **1995**, *25* (9), 2492–2498. <https://doi.org/10.1002/eji.1830250913>.
- (96) Roy, S.; Gupta, P.; Palit, S.; Basu, M.; Ukil, A.; Das, P. K. The Role of PD-1 in Regulation of Macrophage Apoptosis and Its Subversion by Leishmania Donovani. *Clin. Transl. Immunol.* **2017**, *6* (5), e137.
- (97) Teixeira, C.; Gomes, R. Experimental Models in Vaccine Research : Malaria and

- Leishmaniasis. *Braz. J. Med. Biol. Res.* **2013**, *46* (2), 109–116.
- (98) Mauel, J.; Behin, R.; Louis, J. Leishmania Enriettii: Immune Induction of Macrophage Activation in an Experimental Model of Immunoprophylaxis in the Mouse. *Exp. Parasitol.* **1981**, *52* (3), 331–345. [https://doi.org/10.1016/0014-4894\(81\)90091-6](https://doi.org/10.1016/0014-4894(81)90091-6).
- (99) Preston, P. M.; Dumonde, D. C. Experimental Cutaneous Leishmaniasis. V. Protective Immunity in Subclinical and Self-Healing Infection in the Mouse. *Clin. Exp. Immunol.* **1976**, *23* (1), 126–138.
- (100) Handman, E. Leishmaniasis: Current Status of Vaccine Development. *Clin. Microbiol. Rev.* **2001**, *14* (2), 229–243. <https://doi.org/10.1128/CMR.14.2.229>.
- (101) Gupta, S. Visceral Leishmaniasis: Experimental Models for Drug Discovery. *Indian J. Med. Res.* **2011**, *133*, 27–39.
- (102) Chang, K. P.; Dwyer, D. M. Leishmania Donovanii Hamster Macrophage Interactions in Vitro: Cell Entry, Intracellular Survival, and Multiplication of Amastigotes. *J. Exp. Med.* **1978**, *147* (2), 515–530. <https://doi.org/10.1084/jem.147.2.515>.
- (103) Loria-Cervera, E. N.; Andrade-Narvaez, F. J. Animal Models for the Study of Leishmaniasis Immunology. *Rev. Inst. Med. Trop. Sao Paulo* **2014**, *56* (1), 1–11. <https://doi.org/10.1590/S0036-46652014000100001>.
- (104) Baneth, G.; Koutinas, A. F.; Solano-Gallego, L.; Bourdeau, P.; Ferrer, L. Canine Leishmaniosis - New Concepts and Insights on an Expanding Zoonosis: Part One. *Trends Parasitol.* **2008**, *24* (7), 324–330. <https://doi.org/10.1016/j.pt.2008.04.001>.

- (105) Chang, K. P. Leishmanicidal Mechanisms of Human Polymorphonuclear Phagocytes. *Am. J. Trop. Med. Hyg.* **1981**, *30* (2), 322–333.
<https://doi.org/10.4269/ajtmh.1981.30.322>.
- (106) Pearson, R. D.; Steigbigel, R. T. Phagocytosis and Killing of the Protozoan *Leishmania Donovani* by Human Polymorphonuclear Leukocytes. *J. Immunol.* **1981**, *127* (4), 1438–1443.
- (107) Brinkmann, V.; Reichard, U.; Goosmann, C.; Fauler, B.; Uhlemann, Y.; Weiss, D. S.; Weinrauch, Y.; Zychlinsky, A. Neutrophil Extracellular Traps Kill Bacteria. *Science*. **2004**, *303* (5663), 1532–1535.
- (108) Fuchs, T. A.; Abed, U.; Goosmann, C.; Hurwitz, R.; Schulze, I.; Wahn, V.; Weinrauch, Y.; Brinkmann, V.; Zychlinsky, A. Novel Cell Death Program Leads to Neutrophil Extracellular Traps. *J. Cell Biol.* **2007**, *176* (2), 231–241.
<https://doi.org/10.1083/jcb.200606027>.
- (109) Guimaraes-Costa, A. B.; Nascimento, M. T. C.; Froment, G. S.; Soares, R. P. P.; Morgado, F. N.; Conceicao-Silva, F.; Saraiva, E. M. *Leishmania Amazonensis* Promastigotes Induce and Are Killed by Neutrophil Extracellular Traps. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106* (16), 6748–6753.
<https://doi.org/10.1073/pnas.0900226106>.
- (110) Rochael, N. C.; Guimaraes-Costa, A. B.; Nascimento, M. T. C.; DeSouza-Vieira, T. S.; Oliveira, M. P.; Garcia e Souza, L. F.; Oliveira, M. F.; Saraiva, E. M. Classical ROS-Dependent and Early/Rapid ROS-Independent Release of Neutrophil Extracellular Traps Triggered by *Leishmania* Parasites. *Sci. Rep.* **2015**, *5*, 18302.

- https://doi.org/10.1038/srep18302.
- (111) Hurrell, B. P.; Regli, I. B.; Tacchini-Cottier, F. Different Leishmania Species Drive Distinct Neutrophil Functions. *Trends Parasitol.* **2016**, *32* (5), 392–401. https://doi.org/10.1016/j.pt.2016.02.003.
- (112) Oualha, R.; Barhoumi, M.; Marzouki, S.; Harigua-souiai, E. Infection of Human Neutrophils With Leishmania Infantum or Leishmania Major Strains Triggers Activation and Differential Cytokines Release. *Front Cell Infect Microbiol.* **2019**, *9*, 153. https://doi.org/10.3389/fcimb.2019.00153.
- (113) Davis, R. E.; Thalhofer, C. J.; Wilson, M. E. Infection and Activation of Human Neutrophils with Fluorescent Leishmania Infantum. *J. Immunol. Tech. Infect. Dis.* **2016**, *5* (3). https://doi.org/10.4172/2329-9541.1000146.
- (114) Falcao, S. A. C.; Weinkopff, T.; Hurrell, B. P.; Celes, F. S.; Curvelo, R. P.; Prates, D. B.; Barral, A.; Borges, V. M.; Tacchini-Cottier, F.; de Oliveira, C. I. Exposure to Leishmania braziliensis Triggers Neutrophil Activation and Apoptosis. *PLoS Negl. Trop. Dis.* **2015**, *9* (3), e0003601. https://doi.org/10.1371/journal.pntd.0003601.
- (115) Afonso, L.; Borges, V. M.; Cruz, H.; Ribeiro-Gomes, F. L.; DosReis, G. A.; Dutra, A. N.; Clarencio, J.; de Oliveira, C. I.; Barral, A.; Barral-Netto, M.; et al. Interactions with Apoptotic but Not with Necrotic Neutrophils Increase Parasite Burden in Human Macrophages Infected with Leishmania Amazonensis. *J. Leukoc. Biol.* **2008**, *84* (2), 389–396. https://doi.org/10.1189/jlb.0108018.
- (116) Farah, F. S.; Samra, S. A. The Role of the Macrophage in Cutaneous Leishmaniasis. *Immunology.* **1975**, *(29)* 4, 755–764.

- (117) Iniesta, V.; Gomez-Nieto, L. C.; Corraliza, I. The Inhibition of Arginase by N(Omega)-Hydroxy-l-Arginine Controls the Growth of Leishmania inside Macrophages. *J. Exp. Med.* **2001**, *193* (6), 777–784. <https://doi.org/10.1084/jem.193.6.777>.
- (118) Iniesta, V.; Gomez-Nieto, L. C.; Molano, I.; Mohedano, A.; Carcelen, J.; Miron, C.; Alonso, C.; Corraliza, I. Arginase I Induction in Macrophages, Triggered by Th2-Type Cytokines, Supports the Growth of Intracellular Leishmania Parasites. *Parasite Immunol.* **2002**, *24* (3), 113–118. <https://doi.org/10.1046/j.1365-3024.2002.00444.x>.
- (119) Wei, X.; Charles, I. G.; Smith, A.; Ure, J.; Feng, G.; Huang, F.; Xu, D.; Mullers, W.; Moncada, S.; Liew, F. Y. Altered Immune Responses in Mice Lacking Inducible Nitric Oxide Synthase. *Nature* **1995**, *375* (6530), 408–411. <https://doi.org/10.1038/375408a0>.
- (120) Mukbel, R. M.; Patten, C. J.; Gibson, K.; Ghosh, M.; Petersen, C.; Jones, D. E. Macrophage Killing of Leishmania Amazonensis Amastigotes Requires Both Nitric Oxide and Superoxide. *Am. J. Trop. Med. Hyg.* **2007**, *76* (4), 669–675.
- (121) Trinchieri, G. Interleukin-12: A Cytokine at the Interface of Inflammation and Immunity. *Adv. Immunol.* **1998**, *70*, 83–243.
- (122) Fonseca, S. G.; Romao, P. R. T.; Figueiredo, F.; Morais, R. H.; Lima, H. C.; Ferreira, S. H.; Cunha, F. Q. TNF-Alpha Mediates the Induction of Nitric Oxide Synthase in Macrophages but Not in Neutrophils in Experimental Cutaneous Leishmaniasis. *Eur. J. Immunol.* **2003**, *33* (8), 2297–2306.

- https://doi.org/10.1002/eji.200320335.
- (123) Singh, N.; Kumar, R.; Engwerda, C.; Sacks, D.; Nylen, S.; Sundar, S. Tumor Necrosis Factor Alpha Neutralization Has No Direct Effect on Parasite Burden, but Causes Impaired IFN- γ Production by Spleen Cells from Human Visceral Leishmaniasis Patients. *Cytokine* **2016**, *85*, 184–190.
https://doi.org/10.1016/j.cyto.2016.06.013.
- (124) Bajenoff, M.; Breart, B.; Huang, A. Y. C.; Qi, H.; Cazareth, J.; Braud, V. M.; Germain, R. N.; Glaichenhaus, N. Natural Killer Cell Behavior in Lymph Nodes Revealed by Static and Real-Time Imaging. *J. Exp. Med.* **2006**, *203* (3), 619–631.
https://doi.org/10.1084/jem.20051474.
- (125) Ritter, U.; Meissner, A.; Scheidig, C.; Korner, H. CD8 Alpha- and Langerin-Negative Dendritic Cells, but Not Langerhans Cells, Act as Principal Antigen-Presenting Cells in Leishmaniasis. *Eur. J. Immunol.* **2004**, *34* (6), 1542–1550.
https://doi.org/10.1002/eji.200324586.
- (126) Gorak, P. M.; Engwerda, C. R.; Kaye, P. M. Dendritic Cells, but Not Macrophages, Produce IL-12 Immediately Following Leishmania Donovani Infection. *Eur. J. Immunol.* **1998**, *28* (2), 687–695. https://doi.org/10.1002/(SICI)1521-4141(199802)28:02<687::AID-IMMU687>3.0.CO;2-N.
- (127) Von Stebut, E. Immunology of Cutaneous Leishmaniasis: The Role of Mast Cells, Phagocytes and Dendritic Cells for Protective Immunity. *Eur. J. Dermatol.* **2007**, *17* (2), 115–122. https://doi.org/10.1684/ejd.2007.0122.
- (128) Bennett, C. L.; Misslitz, A.; Colledge, L.; Aebscher, T.; Blackburn, C. C. Silent

- Infection of Bone Marrow-Derived Dendritic Cells by Leishmania Mexicana Amastigotes. *Eur. J. Immunol.* **2001**, *31* (3), 876–883. [https://doi.org/10.1002/1521-4141\(200103\)31:3<876::AID-IMMU876gt;3.0.CO;2-I](https://doi.org/10.1002/1521-4141(200103)31:3<876::AID-IMMU876gt;3.0.CO;2-I).
- (129) Xin, L.; Li, K.; Soong, L. Down-Regulation of Dendritic Cell Signaling Pathways by Leishmania Amazonensis Amastigotes. *Mol. Immunol.* **2008**, *45* (12), 3371–3382. <https://doi.org/10.1016/j.molimm.2008.04.018>.
- (130) Kedzierski, L.; Evans, K. J. Immune Responses during Cutaneous and Visceral Leishmaniasis. *Parasitology* **2014**, *141* (12), 1544–1562. <https://doi.org/10.1017/S003118201400095X>.
- (131) Maasho, K.; Sanchez, F.; Schurr, E.; Hailu, A.; Akuffo, H. Indications of the Protective Role of Natural Killer Cells in Human Cutaneous Leishmaniasis in an Area of Endemicity. *Infect. Immun.* **1998**, *66* (6), 2698–2704.
- (132) Zamora-Chimal, J.; Fernandez-Figueroa, E. A.; Ruiz-Remigio, A.; Wilkins-Rodriguez, A. A.; Delgado-Dominguez, J.; Salaiza-Suazo, N.; Gutierrez-Kobeh, L.; Becker, I. NKT Cell Activation by Leishmania Mexicana LPG: Description of a Novel Pathway. *Immunobiology* **2017**, *222* (2), 454–462. <https://doi.org/10.1016/j.imbio.2016.08.003>.
- (133) Scott, P. The Role of TH1 and TH2 Cells in Experimental Cutaneous Leishmaniasis. *Exp. Parasitol.* **1989**, *68* (3), 369–372. [https://doi.org/10.1016/0014-4894\(89\)90120-3](https://doi.org/10.1016/0014-4894(89)90120-3).
- (134) Sacks, D.; Noben-Trauth, N. The Immunology of Susceptibility and Resistance to Leishmania Major in Mice. *Nat. Rev. Immunol.* **2002**, *2* (11), 845–858.

- https://doi.org/10.1038/nri933.
- (135) Uzonna, J. E.; Späth, G. F.; Beverley, S. M.; Scott, P. Vaccination with Phosphoglycan-Deficient Leishmania Major Protects Highly Susceptible Mice from Virulent Challenge without Inducing a Strong Th1 Response. *J. Immunol.* **2004**, *172* (6), 3793–3797.
- (136) Stober, C. B.; Lange, U. G.; Roberts, M. T. M.; Alcami, A.; Blackwell, J. M. IL-10 from Regulatory T Cells Determines Vaccine Efficacy in Murine Leishmania Major Infection. *J. Immunol.* **2005**, *175* (4), 2517–2524.
https://doi.org/10.4049/jimmunol.175.4.2517.
- (137) Kedzierski, L.; Curtis, J. M.; Doherty, P. C.; Handman, E.; Kedzierska, K. Decreased IL-10 and IL-13 Production and Increased CD44hi T Cell Recruitment Contribute to Leishmania Major Immunity Induced by Non-Persistent Parasites. *Eur. J. Immunol.* **2008**, *38* (11), 3090–3100. https://doi.org/10.1002/eji.200838423.
- (138) Belkaid, Y.; Piccirillo, C. A.; Mendez, S.; Shevach, E. M.; Sacks, D. L. CD4+CD25+ Regulatory T Cells Control Leishmania Major Persistence and Immunity. *Nature* **2002**, *420* (6915), 502–507. https://doi.org/10.1038/nature01152.
- (139) Belkaid, Y.; Hoffmann, K. F.; Mendez, S.; Kamhawi, S.; Udey, M. C.; Wynn, T. A.; Sacks, D. L. The Role of Interleukin (IL)-10 in the Persistence of Leishmania Major in the Skin after Healing and the Therapeutic Potential of Anti-IL-10 Receptor Antibody for Sterile Cure. *J. Exp. Med.* **2001**, *194* (10), 1497–1506.
https://doi.org/10.1084/jem.194.10.1497.
- (140) Campanelli, A. P.; Roselino, A. M.; Cavassani, K. A.; Pereira, M. S. F.; Mortara, R.

- A.; Brodskyn, C. I.; Goncalves, H. S.; Belkaid, Y.; Barral-Netto, M.; Barral, A.; et al. CD4+CD25+ T Cells in Skin Lesions of Patients with Cutaneous Leishmaniasis Exhibit Phenotypic and Functional Characteristics of Natural Regulatory T Cells. *J. Infect. Dis.* **2006**, *193* (9), 1313–1322. <https://doi.org/10.1086/502980>.
- (141) Brown, D. R.; Reiner, S. L. Polarized Helper-T-Cell Responses against Leishmania Major in the Absence of B Cells. *Infect. Immun.* **1999**, *67* (1), 266–270.
- (142) Ronet, C.; Voigt, H.; Himmelrich, H.; Doucey, M.-A.; Hauyon-La Torre, Y.; Revaz-Breton, M.; Tacchini-Cottier, F.; Bron, C.; Louis, J.; Launois, P. Leishmania Major-Specific B Cells Are Necessary for Th2 Cell Development and Susceptibility to L. Major LV39 in BALB/c Mice. *J. Immunol.* **2008**, *180* (7), 4825–4835. <https://doi.org/10.4049/jimmunol.180.7.4825>.
- (143) Ronet, C.; Hauyon-La Torre, Y.; Revaz-Breton, M.; Mastelic, B.; Tacchini-Cottier, F.; Louis, J.; Launois, P. Regulatory B Cells Shape the Development of Th2 Immune Responses in BALB/c Mice Infected with Leishmania Major through IL-10 Production. *J. Immunol.* **2010**, *184* (2), 886–894. <https://doi.org/10.4049/jimmunol.0901114>.
- (144) Chu, N.; Thomas, B. N.; Patel, S. R.; Buxbaum, L. U. IgG1 Is Pathogenic in Leishmania Mexicana Infection. *J. Immunol.* **2010**, *185* (11), 6939–6946. <https://doi.org/10.4049/jimmunol.1002484>.
- (145) Rostamian, M.; Sohrabi, S.; Kavosifard, H.; Niknam, H. M. Lower Levels of IgG1 in Comparison with IgG2a Are Associated with Protective Immunity against Leishmania Tropica Infection in BALB/c Mice. *J. Microbiol. Immunol. Infect.* **2017**,

- 50 (2), 160–166. <https://doi.org/https://doi.org/10.1016/j.jmii.2015.05.007>.
- (146) Heinzel, F. P.; Ahmed, F.; Hujer, A. M.; Rerko, R. M. Immunoregulation of Murine Leishmaniasis by Interleukin-12. *Res. Immunol.* **1995**, *146* (7–8), 575–581.
- (147) Heinzel, F. P.; Rerko, R. M.; Ahmed, F.; Pearlman, E. Endogenous IL-12 Is Required for Control of Th2 Cytokine Responses Capable of Exacerbating Leishmaniasis in Normally Resistant Mice. *J. Immunol.* **1995**, *155* (2), 730–739.
- (148) von Stebut, E.; Belkaid, Y.; Jakob, T.; Sacks, D. L.; Udey, M. C. Uptake of Leishmania Major Amastigotes Results in Activation and Interleukin 12 Release from Murine Skin-Derived Dendritic Cells: Implications for the Initiation of Anti-Leishmania Immunity. *J. Exp. Med.* **1998**, *188* (8), 1547–1552. <https://doi.org/10.1084/jem.188.8.1547>.
- (149) Scharton-Kersten, T.; Afonso, L. C.; Wysocka, M.; Trinchieri, G.; Scott, P. IL-12 Is Required for Natural Killer Cell Activation and Subsequent T Helper 1 Cell Development in Experimental Leishmaniasis. *J. Immunol.* **1995**, *154* (10), 5320–5330.
- (150) Martinez-Lopez, M.; Iborra, S.; Conde-Garrosa, R.; Sancho, D. Batf3-Dependent CD103+ Dendritic Cells Are Major Producers of IL-12 That Drive Local Th1 Immunity against Leishmania Major Infection in Mice. *Eur. J. Immunol.* **2015**, *45* (1), 119–129. <https://doi.org/10.1002/eji.201444651>.
- (151) Favila, M. A.; Geraci, N. S.; Zeng, E.; Harker, B.; Condon, D.; Cotton, R. N.; Jayakumar, A.; Tripathi, V.; McDowell, M. A. Human Dendritic Cells Exhibit a Pronounced Type I IFN Signature Following Leishmania Major Infection That Is

- Required for IL-12 Induction. *J. Immunol.* **2014**, *192* (12), 5863–5872.
<https://doi.org/10.4049/jimmunol.1203230>.
- (152) Akbari, M.; Honma, K.; Kimura, D.; Miyakoda, M.; Kimura, K.; Matsuyama, T.; Yui, K. IRF4 in Dendritic Cells Inhibits IL-12 Production and Controls Th1 Immune Responses against Leishmania Major. *J. Immunol.* **2014**, *192* (5), 2271–2279. <https://doi.org/10.4049/jimmunol.1301914>.
- (153) Okwor, I.; Jia, P.; Uzonna, J. E. Interaction of Macrophage Antigen 1 and CD40 Ligand Leads to IL-12 Production and Resistance in CD40-Deficient Mice Infected with Leishmania Major. *J. Immunol.* **2015**, *195* (7), 3218–3226.
<https://doi.org/10.4049/jimmunol.1500922>.
- (154) Pakpour, N.; Zaph, C.; Scott, P. The Central Memory CD4+ T Cell Population Generated during Leishmania Major Infection Requires IL-12 to Produce IFN-Gamma. *J. Immunol.* **2008**, *180* (12), 8299–8305.
<https://doi.org/10.4049/jimmunol.180.12.8299>.
- (155) Reiner, S. L.; Locksley, R. M. The Regulation of Immunity to Leishmania Major. *Annu. Rev. Immunol.* **1995**, *13*, 151–177.
<https://doi.org/10.1146/annurev.iy.13.040195.001055>.
- (156) Kolde, G.; Luger, T.; Sorg, C.; Sunderkotter, C. Successful Treatment of Cutaneous Leishmaniasis Using Systemic Interferon-Gamma. *Dermatology* **1996**, *192* (1), 56–60. <https://doi.org/10.1159/000246316>.
- (157) Nacy, C. A.; Meierovics, A. I.; Belosevic, M.; Green, S. J. Tumor Necrosis Factor-Alpha: Central Regulatory Cytokine in the Induction of Macrophage Antimicrobial

- Activities. *Pathobiology* **1991**, *59* (3), 182–184. <https://doi.org/10.1159/000163640>.
- (158) Gessner, A.; Vieth, M.; Will, A.; Schröppel, K.; Röllinghoff, M. Interleukin-7 Enhances Antimicrobial Activity against Leishmania Major in Murine Macrophages. *Infect. Immun.* **1993**, *61* (9), 4008–4012.
- (159) Carneiro, M. B. H.; Lopes, M. E. de M.; Vaz, L. G.; Sousa, L. M. A.; dos Santos, L. M.; de Souza, C. C.; Campos, A. C. de A.; Gomes, D. A.; Goncalves, R.; Tafuri, W. L.; et al. IFN-Gamma-Dependent Recruitment of CD4(+) T Cells and Macrophages Contributes to Pathogenesis During Leishmania Amazonensis Infection. *J. Interferon Cytokine Res.* **2015**, *35* (12), 935–947. <https://doi.org/10.1089/jir.2015.0043>.
- (160) Ota, H.; Takashima, Y.; Matsumoto, Y.; Hayashi, Y.; Matsumoto, Y. Pretreatment of Macrophages with the Combination of IFN-Gamma and IL-12 Induces Resistance to Leishmania Major at the Early Phase of Infection. *J. Vet. Med. Sci.* **2008**, *70* (6), 589–593. <https://doi.org/10.1292/jvms.70.589>.
- (161) Titus, R. G.; Sherry, B.; Cerami, A. Tumor Necrosis Factor Plays a Protective Role in Experimental Murine Cutaneous Leishmaniasis. *J. Exp. Med.* **1989**, *170* (6), 2097–2104. <https://doi.org/10.1084/jem.170.6.2097>.
- (162) Moll, H.; Binoder, K.; Bogdan, C.; Solbach, W.; Rollinghoff, M. Production of Tumour Necrosis Factor during Murine Cutaneous Leishmaniasis. *Parasite Immunol.* **1990**, *12* (5), 483–494. <https://doi.org/10.1111/j.1365-3024.1990.tb00983.x>.
- (163) Nateghi Rostami, M.; Seyyedan Jasbi, E.; Khamesipour, A.; Mohammadi, A. M.

- Tumour Necrosis Factor-Alpha (TNF-Alpha) and Its Soluble Receptor Type 1 (STNFR I) in Human Active and Healed Leishmaniases. *Parasite Immunol.* **2016**, *38* (4), 255–260. <https://doi.org/10.1111/pim.12305>.
- (164) Nieto Gomez, P.; Casas Hidalgo, I.; Casas Hidalgo, M. de la P.; Alvarez Sanchez, R.; Rodriguez Delgado, A.; Cabeza-Barrera, J. Cutaneous Leishmaniasis Associated with TNF-Alpha Blockers: A Case Report. *European journal of hospital pharmacy : science and practice.* **2019**, *26* (4), 233–234. <https://doi.org/10.1136/ejhhpharm-2018-001521>.
- (165) Polari, L. P.; Carneiro, P. P.; Macedo, M.; Machado, P. R. L.; Scott, P.; Carvalho, E. M.; Bacellar, O. Leishmania Braziliensis Infection Enhances Toll-Like Receptors 2 and 4 Expression and Triggers TNF-Alpha and IL-10 Production in Human Cutaneous Leishmaniasis. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 120. <https://doi.org/10.3389/fcimb.2019.00120>.
- (166) Boulay, J.-L.; O’Shea, J. J.; Paul, W. E. Molecular Phylogeny within Type I Cytokines and Their Cognate Receptors. *Immunity* **2003**, *19* (2), 159–163.
- (167) Oppmann, B.; Lesley, R.; Blom, B.; Timans, J. C.; Xu, Y.; Hunte, B.; Vega, F.; Yu, N.; Wang, J.; Singh, K.; et al. Novel P19 Protein Engages IL-12p40 to Form a Cytokine, IL-23, with Biological Activities Similar as Well as Distinct from IL-12. *Immunity* **2000**, *13* (5), 715–725.
- (168) Yoshida, H.; Hamano, S.; Senaldi, G.; Covey, T.; Faggioni, R.; Mu, S.; Xia, M.; Wakeham, A. C.; Nishina, H.; Potter, J.; et al. WSX-1 Is Required for the Initiation of Th1 Responses and Resistance to L. Major Infection. *Immunity* **2001**, *15* (4),

- 569–578.
- (169) Tolouei, S.; Ghaedi, K.; Khamesipour, A.; Akbari, M.; Baghaei, M.; Hasheminia, S.; Narimani, M.; Hejazi, S. IL-23 and IL-27 Levels in Macrophages Collected from Peripheral Blood of Patients with Healing Vs Non-Healing Form of Cutaneous Leishmaniasis. *Iran. J. Parasitol.* **2012**, *7* (1), 18–25.
- (170) Scott, P.; Natovitz, P.; Coffman, R. L.; Pearce, E.; Sher, A. Immunoregulation of Cutaneous Leishmaniasis. T Cell Lines That Transfer Protective Immunity or Exacerbation Belong to Different T Helper Subsets and Respond to Distinct Parasite Antigens. *J. Exp. Med.* **1988**, *168* (5), 1675–1684.
<https://doi.org/10.1084/jem.168.5.1675>.
- (171) Carter, K. C.; Gallagher, G.; Baillie, A. J.; Alexander, J. The Induction of Protective Immunity to Leishmania Major in the BALB/c Mouse by Interleukin 4 Treatment. *Eur. J. Immunol.* **1989**, *19* (4), 779–782. <https://doi.org/10.1002/eji.1830190432>.
- (172) Nakaya, M.; Hamano, S.; Kawasumi, M.; Yoshida, H.; Yoshimura, A.; Kobayashi, T. Aberrant IL-4 Production by SOCS3-over-Expressing T Cells during Infection with Leishmania Major Exacerbates Disease Manifestations. *Int. Immunol.* **2011**, *23* (3), 195–202. <https://doi.org/10.1093/intimm/dxq472>.
- (173) Costa, D. L.; Carregaro, V.; Lima-Junior, D. S.; Silva, N. M.; Milanezi, C. M.; Cardoso, C. R.; Giudice, A.; de Jesus, A. R.; Carvalho, E. M.; Almeida, R. P.; et al. BALB/c Mice Infected with Antimony Treatment Refractory Isolate of Leishmania Braziliensis Present Severe Lesions Due to IL-4 Production. *PLoS Negl. Trop. Dis.* **2011**, *5* (3), e965. <https://doi.org/10.1371/journal.pntd.0000965>.

- (174) Lazarski, C. A.; Ford, J.; Katzman, S. D.; Rosenberg, A. F.; Fowell, D. J. IL-4 Attenuates Th1-Associated Chemokine Expression and Th1 Trafficking to Inflamed Tissues and Limits Pathogen Clearance. *PLoS One* **2013**, *8* (8), e71949. <https://doi.org/10.1371/journal.pone.0071949>.
- (175) Moore, K. W.; de Waal Malefydt, R.; Coffman, R. L.; O'Garra, A. Interleukin-10 and the Interleukin-10 Receptor. *Annu. Rev. Immunol.* **2001**, *19*, 683–765. <https://doi.org/10.1146/annurev.immunol.19.1.683>.
- (176) Melby, P. C.; Andrade-Narvaez, F.; Darnell, B. J.; Valencia-Pacheco, G. In Situ Expression of Interleukin-10 and Interleukin-12 in Active Human Cutaneous Leishmaniasis. *FEMS Immunol. Med. Microbiol.* **1996**, *15* (2–3), 101–107. <https://doi.org/10.1111/j.1574-695X.1996.tb00059.x>.
- (177) O'Garra, A.; Vieira, P. TH1 Cells Control Themselves by Producing Interleukin-10. *Nat. Rev. Immunol.* **2007**, *7* (6), 425.
- (178) Carvalho, A. M.; Cristal, J. R.; Muniz, A. C.; Carvalho, L. P.; Gomes, R.; Miranda, J. C.; Barral, A.; Carvalho, E. M.; de Oliveira, C. I. Interleukin 10-Dominant Immune Response and Increased Risk of Cutaneous Leishmaniasis After Natural Exposure to Lutzomyia Intermedia Sand Flies. *J. Infect. Dis.* **2015**, *212* (1), 157–165. <https://doi.org/10.1093/infdis/jiv020>.
- (179) Noben-Trauth, N.; Kropf, P.; Muller, I. Susceptibility to *Leishmania* Major Infection in Interleukin-4-Deficient Mice. *Science* **1996**, *271* (5251), 987–990. <https://doi.org/10.1126/science.271.5251.987>.
- (180) Noben-Trauth, N.; Lira, R.; Nagase, H.; Paul, W. E.; Sacks, D. L. The Relative

- Contribution of IL-4 Receptor Signaling and IL-10 to Susceptibility to Leishmania Major. *J. Immunol.* **2003**, *170* (10), 5152–5158.
<https://doi.org/10.4049/jimmunol.170.10.5152>.
- (181) Nagase, H.; Jones, K. M.; Anderson, C. F.; Noben-Trauth, N. Despite Increased CD4+Foxp3+ Cells within the Infection Site, BALB/c IL-4 Receptor-Deficient Mice Reveal CD4+Foxp3-Negative T Cells as a Source of IL-10 in Leishmania Major Susceptibility. *J. Immunol.* **2007**, *179* (4), 2435–2444.
<https://doi.org/10.4049/jimmunol.179.4.2435>.
- (182) Buxbaum, L. U. Interleukin-10 from T Cells, but Not Macrophages and Granulocytes, Is Required for Chronic Disease in Leishmania Mexicana Infection. *Infect. Immun.* **2015**, *83* (4), 1366–1371. <https://doi.org/10.1128/IAI.02909-14>.
- (183) Mera-Ramirez, A.; Castillo, A.; Orobio, Y.; Gomez, M. A.; Gallego-Marin, C. Screening of TNFalpha, IL-10 and TLR4 Single Nucleotide Polymorphisms in Individuals with Asymptomatic and Chronic Cutaneous Leishmaniasis in Colombia: A Pilot Study. *BMC Infect. Dis.* **2017**, *17* (1), 177. <https://doi.org/10.1186/s12879-017-2281-4>.
- (184) Castellano, L. R.; Argiro, L.; Dessein, H.; Dessein, A.; da Silva, M. V.; Correia, D.; Rodrigues, V. Potential Use of Interleukin-10 Blockade as a Therapeutic Strategy in Human Cutaneous Leishmaniasis. *J. Immunol. Res.* **2015**, *2015*, 152741.
<https://doi.org/10.1155/2015/152741>.
- (185) Li, M. O.; Wan, Y. Y.; Sanjabi, S.; Robertson, A.-K. L.; Flavell, R. A. Transforming Growth Factor-Beta Regulation of Immune Responses. *Annu. Rev. Immunol.* **2006**,

- 24, 99–146. <https://doi.org/10.1146/annurev.immunol.24.021605.090737>.
- (186) Barral-Netto, M.; Barral, A.; Brownell, C. E.; Skeiky, Y. A.; Ellingsworth, L. R.; Twardzik, D. R.; Reed, S. G. Transforming Growth Factor-Beta in Leishmanial Infection: A Parasite Escape Mechanism. *Science* **1992**, 257 (5069), 545–548. <https://doi.org/10.1126/science.1636092>.
- (187) Li, J.; Hunter, C. A.; Farrell, J. P. Anti-TGF-Beta Treatment Promotes Rapid Healing of Leishmania Major Infection in Mice by Enhancing in Vivo Nitric Oxide Production. *J. Immunol.* **1999**, 162 (2), 974–979.
- (188) Hejazi, S.; Hoseini, S.; Javanmard, S.; Zarkesh, S.; Khamesipour, A. Interleukin-10 and Transforming Growth Factor-Beta in Early and Late Lesions of Patients with Leishmania Major Induced Cutaneous Leishmaniasis. *Iran. J. Parasitol.* **2012**, 7 (2), 53–60.
- (189) Shehadeh, F. V. B.; Santos, R. R. Dos; Silva, L. A. D. da; Silva Junior, W. V. da; Ribas-Silva, R.; Ribas, A. D.; Silveira, T. G. V.; Borelli, S. D.; Aristides, S. M. A. TGF-Beta1 Polymorphism in American Tegumentary Leishmaniasis in a Southern Brazilian Population. *Rev. Soc. Bras. Med. Trop.* **2019**, 52, e20170415. <https://doi.org/10.1590/0037-8682-0415-2017>.
- (190) Lopez Kostka, S.; Dinges, S.; Griewank, K.; Iwakura, Y.; Udey, M. C.; von Stebut, E. IL-17 Promotes Progression of Cutaneous Leishmaniasis in Susceptible Mice. *J. Immunol.* **2009**, 182 (5), 3039–3046. <https://doi.org/10.4049/jimmunol.0713598>.
- (191) Anderson, C. F.; Stumhofer, J. S.; Hunter, C. A.; Sacks, D. IL-27 Regulates IL-10 and IL-17 from CD4+ Cells in Nonhealing Leishmania Major Infection. *J. Immunol.*
-

- 2009**, *183* (7), 4619–4627. <https://doi.org/10.4049/jimmunol.0804024>.
- (192) Gonzalez-Lombana, C.; Gimblet, C.; Bacellar, O.; Oliveira, W. W.; Passos, S.; Carvalho, L. P.; Goldschmidt, M.; Carvalho, E. M.; Scott, P. IL-17 Mediates Immunopathology in the Absence of IL-10 Following Leishmania Major Infection. *PLoS Pathog.* **2013**, *9* (3), e1003243. <https://doi.org/10.1371/journal.ppat.1003243>.
- (193) Bacellar, O.; Faria, D.; Nascimento, M.; Cardoso, T. M.; Gollob, K. J.; Dutra, W. O.; Scott, P.; Carvalho, E. M. Interleukin 17 Production among Patients with American Cutaneous Leishmaniasis. *J. Infect. Dis.* **2009**, *200* (1), 75–78. <https://doi.org/10.1086/599380>.
- (194) Mueller, S. N.; Gebhardt, T.; Carbone, F. R.; Heath, W. R. Memory T Cell Subsets, Migration Patterns, and Tissue Residence. *Annu. Rev. Immunol.* **2013**, *31* (1), 137–161. <https://doi.org/10.1146/annurev-immunol-032712-095954>.
- (195) Sallusto, F.; Lenig, D.; Forster, R.; Lipp, M.; Lanzavecchia, A. Two Subsets of Memory T Lymphocytes with Distinct Homing Potentials and Effector Functions. *Nature* **1999**, *401* (6754), 708–712. <https://doi.org/10.1038/44385>.
- (196) Masopust, D.; Ha, S.-J.; Vezys, V.; Ahmed, R. Stimulation History Dictates Memory CD8 T Cell Phenotype: Implications for Prime-Boost Vaccination. *J. Immunol.* **2006**, *177* (2), 831–839.
- (197) Masopust, D.; Vezys, V.; Marzo, A. L.; Lefrancois, L. Preferential Localization of Effector Memory Cells in Nonlymphoid Tissue. *Science* **2001**, *291* (5512), 2413–2417. <https://doi.org/10.1126/science.1058867>.
- (198) Uzonna, J. E.; Wei, G.; Yurkowski, D.; Bretscher, P. Immune Elimination of

- Leishmania Major in Mice: Implications for Immune Memory, Vaccination, and Reactivation Disease. *J. Immunol.* **2001**, *167* (12), 6967–6974.
- (199) Zaph, C.; Uzonna, J.; Beverley, S. M.; Scott, P. Central Memory T Cells Mediate Long-Term Immunity to Leishmania Major in the Absence of Persistent Parasites. *Nat. Med.* **2004**, *10* (10), 1104.
- (200) Glennie, N. D.; Yeramilli, V. A.; Beiting, D. P.; Volk, S. W.; Weaver, C. T.; Scott, P. Skin-Resident Memory CD4+ T Cells Enhance Protection against Leishmania Major Infection. *J. Exp. Med.* **2015**, *212* (9), 1405–1414.
- (201) Glennie, N. D.; Volk, S. W.; Scott, P. Skin-Resident CD4+ T Cells Protect against Leishmania Major by Recruiting and Activating Inflammatory Monocytes. *PLoS Pathog.* **2017**, *13* (4), e1006349. <https://doi.org/10.1371/journal.ppat.1006349>.
- (202) Pereira-Carvalho, R.; Mendes-Aguiar, C. O.; Oliveira-Neto, M. P.; Covas, C. J. F.; Bertho, A. L.; Da-Cruz, A. M.; Gomes-Silva, A. Leishmania braziliensis-Reactive T Cells Are down-Regulated in Long-Term Cured Cutaneous Leishmaniasis, but the Renewal Capacity of T Effector Memory Compartments Is Preserved. *PLoS One* **2013**, *8* (11), e81529. <https://doi.org/10.1371/journal.pone.0081529>.
- (203) Colpitts, S. L.; Dalton, N. M.; Scott, P. IL-7 Receptor Expression Provides the Potential for Long-Term Survival of Both CD62Lhigh Central Memory T Cells and Th1 Effector Cells during Leishmania Major Infection. *J. Immunol.* **2009**, *182* (9), 5702–5711. <https://doi.org/10.4049/jimmunol.0803450>.
- (204) Noazin, S.; Modabber, F.; Khamesipour, A.; Smith, P. G.; Moulton, L. H.; Nasseri, K.; Sharifi, I.; Khalil, E. A. G.; Bernal, I. D. V.; Antunes, C. M. F.; et al. First

- Generation Leishmaniasis Vaccines: A Review of Field Efficacy Trials. *Vaccine* **2008**, *26* (52), 6759–6767. <https://doi.org/10.1016/j.vaccine.2008.09.085>.
- (205) Khamesipour, A.; Dowlati, Y.; Asilian, A.; Hashemi-Fesharki, R.; Javadi, A.; Noazin, S.; Modabber, F. Leishmanization: Use of an Old Method for Evaluation of Candidate Vaccines against Leishmaniasis. *Vaccine* **2005**, *23* (28), 3642–3648. <https://doi.org/10.1016/j.vaccine.2005.02.015>.
- (206) Khamesipour, A.; Rafati, S.; Davoudi, N.; Maboudi, F.; Modabber, F. Leishmaniasis Vaccine Candidates for Development: A Global Overview. *Indian J. Med. Res.* **2006**, *123* (3), 423–438.
- (207) Convit, J.; Castellanos, P. L.; Rondon, A.; Pinardi, M. E.; Ulrich, M.; Castes, M.; Bloom, B.; Garcia, L. Immunotherapy versus Chemotherapy in Localised Cutaneous Leishmaniasis. *Lancet* **1987**, *1* (8530), 401–405. [https://doi.org/10.1016/s0140-6736\(87\)90116-4](https://doi.org/10.1016/s0140-6736(87)90116-4).
- (208) Machado-Pinto, J.; Pinto, J.; da Costa, C. A.; Genaro, O.; Marques, M. J.; Modabber, F.; Mayrink, W. Immunochemotherapy for Cutaneous Leishmaniasis: A Controlled Trial Using Killed Leishmania (Leishmania) Amazonensis Vaccine plus Antimonial. *Int. J. Dermatol.* **2002**, *41* (2), 73–78. <https://doi.org/10.1046/j.1365-4362.2002.01336.x>.
- (209) Sharifi, I.; FeKri, A. R.; Aflatonian, M. R.; Khamesipour, A.; Nadim, A.; Mousavi, M. R.; Momeni, A. Z.; Dowlati, Y.; Godal, T.; Zicker, F.; et al. Randomised Vaccine Trial of Single Dose of Killed Leishmania Major plus BCG against Anthroponotic Cutaneous Leishmaniasis in Bam, Iran. *Lancet* **1998**, *351* (9115),

- 1540–1543. [https://doi.org/10.1016/S0140-6736\(98\)09552-X](https://doi.org/10.1016/S0140-6736(98)09552-X).
- (210) Momeni, A. Z.; Jalayer, T.; Emamjomeh, M.; Khamesipour, A.; Zicker, F.; Ghassemi, R. L.; Dowlati, Y.; Sharifi, I.; Aminjavaheri, M.; Shafiei, A.; et al. A Randomised, Double-Blind, Controlled Trial of a Killed *L. Major* Vaccine plus BCG against Zoonotic Cutaneous Leishmaniasis in Iran. *Vaccine* **1999**, *17* (5), 466–472. [https://doi.org/10.1016/s0264-410x\(98\)00220-5](https://doi.org/10.1016/s0264-410x(98)00220-5).
- (211) Khalil, E. A.; El Hassan, A. M.; Zijlstra, E. E.; Mukhtar, M. M.; Ghalib, H. W.; Musa, B.; Ibrahim, M. E.; Kamil, A. A.; Elsheikh, M.; Babiker, A.; et al. Autoclaved *Leishmania Major* Vaccine for Prevention of Visceral Leishmaniasis: A Randomised, Double-Blind, BCG-Controlled Trial in Sudan. *Lancet* **2000**, *356* (9241), 1565–1569. [https://doi.org/10.1016/s0140-6736\(00\)03128-7](https://doi.org/10.1016/s0140-6736(00)03128-7).
- (212) Bruhn, K. W.; Birnbaum, R.; Haskell, J.; Vanchinathan, V.; Greger, S.; Narayan, R.; Chang, P.-L.; Tran, T. A.; Hickerson, S. M.; Beverley, S. M. Killed but Metabolically Active *Leishmania Infantum* as a Novel Whole-Cell Vaccine for Visceral Leishmaniasis. *Clin. Vaccine Immunol.* **2012**, *19* (4), 490–498.
- (213) Evans, K. J.; Kedzierski, L. Development of Vaccines against Visceral Leishmaniasis. *J. Trop. Med.* **2012**, *2012*, 892817. <https://doi.org/10.1155/2012/892817>.
- (214) Kedzierski, L. Leishmaniasis Vaccine: Where Are We Today? *J. Glob. Infect. Dis.* **2010**, *2* (2), 177–185. <https://doi.org/10.4103/0974-777X.62881>.
- (215) Liu, D.; Kebaier, C.; Pakpour, N.; Capul, A. A.; Beverley, S. M.; Scott, P.; Uzonna, J. E. *Leishmania Major* Phosphoglycans Influence the Host Early Immune Response

- by Modulating Dendritic Cell Functions. *Infect. Immun.* **2009**, *77* (8), 3272–3283.
<https://doi.org/10.1128/IAI.01447-08>.
- (216) Selvapandian, A.; Dey, R.; Gannavaram, S.; Lakhal-Naouar, I.; Duncan, R.; Salotra, P.; Nakhси, H. L. Immunity to Visceral Leishmaniasis Using Genetically Defined Live-Attenuated Parasites. *J. Trop. Med.* **2012**, *2012*, 631460.
<https://doi.org/10.1155/2012/631460>.
- (217) Nagill, R.; Kaur, S. Vaccine Candidates for Leishmaniasis: A Review. *Int. Immunopharmacol.* **2011**, *11* (10), 1464–1488.
<https://doi.org/10.1016/j.intimp.2011.05.008>.
- (218) Borja-Cabrera, G. P.; Correia Pontes, N. N.; da Silva, V. O.; Paraguai de Souza, E.; Santos, W. R.; Gomes, E. M.; Luz, K. G.; Palatnik, M.; Palatnik de Sousa, C. B. Long Lasting Protection against Canine Kala-Azar Using the FML-QuilA Saponin Vaccine in an Endemic Area of Brazil (Sao Goncalo Do Amarante, RN). *Vaccine* **2002**, *20* (27–28), 3277–3284. [https://doi.org/10.1016/s0264-410x\(02\)00294-3](https://doi.org/10.1016/s0264-410x(02)00294-3).
- (219) Santos, F. N.; Borja-Cabrera, G. P.; Miyashiro, L. M.; Grechi, J.; Reis, A. B.; Moreira, M. A. B.; Martins Filho, O. A.; Luvizotto, M. C. R.; Menz, I.; Pessoa, L. M.; et al. Immunotherapy against Experimental Canine Visceral Leishmaniasis with the Saponin Enriched-Leishmune Vaccine. *Vaccine* **2007**, *25* (33), 6176–6190.
<https://doi.org/10.1016/j.vaccine.2007.06.005>.
- (220) Borja-Cabrera, G. P.; Santos, F. N.; Bauer, F. S.; Parra, L. E.; Menz, I.; Morgado, A. A.; Soares, I. S.; Batista, L. M. M.; Palatnik-de-Sousa, C. B. Immunogenicity Assay of the Leishmune Vaccine against Canine Visceral Leishmaniasis in Brazil. *Vaccine*

- 2008**, **26** (39), 4991–4997. <https://doi.org/10.1016/j.vaccine.2008.07.029>.
- (221) Mutiso, J. M.; Macharia, J. C.; Kiio, M. N.; Ichagichu, J. M.; Rikoi, H.; Gicheru, M. M. Development of Leishmania Vaccines: Predicting the Future from Past and Present Experience. *J. Biomed. Res.* **2013**, **27** (2), 85–102. <https://doi.org/10.7555/JBR.27.20120064>.
- (222) Resende, D. M.; Caetano, B. C.; Dutra, M. S.; Penido, M. L. O.; Abrantes, C. F.; Verly, R. M.; Resende, J. M.; Piló-Veloso, D.; Rezende, S. A.; Bruna-Romero, O. Epitope Mapping and Protective Immunity Elicited by Adenovirus Expressing the Leishmania Amastigote Specific A2 Antigen: Correlation with IFN- γ and Cytolytic Activity by CD8+ T Cells. *Vaccine* **2008**, **26** (35), 4585–4593.
- (223) Fernandes, C. B.; Junior, J. T. M.; de Jesus, C.; Souza, B. M. P. da S.; Larangeira, D. F.; Fraga, D. B. M.; Tavares Veras, P. S.; Barrouin-Melo, S. M. Comparison of Two Commercial Vaccines against Visceral Leishmaniasis in Dogs from Endemic Areas: IgG, and Subclasses, Parasitism, and Parasite Transmission by Xenodiagnosis. *Vaccine* **2014**, **32** (11), 1287–1295. <https://doi.org/10.1016/j.vaccine.2013.12.046>.
- (224) Coler, R. N.; Reed, S. G. Second-Generation Vaccines against Leishmaniasis. *Trends Parasitol.* **2005**, **21** (5), 244–249.
- (225) Coler, R. N.; Goto, Y.; Bogatzki, L.; Raman, V.; Reed, S. G. Leish-111f, a Recombinant Polyprotein Vaccine That Protects against Visceral Leishmaniasis by Elicitation of CD4+ T Cells. *Infect. Immun.* **2007**, **75** (9), 4648–4654.
- (226) Gradoni, L.; Foglia Manzillo, V.; Pagano, A.; Piantedosi, D.; De Luna, R.;

- Gramiccia, M.; Scalone, A.; Di Muccio, T.; Oliva, G. Failure of a Multi-Subunit Recombinant Leishmanial Vaccine (MML) to Protect Dogs from Leishmania Infantum Infection and to Prevent Disease Progression in Infected Animals. *Vaccine* **2005**, *23* (45), 5245–5251. <https://doi.org/10.1016/j.vaccine.2005.07.001>.
- (227) Velez, I. D.; Gilchrist, K.; Martinez, S.; Ramirez-Pineda, J. R.; Ashman, J. A.; Alves, F. P.; Coler, R. N.; Bogatzki, L. Y.; Kahn, S. J.; Beckmann, A. M.; et al. Safety and Immunogenicity of a Defined Vaccine for the Prevention of Cutaneous Leishmaniasis. *Vaccine* **2009**, *28* (2), 329–337. <https://doi.org/10.1016/j.vaccine.2009.10.045>.
- (228) Nascimento, E.; Fernandes, D. F.; Vieira, E. P.; Campos-Neto, A.; Ashman, J. A.; Alves, F. P.; Coler, R. N.; Bogatzki, L. Y.; Kahn, S. J.; Beckmann, A. M.; et al. A Clinical Trial to Evaluate the Safety and Immunogenicity of the LEISH-F1+MPL-SE Vaccine When Used in Combination with Meglumine Antimoniate for the Treatment of Cutaneous Leishmaniasis. *Vaccine* **2010**, *28* (40), 6581–6587. <https://doi.org/10.1016/j.vaccine.2010.07.063>.
- (229) Llanos-Cuentas, A.; Calderon, W.; Cruz, M.; Ashman, J. A.; Alves, F. P.; Coler, R. N.; Bogatzki, L. Y.; Bertholet, S.; Laughlin, E. M.; Kahn, S. J.; et al. A Clinical Trial to Evaluate the Safety and Immunogenicity of the LEISH-F1+MPL-SE Vaccine When Used in Combination with Sodium Stibogluconate for the Treatment of Mucosal Leishmaniasis. *Vaccine* **2010**, *28* (46), 7427–7435. <https://doi.org/10.1016/j.vaccine.2010.08.092>.
- (230) Chakravarty, J.; Kumar, S.; Trivedi, S.; Rai, V. K.; Singh, A.; Ashman, J. A.;

- Laughlin, E. M.; Coler, R. N.; Kahn, S. J.; Beckmann, A. M. A Clinical Trial to Evaluate the Safety and Immunogenicity of the LEISH-F1+ MPL-SE Vaccine for Use in the Prevention of Visceral Leishmaniasis. *Vaccine* **2011**, *29* (19), 3531–3537.
- (231) Bertholet, S.; Goto, Y.; Carter, L.; Bhatia, A.; Howard, R. F.; Carter, D.; Coler, R. N.; Vedvick, T. S.; Reed, S. G. Optimized Subunit Vaccine Protects against Experimental Leishmaniasis. *Vaccine* **2009**, *27* (50), 7036–7045.
<https://doi.org/10.1016/j.vaccine.2009.09.066>.
- (232) IDRI. First Vaccine Against Fatal Visceral Leishmaniasis Enters Clinical Trial
<https://www.idri.org/first-vaccine-against-visceral-leish/>.
- (233) Coler, R. N.; Duthie, M. S.; Hofmeyer, K. A.; Guderian, J.; Jayashankar, L.; Vergara, J.; Rolf, T.; Misquith, A.; Laurance, J. D.; Raman, V. S.; et al. From Mouse to Man: Safety, Immunogenicity and Efficacy of a Candidate Leishmaniasis Vaccine LEISH-F3+GLA-SE. *Clin. Transl. Immunol.* **2015**, *4* (4), e35.
<https://doi.org/10.1038/cti.2015.6>.
- (234) Julia, V.; Rassoulzadegan, M.; Glaichenhaus, N. Resistance to Leishmania Major Induced by Tolerance to a Single Antigen. *Science* **1996**, *274* (5286), 421–423.
<https://doi.org/10.1126/science.274.5286.421>.
- (235) Warnock, M. G.; Goodacre, J. A. Cryptic T-Cell Epitopes and Their Role in the Pathogenesis of Autoimmune Diseases. *Br. J. Rheumatol.* **1997**, *36* (11), 1144–1150. <https://doi.org/10.1093/rheumatology/36.11.1144>.
- (236) Jardim, A.; Alexander, J.; Teh, H. S.; Ou, D.; Olafson, R. W. Immunoprotective Leishmania Major Synthetic T Cell Epitopes. *J. Exp. Med.* **1990**, *172* (2), 645–648.

- https://doi.org/10.1084/jem.172.2.645.
- (237) Alves, C. R.; Benevolo-De-Andrade, T. C.; Alves, J. L.; Pirmez, C. Th1 and Th2 Immunological Profile Induced by Cysteine Proteinase in Murine Leishmaniasis. *Parasite Immunol.* **2004**, *26* (3), 127–135. https://doi.org/10.1111/j.0141-9838.2004.00691.x.
- (238) Solioz, N.; Blum-Tirouvanziam, U.; Jacquet, R.; Rafati, S.; Corradin, G.; Mauel, J.; Fasel, N. The Protective Capacities of Histone H1 against Experimental Murine Cutaneous Leishmaniasis. *Vaccine* **1999**, *18* (9–10), 850–859. https://doi.org/10.1016/s0264-410x(99)00340-0.
- (239) Spitzer, N.; Jardim, A.; Lippert, D.; Olafson, R. W. Long-Term Protection of Mice against Leishmania Major with a Synthetic Peptide Vaccine. *Vaccine* **1999**, *17* (11–12), 1298–1300. https://doi.org/10.1016/s0264-410x(98)00363-6.
- (240) Howard, J. C. Restrictions on the Use of Antigenic Peptides by the Immune System. *Proc. Natl. Acad. Sci.* **1993**, *90* (9), 3777–3779. https://doi.org/10.1073/pnas.90.9.3777.
- (241) Hasan, U. A.; Abai, A. M.; Harper, D. R.; Wren, B. W.; Morrow, W. J. Nucleic Acid Immunization: Concepts and Techniques Associated with Third Generation Vaccines. *J. Immunol. Methods* **1999**, *229* (1–2), 1–22. https://doi.org/10.1016/s0022-1759(99)00104-0.
- (242) Wahren, B. Gene Vaccines. *Immunotechnology* **1996**, *2* (2), 77–83.
- (243) Donnelly, J. J.; Wahren, B.; Liu, M. A. DNA Vaccines: Progress and Challenges. *J. Immunol.* **2005**, *175* (2), 633–639. https://doi.org/10.4049/jimmunol.175.2.633.

- (244) Gurunathan, S.; Klinman, D. M.; Seder, R. A. DNA Vaccines: Immunology, Application, and Optimization*. *Annu. Rev. Immunol.* **2000**, *18*, 927–974. <https://doi.org/10.1146/annurev.immunol.18.1.927>.
- (245) Ramiro, M. J.; Zarate, J. J.; Hanke, T.; Rodriguez, D.; Rodriguez, J. R.; Esteban, M.; Lucientes, J.; Castillo, J. A.; Larraga, V. Protection in Dogs against Visceral Leishmaniasis Caused by *Leishmania infantum* Is Achieved by Immunization with a Heterologous Prime-Boost Regime Using DNA and Vaccinia Recombinant Vectors Expressing LACK. *Vaccine* **2003**, *21* (19–20), 2474–2484. [https://doi.org/10.1016/s0264-410x\(03\)00032-x](https://doi.org/10.1016/s0264-410x(03)00032-x).
- (246) Lu, S. Heterologous Prime-Boost Vaccination. *Curr. Opin. Immunol.* **2009**, *21* (3), 346–351. <https://doi.org/10.1016/j.coи.2009.05.016>.
- (247) Das, S.; Freier, A.; Boussoffara, T.; Das, S.; Oswald, D.; Losch, F. O.; Selka, M.; Sacerdoti-Sierra, N.; Schönian, G.; Wiesmüller, K.-H. Modular Multiantigen T Cell Epitope-Enriched DNA Vaccine against Human Leishmaniasis. *Sci. Transl. Med.* **2014**, *6* (234), 234ra56-234ra56.
- (248) Faurez, F.; Dory, D.; Le Moigne, V.; Gravier, R.; Jestin, A. Biosafety of DNA Vaccines: New Generation of DNA Vectors and Current Knowledge on the Fate of Plasmids after Injection. *Vaccine* **2010**, *28* (23), 3888–3895. <https://doi.org/10.1016/j.vaccine.2010.03.040>.
- (249) Ledwith, B. J.; Manam, S.; Troilo, P. J.; Barnum, A. B.; Pauley, C. J.; Griffiths, T. G. 2nd; Harper, L. B.; Beare, C. M.; Bagdon, W. J.; Nichols, W. W. Plasmid DNA Vaccines: Investigation of Integration into Host Cellular DNA Following

- Intramuscular Injection in Mice. *Intervirology* **2000**, *43* (4–6), 258–272.
<https://doi.org/10.1159/000053993>.
- (250) Das, A.; Ali, N. Vaccine Development Against *Leishmania Donovani*. *Front. Immunol.* **2012**, *3*, 99. <https://doi.org/10.3389/fimmu.2012.00099>.
- (251) Remer, K. A.; Apetrei, C.; Schwarz, T.; Linden, C.; Moll, H. Vaccination with Plasmacytoid Dendritic Cells Induces Protection against Infection with *Leishmania Major* in Mice. *Eur. J. Immunol.* **2007**, *37* (9), 2463–2473.
- (252) Ahuja, S. S.; Reddick, R. L.; Sato, N.; Montalbo, E.; Kostecki, V.; Zhao, W.; Dolan, M. J.; Melby, P. C.; Ahuja, S. K. Dendritic Cell (DC)-Based Anti-Infective Strategies: DCs Engineered to Secrete IL-12 Are a Potent Vaccine in a Murine Model of an Intracellular Infection. *J. Immunol.* **1999**, *163* (7), 3890–3897.
- (253) Moll, H.; Berberich, C. Dendritic Cell-Based Vaccination Strategies: Induction of Protective Immunity against Leishmaniasis. *Immunobiology* **2001**, *204* (5), 659–666. <https://doi.org/10.1078/0171-2985-00105>.
- (254) Ramirez-Pineda, J. R.; Frohlich, A.; Berberich, C.; Moll, H. Dendritic Cells (DC) Activated by CpG DNA Ex Vivo Are Potent Inducers of Host Resistance to an Intracellular Pathogen That Is Independent of IL-12 Derived from the Immunizing DC. *J. Immunol.* **2004**, *172* (10), 6281–6289.
<https://doi.org/10.4049/jimmunol.172.10.6281>.
- (255) Selvapandiyan, A.; Duncan, R.; Debrabant, A.; Lee, N.; Sreenivas, G.; Salotra, P.; Nakhasi, H. L. Genetically Modified Live Attenuated Parasites as Vaccines for Leishmaniasis. *Indian J. Med. Res.* **2006**, *123* (3), 455–466.

- (256) Kubar, J.; Fragaki, K. Recombinant DNA-Derived Leishmania Proteins: From the Laboratory to the Field. *Lancet. Infect. Dis.* **2005**, *5* (2), 107–114. [https://doi.org/10.1016/S1473-3099\(05\)01282-X](https://doi.org/10.1016/S1473-3099(05)01282-X).
- (257) Singh, B.; Sundar, S. Leishmaniasis: Vaccine Candidates and Perspectives. *Vaccine* **2012**, *30* (26), 3834–3842. <https://doi.org/10.1016/j.vaccine.2012.03.068>.
- (258) Zadeh-Vakili, A.; Taheri, T.; Taslimi, Y.; Doustdari, F.; Salmanian, A.-H.; Rafati, S. Immunization with the Hybrid Protein Vaccine, Consisting of Leishmania Major Cysteine Proteinases Type I (CPB) and Type II (CPA), Partially Protects against Leishmaniasis. *Vaccine* **2004**, *22* (15–16), 1930–1940.
- (259) Duthie, M. S.; Raman, V. S.; Piazza, F. M.; Reed, S. G. The Development and Clinical Evaluation of Second-Generation Leishmaniasis Vaccines. *Vaccine* **2012**, *30* (2), 134–141. <https://doi.org/10.1016/j.vaccine.2011.11.005>.
- (260) Saljoughian, N.; Taheri, T.; Rafati, S. Live Vaccination Tactics: Possible Approaches for Controlling Visceral Leishmaniasis. *Front. Immunol.* **2014**, *5*, 134. <https://doi.org/10.3389/fimmu.2014.00134>.
- (261) Papierok G. RAPSODI: Pre-clinical studies of a PSA-based human vaccine candidate targeting visceral, cutaneous and monocutaneous Leishmaniasis and development of the associated procedures for further clinical trials. <http://www.fp7-rapsodi.eu/48/>.
- (262) Okwor, I.; Uzonna, J. Social and Economic Burden of Human Leishmaniasis. *Am. J. Trop. Med. Hyg.* **2016**, *94* (3), 489–493. <https://doi.org/10.4269/ajtmh.15-0408>.
- (263) Bhowmick, S.; Ali, N. Recent Developments in Leishmaniasis Vaccine Delivery

- Systems. *Expert Opin. Drug Deliv.* **2008**, *5* (7), 789–803.
<https://doi.org/10.1517/17425247.5.7.789>.
- (264) Rezvan, H.; Moafi, M. An Overview on Leishmania Vaccines: A Narrative Review Article. *Vet. Res. forum an Int. Q. J.* **2015**, *6* (1), 1–7.
- (265) Gillespie, P. M.; Beaumier, C. M.; Strych, U.; Hayward, T.; Hotez, P. J.; Bottazzi, M. E. Status of Vaccine Research and Development of Vaccines for Leishmaniasis. *Vaccine* **2016**, *34* (26), 2992–2995. <https://doi.org/10.1016/j.vaccine.2015.12.071>.
- (266) Ozbilge, H.; Aksoy, N.; Gurel, M. S.; Yazar, S. IgG and IgG Subclass Antibodies in Patients with Active Cutaneous Leishmaniasis. *J. Med. Microbiol.* **2006**, *55* (Pt 10), 1329–1331. <https://doi.org/10.1099/jmm.0.46667-0>.
- (267) Kima, P. E.; Soong, L. Interferon Gamma in Leishmaniasis. *Front. Immunol.* **2013**, *4*, 156. <https://doi.org/10.3389/fimmu.2013.00156>.
- (268) Zubairi, S.; Sanos, S. L.; Hill, S.; Kaye, P. M. Immunotherapy with OX40L-Fc or Anti-CTLA-4 Enhances Local Tissue Responses and Killing of Leishmania Donovanii. *Eur. J. Immunol.* **2004**, *34* (5), 1433–1440.
<https://doi.org/10.1002/eji.200324021>.
- (269) Saha, B.; Chattopadhyay, S.; Germond, R.; Harlan, D. M.; Perrin, P. J. CTLA4 (CD152) Modulates the Th Subset Response and Alters the Course of Experimental Leishmania Major Infection. *Eur. J. Immunol.* **1998**, *28* (12), 4213–4220.
[https://doi.org/10.1002/\(SICI\)1521-4141\(199812\)28:12<4213::AID-IMMU4213>3.0.CO;2-C](https://doi.org/10.1002/(SICI)1521-4141(199812)28:12<4213::AID-IMMU4213>3.0.CO;2-C).
- (270) Watt, W. C.; Cecil, D. L.; Disis, M. L. Selection of Epitopes from Self-Antigens for

- Eliciting Th2 or Th1 Activity in the Treatment of Autoimmune Disease or Cancer. *Semin. Immunopathol.* **2017**, *39* (3), 245–253. <https://doi.org/10.1007/s00281-016-0596-7>.
- (271) Melby, P. C.; Yang, J.; Zhao, W.; Perez, L. E.; Cheng, J. Leishmania Donovanii P36 (LACK) DNA Vaccine Is Highly Immunogenic but Not Protective against Experimental Visceral Leishmaniasis. *Infect. Immun.* **2001**, *69* (8), 4719–4725.
- (272) Dondji, B.; Pérez-Jimenez, E.; Goldsmith-Pestana, K.; Esteban, M.; McMahon-Pratt, D. Heterologous Prime-Boost Vaccination with the LACK Antigen Protects against Murine Visceral Leishmaniasis. *Infect. Immun.* **2005**, *73* (8), 5286–5289.
- (273) Heinzel, F. P.; Maier, R. A. J. Interleukin-4-Independent Acceleration of Cutaneous Leishmaniasis in Susceptible BALB/c Mice Following Treatment with Anti-CTLA4 Antibody. *Infect. Immun.* **1999**, *67* (12), 6454–6460.
- (274) Gannavaram, S.; Bhattacharya, P.; Ismail, N.; Kaul, A.; Singh, R.; Nakhasi, H. L. Modulation of Innate Immune Mechanisms to Enhance Leishmania Vaccine-Induced Immunity: Role of Coinhibitory Molecules. *Front. Immunol.* **2016**, *7*, 187.