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Modelagem molecular das interações do complexo antígeno-anticorpo na investigação de doenças desmielinizantes autoimunes

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RESUMO

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O reconhecimento e interação intermoleculares são cruciais na patogênese de doenças desmielinizantes autoimunes, como a esclerose múltipla (EM). A EM é uma doença que acomete o sistema nervoso central (SNC) e leva à desmielinização e axonopatia. Os alvos da resposta não são claros, mas proteínas da mielina, como a glicoproteína oligodendrocítica da mielina (MOG) e a proteína básica da mielina (MBP), são potenciais candidatas ao reconhecimento por células e autoanticorpos durante o processo autoimune. Assim, métodos de modelagem e simulações de dinâmica molecular (MD) e *steered molecular dynamics* (SMD) foram empregados para detalhar o reconhecimento e ligação do domínio externo da MOG e do peptídeo imunogênico MBP_{85-99} por anticorpos específicos. Para a obtenção das estruturas 3D dos anticorpos, particularmente do anti-MBP, um protocolo computacional envolvendo mutações sequenciais da região determinante de complementaridade (CDR) de estruturas-molde foi proposto. Dados obtidos evidenciaram grande contribuição das ligações de hidrogênio na manutenção dos complexos antígeno-anticorpo. Treze resíduos da MOG foram identificados como âncoras da ligação com o anti-MOG, os quais se relacionaram a peptídeos importantes descritos na literatura, principalmente o MOG_{92-106}. No caso da MBP, os resíduos do MBP_{85-99} com maior interação com o anti-MBP envolveram a Arginina 99, Lisina 93, Asparagina 94 e Histidina 90, corroborando achados na literatura acerca da resposta celular e análises do anti-MBP em casos *postmortem*. Dados de SMD envolvendo os sistemas moleculares foram confirmados por dados de microscópio de força atômica, sugerindo grande participação do peptídeo MOG_{92-106} na manutenção da ligação com o anti-MOG. Com relação à MBP, os estudos computacionais indicaram que o ponto de interação da região da Arginina 99 é muito importante para a ligação com o anti-MBP. A consonância entre dados computacionais e dados experimentais resultantes de décadas de pesquisas da MOG e a MBP, bem como com dos experimentos de AFM, ficou evidente. Desta forma, as aproximações teórico-experimentais aplicadas neste trabalho para a caracterização de moléculas ainda não estudadas é uma via em potencial para otimização de passos iniciais e pré-clínicos de investigações de doenças autoimunes, guiando experimentos, reduzindos custos e o uso de modelos animais.

Descritores: Modelagem Molecular. Química Teórica. Imunoglobulinas. Epitopos. Esclerose Múltipla. Neuromielite Óptica.

ABSTRACT

Ierich JCM. Molecular modeling of the antigen-antibody complex to the investigation of autoimmune demyelinating diseases (thesis). São Paulo: Instituto de Medicina Tropical de São Paulo da Universidade de São Paulo; 2018.

Intermolecular recognition and interaction are crucial in autoimmune demyelinating diseases pathogenesis as multiple sclerosis (MS). MS causes demyelination and axonopathy in the central nervous system (CNS). The targets of immune cells and autoantibodies are not clear, but myelin proteins, such as myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP), are potential candidates. Thus, methods of molecular modeling, molecular dynamics (MD), and steered molecular dynamics (SMD) simulation were applied to detail the recognition and binding of MOG external domain and the immunogenic MBP_{85-99} peptide by specific antibodies. A computational protocol based on mutations of complement determinant regions (CDR) in template structures was proposed to obtain antibodies 3D structures, especially the anti-MBP. The obtained data evidenced a significant contribution of hydrogen bonds in the maintenance of antigen-antibody complexes. Thirteen anchor residues were found in the MOG structure. These residues were related to three well-known epitopes recognized by immunologic components, mainly MOG_{92-106}. In the case of MBP, the most interactive residues of the MBP_{85-99} with the anti-MBP were Arginine 99, Lysine 93, Asparagine 94, and Histidine 90. These data complied with several studies concern cellular recognition of MBP and *postmortem* cases involving anti-MBP. SMD information of both molecular systems was confirmed by atomic force microscopy and suggested the MOG_{92-106} acting as an anchor for the complex with the anti-MOG. Regarding MBP, the computational force study evidenced the importance of Arginine 99 interaction region for the antigen-antibody binding. The agreement between the obtained computational data and experimental information resulted of decades of MOG and MBP research was evident. In this context, theoretical and experimental approaches application as described here for characterizing novel molecules in autoimmune disease is a potential pathway to optimize early-stage and pre-clinical steps of investigations, guiding experiments, reducing costs, and animal model usage.

Descriptors: Molecular Modeling. Theoretical Chemistry. Immunoglobulins. Epitopes. Multiple Sclerosis. Neuromyelitis Optica.

CONCLUSÃO

Neste trabalho, técnicas computacionais de modelagem e simulação foram aplicadas para o entendimento do reconhecimento de proteínas de mielina por anticorpos específicos inseridos num contexto de desmielinização, particularmente relacionados à EM. Modelos representativos refinados dos complexos antígeno-anticorpo de interesse foram obtidos, especialmente a descrição computacional de um modelo aproximado para o anticorpo anti-MBP com afinidade ao peptídeo imunogênico MBP_{85-99}. O protocolo de obtenção de estruturas de anticorpos a partir da estrutura dos antígenos-alvo baseado em mutação de estruturas conhecidas foi efetivo em caracterizar um modelo de anticorpo anti-MBP, mostrando perspectivas promissoras nas pesquisas envolvendo a resposta humoral em doenças desmielinizantes. As atividades de modelagem não apresentaram impacto na qualidade global das estruturas, permitindo a condução de simulações computacionais descritivas dos sistemas em estudo.

As simulações foram efetivas no detalhamento dos sistemas em termos da flutuação estrutural dos complexos, ligações químicas estabelecidas e forças envolvidas na ligação antígeno-anticorpo. Estruturalmente, os complexos formados entre anti-MOG e domínio externo da MOG bem como anti-MBP e MBP_{85-99} apresentaram indícios de estabilidade em meio aquoso tanto em termos de flutuação conformacional e energias de interação como com base em dados acerca de ligações de hidrogênio e pontes salinas. Com a condução das simulações, para ambos os sistemas, foi constatada uma contribuição importante dos resíduos das CDR no processo de ligação das proteínas MOG e MBP por anticorpos específicos. Na estrutura autoantigênica, resíduos âncoras do complexo antígeno-anticorpo tanto para o reconhecimento do domínio externo da MOG quanto do peptídeo MBP_{85-99} foram identificados, mostrando-se similares a resíduos identificados em pesquisas anteriores, especialmente aquelas envolvendo o reconhecimento das proteínas MOG e MBP por linfócitos T mediado por receptores específicos.

No caso da MOG, os resíduos mais interativos mostraram-se posicionados em regiões referentes a três resíduos encefalitogênicos de grande relevância em pesquisas de doenças desmielinizantes ($MOG_{1-22,}$ MOG_{35-55} e MOG_{92-106}). Com relação à MBP, resíduos carregados, como a Arginina 99, Lisina 93 e Histidina 90, se mostraram

essenciais para a ligação antígeno-anticorpo a qual, tanto para o sistema da MOG quanto da MBP, contou com grande contribuição eletrostática. Foi verificado tanto com relação às energias de ligação antígeno-anticorpo, refletidas na forma de ΔG_{Lig}, quanto em relação ao mapa de potencial eletrostático dos complexos, que as energias eletrostáticas em ambos os casos foram essenciais para o reconhecimento e ligação das referidas proteínas de mielina por seus anticorpos específicos. Regiões âncoras do complexo tanto na estrutura dos autoantígenos quanto nos anticorpos se mostraram opostamente carregadas, sugerindo uma interação forte entre os resíduos envolvidos.

A afinidade e especificidade tanto para o *sistema 1* quanto para o *sistema 2* foram analisadas e comprovadas considerando dados computacionais e aqueles advindos do AFM. As simulações de SMD para ambos os sistemas foram corroboradas por dados experimentais, validando os modelos computacionais propostos. A abordagem de SMD, no caso da MOG, sugeriu um papel central do peptídeo MOG_{92-106} durante o processo de reconhecimento estrutural desta proteína. Sobre a MBP, a SMD foi capaz de fornecer indícios acerca dos pontos mais interativos do sistema, mostrando que a região carboxi-terminal (região do resíduo Arginina 99) é muito importante na ligação MBP_{85-99} e anti-MBP, corroborando achados nas simulações de DM e nos experimentos de AFM.

Por fim, os resultados computacionais obtidos mostraram-se consistentes com as informações estruturais acerca do reconhecimento das proteínas MOG e MBP, especialmente considerando as regiões mais interativas destas proteínas. Os dados descritos se mostram de acordo com décadas de pesquisas envolvendo tais proteínas, o que sugere que os protocolos aqui detalhados mostram potencialidades descritivas para serem aplicadas em moléculas ainda não exploradas em pesquisas de doenças desmielinizantes, de forma a caracterizar novos alvos e mecanismos envolvidos em tais doenças. Desta forma, a modelagem e simulação podem contribuir substancialmente para esforços futuros neste campo, reduzindo custos e utilização de modelos animais nas pesquisas relacionadas.

REFERÊNCIAS

1. Tsai N, Lee B, Kim A, Yang R, Pan R, Lee D-K, et al. Nanomedicine for global health. J Lab Autom. 2014;19(6):511–6.

2. Ramachandran S, Lal R. Scope of atomic force microscopy in the advancement of nanomedicine. Indian J Exp Biol. 2010;48(10):1020–36.

3. Bayford R, Rademacher T, Roitt I, Wang SX. Emerging applications of nanotechnology for diagnosis and therapy of disease: a review. Physiol Meas. 2017;38(8):R183.

4. Ramsden J. Applied nanotechnology: the conversion of research results to products. New York: William Andrew; 2018. 312 p.

5. Wong HL, Wu XY, Bendayan R. Nanotechnological advances for the delivery of CNS therapeutics. Adv Drug Deliv Rev. 2012;64(7):686–700.

6. Sharma HS, Muresanu DF, Sharma A. Drug and Gene Delivery to the Central Nervous System for Neuroprotection: Nanotechnological Advances. New York: Springer; 2017. 244 p.

7. Ramachandran KI, Deepa G, Namboori K. Computational Chemistry and Molecular Modelling: Principles and Applications. 1. ed. Heidelberg: Springer; 2008. 397 p.

8. Srikanth M, Kessler JA. Nanotechnology—novel therapeutics for CNS disorders. Nat Rev Neurol. 2012;8(6):307–18.

9. Ghalamfarsa G, Hojjat-Farsangi M, Mohammadnia-Afrouzi M, Anvari E, Farhadi S, Yousefi M, et al. Application of nanomedicine for crossing the blood-brain barrier: Theranostic opportunities in multiple sclerosis. J Immunotoxicol. 2016;13(5):603–19.

10. Ballerini C, Baldi G, Aldinucci A, Maggi P. Nanomaterial applications in multiple sclerosis inflamed brain. J Neuroimmune Pharmacol. 2015;10(1):1–13.

11. Leite FL, Hausen M, Oliveira GS, Brum DG, Oliveira ON. Nanoneurobiophysics: new challenges for diagnosis and therapy of neurologic disorders. Nanomedicine (Lond). 2015;10(23):3417–9.

12. Marcus F. Bioinformatics and Systems Biology: Collaborative Research and Resources. New York: Springer; 2008. 296 p.

13. Tran QN, Arabnia HR. Emerging trends in applications and infrastructures for computational biology, bioinformatics, and system: biology systems and applications. New York: Elsevier; 2016. 558 p.

14. Ghosh S, Matsuoka Y, Asai Y, Hsin K-Y, Kitano H. Software for systems biology: from tools to integrated platforms. Nat Rev Genet. 2011;12(12):821.

15. Johnson BN, Mutharasan R. Biosensing using dynamic-mode cantilever sensors: A review. Biosens Bioelectron. 2012;32(1):1–18.

16. Justino CIL, Freitas AC, Pereira R, Duarte AC, Rocha Santos TAP. Recent developments in recognition elements for chemical sensors and biosensors. Trends Analyt Chem. 2015;68:2–17.

17. Kann MG. Protein interactions and disease: computational approaches to uncover the etiology of diseases. Brief Bioinformatics. 2007;8(5):333–46.

18. Gonzalez MW, Kann MG. Chapter 4: Protein Interactions and Disease. PLoS Comput Biol. 2012;8(12):e1002819.

19. Kuzmanov U, Emili A. Protein-protein interaction networks: probing disease mechanisms using model systems. Genome Med. 2013;5(4):37.

20. Casserly CS, Nantes JC, Whittaker Hawkins RF, Vallières L. Neutrophil perversion in demyelinating autoimmune diseases: Mechanisms to medicine. Autoimmun Rev. 2017;16(3):294–307.

21. Mayo L, Quintana FJ, Weiner HL. The innate immune system in demyelinating disease. Immunol Rev. 2012;248(1):170–87.

22. Mathey G, Michaud M, Pittion-Vouyovitch S, Debouverie M. Classification and diagnostic criteria for demyelinating diseases of the central nervous system: Where do we stand today? Rev Neurol. 2018;174(6):378–90.

23. Popescu BFG, Lucchinetti CF. Pathology of Demyelinating Diseases. Annu Rev Pathol. 2012;7(1):185–217.

24. Frota ER, Mendes MF, Vasconcelos CCF. Recomendações no tratamento da esclerose múltipla e neuromielite óptica. 2º ed. São Paulo: Omnifarma; 2016. 232 p.

25. Amor S, Peferoen LAN, Vogel DYS, Breur M, van der Valk P, Baker D, et al. Inflammation in neurodegenerative diseases--an update. Immunology. 2014;142(2):151–66.

26. Zipp F, Aktas O. The brain as a target of inflammation: common pathways link inflammatory and neurodegenerative diseases. Trends Neurosci. 2006;29(9):518–27.

27. Herz J, Zipp F, Siffrin V. Neurodegeneration in autoimmune CNS inflammation. Exp Neurol. 2010;225(1):9–17.

28. Stoeckle C, Tolosa E. Antigen processing and presentation in multiple sclerosis. Results Probl Cell Differ. 2010;51:149–72.

29. von Büdingen H-C, Bar-Or A, Zamvil SS. B cells in multiple sclerosis: connecting the dots. Curr Opin Immunol. 2011;23(6):713–20.

30. Meinl E, Derfuss T, Krumbholz M, Pröbstel A-K, Hohlfeld R. Humoral autoimmunity in multiple sclerosis. J Neurol Sci. 2011;306(1–2):180–2.

31. Hemmer B, Kowarik MC, Weber MS. The Role of B Cells in Multiple Sclerosis. In: Yamamura T, Gran B, organizadores. Multiple Sclerosis Immunology. New York: Springer; 2013. p. 95–114.

32. Mirshafiey A, Kianiaslani M. Autoantigens and autoantibodies in multiple sclerosis. Iran J Allergy Asthma Immunol. 2013;12(4):292–303.

33. Mayer MC, Meinl E. Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more. Ther Adv Neurol Disord. 2015;5(3):147–59.

34. Wu GF, Alvarez E. The immuno-pathophysiology of multiple sclerosis. Neurol Clin. 2011;29(2):257–78.

35. Fraussen J, Claes N, de Bock L, Somers V. Targets of the humoral autoimmune response in multiple sclerosis. Autoimmun Rev. 2014;13(11):1126–37.

36. Olsson T. White matter disease: Roles of anti-MOG antibodies in demyelinating diseases. Nat Rev Neurol. 2011;7(5):248–9.

37. Chiras DD. Human Biology. Burlington: Jones & Bartlett Learning; 2018. 711 p.

38. Johns P. Clinical Neuroscience E-Book. London: Elsevier Health Sciences; 2014. 219 p.

39. Brodal P. The Central Nervous System. New York: Oxford; 2016. 721 p.

40. Holtz JL. Applied Clinical Neuropsychology: An Introduction. New York: Springer; 2010. 538 p.

41. Salzer JL, Zalc B. Myelination. Curr Biol. 2016;26(20):R971–5.

42. Suzumura A, Ikenaka K. Neuron-Glia Interaction in Neuroinflammation. New York: Springer; 2013. 187 p.

43. Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD. Basic Neurochemistry. 6th ed. Philadelphia: Lippincott-Raven; 1999.

44. Hemmer B, Archelos JJ, Hartung H-P. New concepts in the immunopathogenesis of multiple sclerosis. Nat Rev Neurosci. 2002;3(4):291–301.

45. Reindl M, Di Pauli F, Rostásy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. Nat Rev Neurol. 2013;9(8):455–61.

46. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev. 2016;15(4):307–24.

47. Johns TG, Bernard CC. The structure and function of myelin oligodendrocyte glycoprotein. J Neurochem. 1999;72(1):1–9.

48. Vassall KA, Bamm VV, Harauz G. MyelStones: the executive roles of myelin basic protein in myelin assembly and destabilization in multiple sclerosis. Biochem J. 2015;472(1):17–32.

49. Boggs JM. Myelin basic protein: a multifunctional protein. Cell Mol Life Sci. 2006;63(17):1945–61.

50. Love S. Demyelinating diseases. J Clin Pathol. 2006;59(11):1151–9.

51. Waldman AT, Gorman MP, Rensel MR, Austin TE, Hertz DP, Kuntz NL, et al. Management of pediatric central nervous system demyelinating disorders: consensus of United States neurologists. J Child Neurol. 2011;26(6):675–82.

52. Berger T, Reindl M. Antibody biomarkers in CNS demyelinating diseases - a long and winding road. Eur J Neurol. 2015;22(8):1162–8.

53. Watanabe M, Kondo T. Autoantibodies to neural antigens in CNS demyelinating disorders. Curr Neurobiol. 2016;7(1):155–60.

54. Reindl M, Jarius S, Rostasy K, Berger T. Myelin oligodendrocyte glycoprotein antibodies: How clinically useful are they? Curr Opin Neurol. 2017;30(3):295–301.

55. Comabella M, Khoury SJ. Immunopathogenesis of multiple sclerosis. Clin Immunol. 2012;142(1):2–8.

56. Pröbstel A-K, Hauser SL. Multiple Sclerosis: B Cells Take Center Stage. J Neuroophthalmol. 2018;38(2):251.

57. Di Pauli F, Mader S, Rostasy K, Schanda K, Bajer-Kornek B, Ehling R, et al. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin Immunol. 2011;138(3):247–54.

58. Rahmlow MR, Kantarci O. Fulminant Demyelinating Diseases. Neurohospitalist. 2013;3(2):81–91.

59. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis. Neurology. 2014;83(3):278–86.

60. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. Cold Spring Harb Perspect Med. 2018;8(9):pii: a028928.

61. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. Cell J. 2017;19(1):1–10.

62. Wakerley B, Nicholas R, Malik O. Multiple sclerosis. Medicine. 2012;40(10):523–8.

63. Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. Brain Behav. 2015;5(9).

64. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol. 2015;15(9):545–58.

65. Stadelmann C. Multiple sclerosis as a neurodegenerative disease: pathology, mechanisms and therapeutic implications. Curr Opin Neurol. 2011;24(3):224–9.

66. Loma I, Heyman R. Multiple Sclerosis: Pathogenesis and Treatment. Curr Neuropharmacol. 2011;9(3):409–16.

67. Larochelle C, Alvarez JI, Prat A. How do immune cells overcome the blood-brain barrier in multiple sclerosis? FEBS Lett. 2011;585(23):3770–80.

68. Ortiz GG, Pacheco-Moisés FP, Macías-Islas MÁ, Flores-Alvarado LJ, Mireles-Ramírez MA, González-Renovato ED, et al. Role of the Blood–Brain Barrier in Multiple Sclerosis. Arch Med Res. 2014;45(8):687–97.

69. Lopes Pinheiro MA, Kooij G, Mizee MR, Kamermans A, Enzmann G, Lyck R, et al. Immune cell trafficking across the barriers of the central nervous system in multiple sclerosis and stroke. Biochim Biophys Acta. 2016;1862(3):461–71.

70. Kasper LH, Shoemaker J. Multiple sclerosis immunology: The healthy immune system vs the MS immune system. Neurology. 2010;74 Suppl 1:S2-8.

71. Disanto G, Morahan JM, Barnett MH, Giovannoni G, Ramagopalan SV. The evidence for a role of B cells in multiple sclerosis. Neurology. 2012;78(11):823–32.

72. Krumbholz M, Meinl E. B cells in MS and NMO: pathogenesis and therapy. Semin Immunopathol. 2014;36(3):339–50.

73. Abbas AK, Lichtman AHH, Pillai S. Basic Immunology: Functions and Disorders of the Immune System. 4th ed. Philadelphia: Saunders; 2012. 336 p.

74. Sospedra M. B cells in multiple sclerosis. Curr Opin Neurol. 2018;31(3):256–62.

75. Rahmanzadeh R, Brück W, Minagar A, Sahraian MA. Multiple sclerosis pathogenesis: missing pieces of an old puzzle. Nat Rev Neurosci. 2018;1–17.

76. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–88.

77. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378(9805):1779–87.

78. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221–34.

79. Pryce G, Baker D. Oligoclonal bands in multiple sclerosis; Functional significance and therapeutic implications. Does the specificity matter? Mult Scler Relat Disord. 2018;25:131–7.

80. Eixarch H, Gutiérrez-Franco A, Montalban X, Espejo C. Semaphorins 3A and 7A: potential immune and neuroregenerative targets in multiple sclerosis. Trends Mol Med. 2013;19(3):157–64.

81. Claes N, Fraussen J, Stinissen P, Hupperts R, Somers V. B Cells Are Multifunctional Players in Multiple Sclerosis Pathogenesis: Insights from Therapeutic Interventions. Front Immunol. 2015;6:642.

82. Blauth K, Owens GP, Bennett JL. The ins and outs of B cells in multiple sclerosis. Front Immunol. 2015;565.

83. Krumbholz M, Derfuss T, Hohlfeld R, Meinl E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. Nat Rev Neurol. 2012;8(11):613–23.

84. Dobson R, Meier UC, Giovannoni G. More to come: humoral immune responses in MS. J Neuroimmunol. 2011;240–241:13–21.

85. Weber MS, Hemmer B, Cepok S. The role of antibodies in multiple sclerosis. Biochim Biophys Acta. 2011;1812(2):239–45.

86. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol. 2000;47(6):707–17.

87. Breij ECW, Brink BP, Veerhuis R, van den Berg C, Vloet R, Yan R, et al. Homogeneity of active demyelinating lesions in established multiple sclerosis. Ann Neurol. 2008;63(1):16–25.

88. Lehmann-Horn K, Kronsbein HC, Weber MS. Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges. Ther Adv Neurol Disord. 2013;6(3):161–73.

89. Winger RC, Zamvil SS. Antibodies in multiple sclerosis oligoclonal bands target debris. Proc Natl Acad Sci USA. 2016;113(28):7696–8.

90. Kinzel S, Lehmann-Horn K, Torke S, Häusler D, Winkler A, Stadelmann C, et al. Myelin-reactive antibodies initiate T cell-mediated CNS autoimmune disease by opsonization of endogenous antigen. Acta Neuropathol. 2016;132(1):43–58.

91. Link H, Huang Y-M. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J Neuroimmunol. 2006;180(1–2):17–28.

92. Brändle SM, Obermeier B, Senel M, Bruder J, Mentele R, Khademi M, et al. Distinct oligoclonal band antibodies in multiple sclerosis recognize ubiquitous self-proteins. Proc Natl Acad Sci USA. 2016;113(28):7864–9.

93. Michel L, Touil H, Pikor NB, Gommerman JL, Prat A, Bar-Or A. B Cells in the Multiple Sclerosis Central Nervous System: Trafficking and Contribution to CNS-Compartmentalized Inflammation. Front Immunol. 2015;6.

94. Correale J, de los Milagros Bassani Molinas M. Oligoclonal bands and antibody responses in multiple sclerosis. J Neurol. 2002;249(4):375–89.

95. Rouwette M, Somers K, Govarts C, De Deyn PP, Hupperts R, Van Wijmeersch B, et al. Novel cerebrospinal fluid and serum autoantibody targets for clinically isolated syndrome. J Neurochem. 2012;123(4):568–77.

96. Rouwette M, Noben J-P, Van Horssen J, Van Wijmeersch B, Hupperts R, Jongen PJ, et al. Identification of coronin-1a as a novel antibody target for clinically isolated syndrome and multiple sclerosis. J Neurochem. 2013;126(4):483–92.

97. Erdağ E, Tüzün E, Uğurel E, Cavuş F, Sehitoğlu E, Giriş M, et al. Switch-associated protein 70 antibodies in multiple sclerosis: relationship between increased serum levels and clinical relapse. Inflamm Res. 2012;61(9):927–30.

98. Zhou D, Srivastava R, Nessler S, Grummel V, Sommer N, Brück W, et al. Identification of a pathogenic antibody response to native myelin oligodendrocyte glycoprotein in multiple sclerosis. Proc Natl Acad Sci USA. 2006;103(50):19057–62.

99. Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med. 1999;5(2):170–5.

100. Storch M, Lassmann H. Pathology and pathogenesis of demyelinating diseases. Curr Opin Neurol. 1997;10(3):186–92.

101. Piddlesden SJ, Lassmann H, Zimprich F, Morgan BP, Linington C. The demyelinating potential of antibodies to myelin oligodendrocyte glycoprotein is related to their ability to fix complement. Am J Pathol. 1993;143(2):555–64.

102. Marta CB, Oliver AR, Sweet RA, Pfeiffer SE, Ruddle NH. Pathogenic myelin oligodendrocyte glycoprotein antibodies recognize glycosylated epitopes and perturb oligodendrocyte physiology. Proc Natl Acad Sci USA. 2005;102(39):13992–7.

103. Marta CB, Montano MB, Taylor CM, Taylor AL, Bansal R, Pfeiffer SE. Signaling cascades activated upon antibody cross-linking of myelin oligodendrocyte glycoprotein: potential implications for multiple sclerosis. J Biol Chem. 2005;280(10):8985–93.

104. Steinman L, Zamvil S. Transcriptional analysis of targets in multiple sclerosis. Nat Rev Immunol. 2003;3(6):483–92.

105. Burgoon MP, Gilden DH, Owens GP. B Cells in Multiple Sclerosis. Front Biosci. 2004;9:786–96.

106. Fitzner B, Hecker M, Zettl UK. Molecular biomarkers in cerebrospinal fluid of multiple sclerosis patients. Autoimmun Rev. 2015;14(10):903–13.

107. Riedhammer C, Weissert R. Antigen Presentation, Autoantigens, and Immune Regulation in Multiple Sclerosis and Other Autoimmune Diseases. Front Immunol. 2015;6.

108. Fraussen J, de Bock L, Somers V. B cells and antibodies in progressive multiple sclerosis: Contribution to neurodegeneration and progression. Autoimmun Rev. 2016;15(9):896–9.

109. O'Connor KC, McLaughlin KA, De Jager PL, Chitnis T, Bettelli E, Xu C, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. Nat Med. 2007;13(2):211–7.

110. Brilot F, Dale RC, Selter RC, Grummel V, Kalluri SR, Aslam M, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann Neurol. 2009;66(6):833–42.

111. Clements CS, Reid HH, Beddoe T, Tynan FE, Perugini MA, Johns TG, et al. The crystal structure of myelin oligodendrocyte glycoprotein, a key autoantigen in multiple sclerosis. Proc Natl Acad Sci USA. 2003;100(19):11059–64.

112. Lebar R, Boutry JM, Vincent C, Robineaux R, Voisin GA. Studies on autoimmune encephalomyelitis in the guinea pig. II. An in vitro investigation on the nature, properties, and specificity of the serum-demyelinating factor. J Immunol. 1976;116(5):1439–46.

113. Lebar R, Lubetzki C, Vincent C, Lombrail P, Boutry JM. The M2 autoantigen of central nervous system myelin, a glycoprotein present in oligodendrocyte membrane. Clin Exp Immunol. 1986;66(2):423–34.

114. Baumann M, Sahin K, Lechner C, Hennes EM, Schanda K, Mader S, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatr. 2015;86(3):265–72.

115. Numa S, Kasai T, Kondo T, Kushimura Y, Kimura A, Takahashi H, et al. An Adult Case of Anti-Myelin Oligodendrocyte Glycoprotein (MOG) Antibody-associated Multiphasic Acute Disseminated Encephalomyelitis at 33-year Intervals. Intern Med. 2016;55(6):699–702.

116. Pröbstel AK, Dornmair K, Bittner R, Sperl P, Jenne D, Magalhaes S, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011;77(6):580–8.

117. Dale RC, Tantsis EM, Merheb V, Kumaran R-YA, Sinmaz N, Pathmanandavel K, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurol Neuroimmunol Neuroinflamm. 2014;1(1):e12.

118. Jarius S, Metz I, König FB, Ruprecht K, Reindl M, Paul F, et al. Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in "pattern II multiple sclerosis" and brain biopsy findings in a MOG-IgG-positive case. Mult Scler. 2016;22(12):1541–9.

119. Spadaro M, Gerdes LA, Krumbholz M, Ertl-Wagner B, Thaler FS, Schuh E, et al. Autoantibodies to MOG in a distinct subgroup of adult multiple sclerosis. Neurol Neuroimmunol Neuroinflamm. 2016;3(5).

120. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016;13(1):279.

121. Bernard-Valnet R, Liblau RS, Vukusic S, Marignier R. Neuromyelitis optica: a positive appraisal of seronegative cases. Eur J Neurol. 2015;22(12):1511–8, e82-83.

122. Lovett-Racke AE. Contribution of EAE to understanding and treating multiple sclerosis. J Neuroimmunol. 2017;304:40–2.

123. Di Pauli F, Höftberger R, Reindl M, Beer R, Rhomberg P, Schanda K, et al. Fulminant demyelinating encephalomyelitis: Insights from antibody studies and neuropathology. Neurol Neuroimmunol Neuroinflamm. 2015;2(6):e175.

124. Weber MS, Derfuss T, Metz I, Brück W. Defining distinct features of anti-MOG antibody associated central nervous system demyelination. Ther Adv Neurol Disord. 2018;11:1756286418762083.

125. Harauz G, Ladizhansky V, Boggs JM. Structural polymorphism and multifunctionality of myelin basic protein. Biochemistry. 2009;48(34):8094–104.

126. Harauz G, Boggs JM. Myelin management by the 18.5-kDa and 21.5-kDa classic myelin basic protein isoforms. J Neurochem. 2013;125(3):334–61.

127. Frohman EM, Racke MK, Raine CS. Multiple Sclerosis — The Plaque and Its Pathogenesis. N Engl J Med. 2006;354(9):942–55.

128. Wilson R, Tocher DR. Lipid and fatty acid composition is altered in plaque tissue from multiple sclerosis brain compared with normal brain white matter. Lipids. 1991;26(1):9–15.

129. Harauz G, Musse AA. A tale of two citrullines--structural and functional aspects of myelin basic protein deimination in health and disease. Neurochem Res. 2007;32(2):137–58.

130. Yang L, Tan D, Piao H. Myelin Basic Protein Citrullination in Multiple Sclerosis: A Potential Therapeutic Target for the Pathology. Neurochem Res. 2016;41(8):1845–56.

131. Antel JP, Bar-Or A. Do myelin-directed antibodies predict multiple sclerosis? N Engl J Med. 2003;349(2):107–9.

132. Janeway Jr. CA, Travers P, Walport M, Shlomchik MJ, Jr CAJ, Travers P, et al. Immunobiology. 5th ed. New York: Garland Science; 2001.

133. Nelson DL, Cox MM. Lehninger Principles of Biochemistry. 5th ed. New York: W. H. Freeman and Company; 2008. 1302 p.

134. Voet D, Voet JG. Biochemistry. 4th ed. Kendallville: Wiley; 2011. 1515 p.

135. Sharma RK. Basic techniques in biochemistry and molecular biology. New Delhi: IK International Pvt; 2008. 260 p.

136. Whitford D. Proteins: structure and function. Chichester: John Wiley & Sons; 2013.

137. Harris LJ, Skaletsky E, McPherson A. Crystallographic structure of an intact IgG1 monoclonal antibody. J Mol Biol. 1998;275(5):861–72.

138. Rajpal A, Strop P, Yeung YA, Chaparro-Riggers J, Pons J. Introduction: Antibody Structure and Function. In: Chamow SM, Ryll T, Lowman HB, Farson D, organizadores. Therapeutic Fc-Fusion Proteins. New York: Wiley; 2014. p. 1–44.

139. Elgert KD. Immunology: Understanding The Immune System. New York: Wiley; 2009. 740 p.

140. Wang W, Singh S, Zeng DL, King K, Nema S. Antibody structure, instability, and formulation. J Pharm Sci. 2007;96(1):1–26.

141. Breithaupt C, Schubart A, Zander H, Skerra A, Huber R, Linington C, et al. Structural insights into the antigenicity of myelin oligodendrocyte glycoprotein. Proc Natl Acad Sci USA. 2003;100(16):9446–51.

142. Sela-Culang I, Kunik V, Ofran Y. The structural basis of antibody-antigen recognition. Front Immunol. 2013;4:302.

143. Weitzner BD, Dunbrack RL, Gray JJ. The origin of CDR H3 structural diversity. Structure. 2015;23(2):302–11.

144. Tsuchiya Y, Mizuguchi K. The diversity of H3 loops determines the antigen-binding tendencies of antibody CDR loops. Protein Sci. 2016;25(4):815–25.

145. Zhu K, Day T. Ab initio structure prediction of the antibody hypervariable H3 loop. Proteins. 2013;81(6):1081–9.

146. Zhu K, Day T, Warshaviak D, Murrett C, Friesner R, Pearlman D. Antibody structure determination using a combination of homology modeling, energy-based refinement, and loop prediction. Proteins. 2014;82(8):1646–55.

147. Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: from structure to effector functions. Front Immunol. 2014;5:520.

148. Schur PH. IgG subclasses. A historical perspective. Monogr Allergy. 1988;23:1–11.

149. Fukuda N, Suwa Y, Uchida M, Kobashigawa Y, Yokoyama H, Morioka H. Role of the mobility of antigen binding site in high affinity antibody elucidated by surface plasmon resonance. J Biochem. 2017;161(1):37–43.

150. Rodrigues ME, Costa AR, Henriques M, Azeredo J, Oliveira R. Technological progresses in monoclonal antibody production systems. Biotechnol Prog. 2010;26(2):332–51.

151. Fuhrmann A, Ros R. Single-molecule force spectroscopy: a method for quantitative analysis of ligand-receptor interactions. Nanomedicine (Lond). 2010;5(4):657–66.

152. Proetzel G, Ebersbach H. Antibody Methods and Protocols. New York: Humana Press; 2012. 325 p.

153. Kozlowski S, Swann P. Current and future issues in the manufacturing and development of monoclonal antibodies. Adv Drug Deliv Rev. 2006;58(5):707–22.

154. Beck A, Wurch T, Bailly C, Corvaia N. Strategies and challenges for the next generation of therapeutic antibodies. Nat Rev Immunol. 2010;10(5):345–52.

155. Golay J, Introna M. Mechanism of action of therapeutic monoclonal antibodies: promises and pitfalls of in vitro and in vivo assays. Arch Biochem Biophys. 2012;526(2):146–53.

156. Niwa R, Satoh M. The current status and prospects of antibody engineering for therapeutic use: focus on glycoengineering technology. J Pharm Sci. 2015;104(3):930–41.

157. Zeng X, Shen Z, Mernaugh R. Recombinant antibodies and their use in biosensors. Anal Bioanal Chem. 2012;402(10):3027–38.

158. Eggins BR. Biosensors: an introduction. New York: Springer; 2013. 212 p.

159. Sharma S, Byrne H, O'Kennedy RJ. Antibodies and antibody-derived analytical biosensors. Essays Biochem. 2016;60(1):9–18.

160. Pedotti M, Simonelli L, Livoti E, Varani L. Computational Docking of Antibody-Antigen Complexes, Opportunities and Pitfalls Illustrated by Influenza Hemagglutinin. Int J Mol Sci. 2011;12(1):226–51.

161. Teplyakov A, Luo J, Obmolova G, Malia TJ, Sweet R, Stanfield RL, et al. Antibody modeling assessment II. Structures and models. Proteins. 2014;82(8):1563–82.

162. Saeed AFUH, Wang R, Ling S, Wang S. Antibody Engineering for Pursuing a Healthier Future. Front Microbiol. 2017;8.

163. Filpula D. Antibody engineering and modification technologies. Biomol Eng. 2007;24(2):201–15.

164. Nowak J, Baker T, Georges G, Kelm S, Klostermann S, Shi J, et al. Length-independent structural similarities enrich the antibody CDR canonical class model. MAbs. 2016;8(4):751–60.

165. Sevy AM, Meiler J. Antibodies: Computer-Aided Prediction of Structure and Design of Function. Microbiol Spectr. 2014;2(6).

166. Kunik V, Ashkenazi S, Ofran Y. Paratome: an online tool for systematic identification of antigen-binding regions in antibodies based on sequence or structure. Nucleic Acids Res. 2012;40(Web Server issue):W521–4.

167. Sela-Culang I, Benhnia MR-E-I, Matho MH, Kaever T, Maybeno M, Schlossman A, et al. Using a combined computational-experimental approach to predict antibody-specific B cell epitopes. Structure. 2014;22(4):646–57.

168. Ponomarenko J, Bui H-H, Li W, Fusseder N, Bourne PE, Sette A, et al. ElliPro: a new structure-based tool for the prediction of antibody epitopes. BMC Bioinformatics. 2008;9:514.

169. Vita R, Overton JA, Greenbaum JA, Ponomarenko J, Clark JD, Cantrell JR, et al. The immune epitope database (IEDB) 3.0. Nucleic Acids Res. 2015;43(Database issue):D405–12.

170. Swindells MB, Porter CT, Couch M, Hurst J, Abhinandan KR, Nielsen JH, et al. abYsis: Integrated Antibody Sequence and Structure-Management, Analysis, and Prediction. J Mol Biol. 2016;429(3):356–64.

171. Meier A, Söding J. Automatic Prediction of Protein 3D Structures by Probabilistic Multi-template Homology Modeling. PLoS Comput Biol. 2015;11(10):e1004343.

172. Orry AJW, Abagyan R. Homology Modelling: Methods and Protocols. New York: Springer; 2012. 419 p.

173. Wallner B, Elofsson A. All are not equal: a benchmark of different homology modeling programs. Protein Sci. 2005;14:1315–27.

174. Xu J, Wang S, Ma J. Protein Homology Detection Through Alignment of Markov Random Fields: Using MRFalign. New York: Springer; 2015. 51 p.

175. Marcatili P, Rosi A, Tramontano A. PIGS: automatic prediction of antibody structures. Bioinformatics. 2008;24(17):1953–4.

176. Sircar A, Kim ET, Gray JJ. RosettaAntibody: antibody variable region homology modeling server. Nucleic Acids Res. 2009;37(Web Server issue):W474–9.

177. Weitzner BD, Jeliazkov JR, Lyskov S, Marze N, Kuroda D, Frick R, et al. Modeling and docking of antibody structures with Rosetta. Nat Protocols. 2017;12(2):401–16.

178. Chothia C, Lesk AM. Canonical structures for the hypervariable regions of immunoglobulins. J Mol Biol. 1987;196(4):901–17.

179. Marcatili P, Olimpieri PP, Chailyan A, Tramontano A. Antibody modeling using the Prediction of ImmunoGlobulin Structure (PIGS) web server. Nat Protoc. 2014;9(12):2771–83.

180. Kuroda D, Shirai H, Jacobson MP, Nakamura H. Computer-aided antibody design. Protein Eng Des Sel. 2012;25(10):507–21.

181. Halperin I, Ma B, Wolfson H, Nussinov R. Principles of docking: An overview of search algorithms and a guide to scoring functions. Proteins. 2002;47(4):409–43.

182. Holford TRJ, Davis F, Higson SPJ. Recent trends in antibody based sensors. Biosens Bioelectron. 2012;34(1):12–24.

183. Morgon NH, Coutinho K. Métodos de Química Teórica E Modelagem Molecular. São Paulo: Editora Livraria da Física; 2007. 539 p.

184. Franca EF, Oliveira GS, Ierich JCM, Vig ACA, Brandini CP, Moraes AS, et al. Desenvolvimento de Nanodispositivos Baseados em Biomoléculas. In: Aplicações de Química Teórica no Estudo de Materiais. São Carlos: EdUFSCar; 2018. p. 117–55.

185. Gromiha MM, Yugandhar K, Jemimah S. Protein-protein interactions: scoring schemes and binding affinity. Curr Opin Struct Biol. 2017;44:31–8.

186. Akiba H, Tsumoto K. Thermodynamics of antibody-antigen interaction revealed by mutation analysis of antibody variable regions. J Biochem. 2015;158(1):1–13.

187. Osajima T, Suzuki M, Neya S, Hoshino T. Computational and statistical study on the molecular interaction between antigen and antibody. J Mol Graph Model. 2014;53:128–39.

188. Osajima T, Hoshino T. Roles of the respective loops at complementarity determining region on the antigen-antibody recognition. Comput Biol Chem. 2016;64:368–83.

189. Perilla JR, Goh BC, Cassidy CK, Liu B, Bernardi RC, Rudack T, et al. Molecular dynamics simulations of large macromolecular complexes. Curr Opin Struct Biol. 2015;31:64–74.

190. Lee EH, Hsin J, Sotomayor M, Comellas G, Schulten K. Discovery through the computational microscope. Structure. 2009;17(10):1295–306.

191. Alder BJ, Wainwright TE. Phase Transition for a Hard Sphere System. J Chem Phys. 1957;27(5):1208–9.

192. Alder BJ, Wainwright TE. Studies in Molecular Dynamics. I. General Method*. J Chem Phys. 1959;31(2):459–66.

193. Karplus M, McCammon JA. Molecular dynamics simulations of biomolecules. Nat Struct Mol Biol. 2002;9(9):646–52.

194. Jensen F. Introduction to Computational Chemistry. 2nd ed. Hoboken: Wiley; 2007. 599 p.

195. Kukol A. Molecular modeling of proteins. 2nd ed. New York: Springer; 2015. 474 p.

196. Cramer CJ. Essentials of computational chemistry: theories and models. 2nd ed. New York: Wiley; 2004. 596 p.

197. Satoh A. Introduction to practice of molecular simulation: Molecular dynamics, Monte-Carlo, Brownian ynamics, Lattice Boltzmann and Dissipative particle dynamics. London: Elsevier; 2011. 322 p.

198. MacKerell AD, Bashford D, Bellott M, Dunbrack RL, Evanseck JD, Field MJ, et al. All-atom empirical potential for molecular modeling and dynamics studies of proteins. J Phys Chem B. 1998;102(18):3586–616.

199. Huang J, MacKerell AD. CHARMM36 all-atom additive protein force field: validation based on comparison to NMR data. J Comput Chem. 2013;34(25):2135–45.

200. Brooks BR, Brooks CL 3rd, Mackerell AD Jr, Nilsson L, Petrella RJ, Roux B, et al. CHARMM: the biomolecular simulation program. J Comput Chem. 2009;30(10):1545–614.

201. Frenkel D, Smit B. Understanding molecular simulation: from algorithms to applications. Vol. 1. New York: Elsevier; 2001. 638 p.

202. Rapaport DC. The Art of Molecular Dynamics Simulation. 2nd ed. Cambridge: Cambridge University Press; 2004. 564 p.

203. Friedman R, Boye K, Flatmark K. Molecular modelling and simulations in cancer research. Biochim Biophys Acta. 2013;1836(1):1–14.

204. Mansoori GA. Principles of nanotechnology: molecular-based study of condensed matter in small systems. London: World Scientific; 2005. 341 p.

205. Verlet L. Computer" experiments" on classical fluids. I. Thermodynamical properties of Lennard-Jones molecules. Phys Rev. 1967;159(1):98.

206. Swope WC, Andersen HC, Berens PH, Wilson KR. A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: Application to small water clusters. J Chem Phys. 1982;76(1):637–49.

207. Hockney RW, Eastwood JW. Computer simulation using particles. New York: CRC Press; 1988. 540 p.

208. van Gunsteren WF, Berendsen HJ. Computer simulation of molecular dynamics: Methodology, applications, and perspectives in chemistry. Angew Chem Int Ed. 1990;29(9):992–1023.

209. Hospital A, Goñi JR, Orozco M, Gelpí JL. Molecular dynamics simulations: advances and applications. Adv Appl Bioinform Chem. 2015;8:37–47.

210. Dykstra C, Frenking G, Kim K, Scuseria G. Theory and Applications of Computational Chemistry: the first forty years. New York: Elsevier; 2011. 1308 p.

211. Tuckerman M. Statistical mechanics: theory and molecular simulation. New York: Oxford; 2010. 696 p.

212. Gibbs JW. Elementary principles in statistical mechanics. New York: Courier Corporation; 2014. 224 p.

213. Fyta M. Computational Approaches in Physics. San Raphael: Morgan & Claypool; 2016. 179 p.

214. Enge W, Xin-zheng L. Computer Simulations Of Molecules And Condensed Matter: From Electronic Structures To Molecular Dynamics. Vol. 3. London: World Scientific; 2018. 263 p.

215. Klapp J, Chavarría GR, Ovando AM, Villa AL, Sigalotti LDG. Selected Topics of Computational and Experimental Fluid Mechanics. New York: Springer; 2015. 548 p.

216. Phillips JC, Braun R, Wang W, Gumbart J, Tajkhorshid E, Villa E, et al. Scalable molecular dynamics with NAMD. J Comput Chem. 2005;26(16):1781–802.

217. Wells BA, Chaffee AL. Ewald Summation for Molecular Simulations. J Chem Theory Comput. 2015;11(8):3684–95.

218. Toukmaji AY, Board JA. Ewald summation techniques in perspective: a survey. Comput Phys Commun. 1996;95(2):73–92.

219. Kabadshow I. Periodic boundary conditions and the error-controlled fast multipole method. Vol. 11. Jülich: Forschungszentrum Jülich; 2012. 129 p.

220. Darden T, York D, Pedersen L. Particle mesh Ewald: An N·log(N) method for Ewald sums in large systems. J Chem Phys. 1993;98(12):10089–92.

221. Martin R, Howell MD, Jaraquemada D, Flerlage M, Richert J, Brostoff S, et al. A myelin basic protein peptide is recognized by cytotoxic T cells in the context of four HLA-DR types associated with multiple sclerosis. J Exp Med. 1991;173(1):19–24.

222. Ellmerich S, Mycko M, Takacs K, Waldner H, Wahid FN, Boyton RJ, et al. High incidence of spontaneous disease in an HLA-DR15 and TCR transgenic multiple sclerosis model. J Immunol. 2005;174(4):1938–46.

223. Franca EF, Leite FL, Cunha RA, Oliveira ON, Freitas LCG. Designing an enzyme-based nanobiosensor using molecular modeling techniques. Phys Chem Chem Phys. 2011;13(19):8894–9.

224. Ierich JCM, Oliveira GS, Vig ACA, Amarante AM, Franca EF, Leite FL, et al. A Computational Protein Structure Refinement of the Yeast Acetohydroxyacid Synthase. J Braz Chem Soc. 2015;26(8):1702–9.

225. Smith KJ, Pyrdol J, Gauthier L, Wiley DC, Wucherpfennig KW. Crystal structure of HLA-DR2 (DRA*0101, DRB1*1501) complexed with a peptide from human myelin basic protein. J Exp Med. 1998;188(8):1511–20.

226. Atiqah Abdul Karim H, Tayapiwatana C, Nimmanpipug P, M Zain S, Abdul Rahman N, Lee VS. Molecular Dynamics Simulation on Designed Antibodies of HIV-1 Capsid Protein (p24). In: 3rd International Conference on Computation for Science and Technology (ICCST-3). Atlantis Press; 2015.

227. Laskowski RA, Hutchinson EG, Michie AD, Wallace AC, Jones ML, Thornton JM. PDBsum: a Web-based database of summaries and analyses of all PDB structures. Trends Biochem Sci. 1997;22(12):488–90.

228. Laskowski RA. PDBsum: summaries and analyses of PDB structures. Nucleic Acids Res. 2001;29(1):221–2.

229. de Beer TAP, Berka K, Thornton JM, Laskowski RA. PDBsum additions. Nucleic Acids Res. 2014;42(Database issue):D292-296.

230. Sali A, Blundell TL. Comparative protein modelling by satisfaction of spatial restraints. J Mol Biol. 1993;234:779–815.

231. Martí-Renom MA, Stuart AC, Fiser A, Sánchez R, Melo F, Sali A. Comparative protein structure modeling of genes and genomes. Annu Rev Biophys Biomol Struct. 2000;29:291–325.

232. Eswar N, Webb B, Marti-Renom MA, Madhusudhan MS, Eramian D, Shen MY, et al. Comparative protein structure modeling using MODELLER. Curr Protoc Protein Sci. 2007;Chapter 2:Unit 2 9.

233. Sali A. Mutate model - Modeller [Internet]. 2016 [citado 6 de novembro de 2018]. Disponível em: https://salilab.org/modeller/wiki/Mutate%20model

234. Feyfant E, Sali A, Fiser A. Modeling mutations in protein structures. Protein Sci. 2007;16(9):2030–41.

235. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J Comput Chem. 2010;31(2):455–61.

236. Lin C-P, Boysen RI, Campi EM, Saito K, Hearn MTW. Studies on the binding sites of IgG2 monoclonal antibodies recognized by terpyridine-based affinity ligands. J Mol Recognit. 2016;29(7):334–42.

237. Makeneni S, Ji Y, Watson DC, Young NM, Woods RJ. Predicting the Origins of Anti-Blood Group Antibody Specificity: A Case Study of the ABO A- and B-Antigens. Front Immunol. 2014;5.

238. Rajapaksha H, Petrovsky N. In Silico Structural Homology Modelling and Docking for Assessment of Pandemic Potential of a Novel H7N9 Influenza

Virus and Its Ability to Be Neutralized by Existing Anti-Hemagglutinin Antibodies. PLoS One. 2014;9(7):e102618.

239. Ramachandran GN, Venkatachalam CM, Krimm S. Stereochemical Criteria for Polypeptide and Protein Chain Conformations. Biophys J. 1966;6(6):849–72.

240. Laskowski RA, MacArthur MW, Moss DS, Thornton JM. PROCHECK: a program to check the stereochemical quality of protein structures. J Appl Cryst. 1993;26(2):283–91.

241. Mahoney MW, Jorgensen WL. A five-site model for liquid water and the reproduction of the density anomaly by rigid, nonpolarizable potential functions. J Chem Phys. 2000;112(20):8910–22.

242. Humphrey W, Dalke A, Schulten K. VMD: visual molecular dynamics. J Mol Graph. 1996;14(1):33–8.

243. Solvate Plugin, Version 1.5 [Internet]. [citado 1º de agosto de 2018]. Disponível em: http://www.ks.uiuc.edu/Research/vmd/plugins/solvate/

244. Peschl P, Bradl M, Höftberger R, Berger T, Reindl M. Myelin Oligodendrocyte Glycoprotein: Deciphering a Target in Inflammatory Demyelinating Diseases. Front Immunol. 2017;8:529.

245. Wang X, Kumar S, Singh SK. Disulfide Scrambling in IgG2 Monoclonal Antibodies: Insights from Molecular Dynamics Simulations. Pharm Res. 2011;28(12):3128–44.

246. Fortunato ME, Colina CM. Effects of Galactosylation in Immunoglobulin G from All-Atom Molecular Dynamics Simulations. J Phys Chem B. 2014;118(33):9844–51.

247. Kayser V, Chennamsetty N, Voynov V, Forrer K, Helk B, Trout BL. Glycosylation influences on the aggregation propensity of therapeutic monoclonal antibodies. Biotechnol J. 2011;6(1):38–44.

248. Pacholarz KJ, Porrini M, Garlish RA, Burnley RJ, Taylor RJ, Henry AJ, et al. Dynamics of Intact Immunoglobulin G Explored by Drift-Tube Ion-Mobility Mass Spectrometry and Molecular Modeling. Angew Chem Int Ed. 2014;53(30):7765–9.

249. Wang T, Duan Y. Probing the stability-limiting regions of an antibody single-chain variable fragment: a molecular dynamics simulation study. Protein Eng Des Sel. 2011;24(9):gzr029.

250. Feller SE, Zhang Y, Pastor RW, Brooks BR. Constant pressure molecular dynamics simulation: The Langevin piston method. J Chem Phys. 1995;103(11):4613–21.

251. Martyna GJ, Tobias DJ, Klein ML. Constant pressure molecular dynamics algorithms. J Chem Phys. 1994;101(5):4177–89.

252. Schulten K. NAMD Energy Plugin, Version 1.4 [Internet]. 2011 [citado 19 de outubro de 2018]. Disponível em: http://www.ks.uiuc.edu/Research/vmd/plugins/namdenergy/

253. Gumbart JC, Luo D. HBonds Plugin, Version 1.2 [Internet]. 2011 [citado 19 de outubro de 2018]. Disponível em: http://www.ks.uiuc.edu/Research/vmd/plugins/hbonds/

254. Trabuco L, Villa E. Salt bridges plugin, version 1.1 [Internet]. 2006 [citado 6 de novembro de 2018]. Disponível em: http://www.ks.uiuc.edu/Research/vmd/plugins/saltbr/

255. Takamatsu Y, Sugiyama A, Purqon A, Nagao H, Nishikawa K. Binding Free Energy Calculation and Structural Analysis for Antigen-Antibody Complex. AIP Conf Proc. 2006;832(1):566–9.

256. Zhang Y, Pan D, Shen Y, Jin N, Liu H, Yao X. Understanding the molecular mechanism of the broad and potent neutralization of HIV-1 by antibody VRC01 from the perspective of molecular dynamics simulation and binding free energy calculations. J Mol Model. 2012;18(9):4517–27.

257. Guo J, Wang X, Sun H, Liu H, Yao X. The molecular basis of IGF-II/IGF2R recognition: a combined molecular dynamics simulation, free-energy calculation and computational alanine scanning study. J Mol Model. 2012;18(4):1421–30.

258. Andrianov AM, Kashyn IA, Tuzikov AV. Computational discovery of novel HIV-1 entry inhibitors based on potent and broad neutralizing antibody VRC01. J Mol Graph Model. 2015;61:262–71.

259. Kollman PA, Massova I, Reyes C, Kuhn B, Huo S, Chong L, et al. Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models. Acc Chem Res. 2000;33(12):889–97.

260. Homeyer N, Gohlke H. Free Energy Calculations by the Molecular Mechanics Poisson-Boltzmann Surface Area Method. Mol Inform. 2012;31(2):114–22.

261. Hou T, Wang J, Li Y, Wang W. Assessing the performance of the MM/PBSA and MM/GBSA methods: I. The accuracy of binding free energy calculations based on molecular dynamics simulations. J Chem Inf Model. 2011;51(1):69–82.

262. Adamczak R, Porollo A, Meller J. Combining prediction of secondary structure and solvent accessibility in proteins. Proteins. 2005;59(3):467–75.

263. Kollman P. Free energy calculations: Applications to chemical and biochemical phenomena. Chem Rev. 1993;93(7):2395–417.

264. Liu H, Hou T. CaFE: a tool for binding affinity prediction using end-point free energy methods. Bioinformatics. 2016;32(14):2216–8.

265. Kamberaj H. Thermodynamics of biological phenomena. In: Implicit models for free energy calculations. Escópia: International Balkan University; 2016. p. 123–92.

266. Chipot C, Pohorille A. Free energy calculations. New York: Springer; 2007. 517 p.

267. Baker NA, Sept D, Joseph S, Holst MJ, McCammon JA. Electrostatics of nanosystems: application to microtubules and the ribosome. Proc Natl Acad Sci USA. 2001;98(18):10037–41.

268. Isralewitz B, Baudry J, Gullingsrud J, Kosztin D, Schulten K. Steered molecular dynamics investigations of protein function. J Mol Graph Model. 2001;19(1):13–25.

269. Izrailev S, Stepaniants S, Isralewitz B, Kosztin D, Lu H, Molnar F, et al. Steered molecular dynamics. In: Computational molecular dynamics: challenges, methods, ideas. Berlin: Springer; 1999. p. 39–65.

270. Amor S, Groome N, Linington C, Morris MM, Dornmair K, Gardinier MV, et al. Identification of epitopes of myelin oligodendrocyte glycoprotein for the induction of experimental allergic encephalomyelitis in SJL and Biozzi AB/H mice. J Immunol. 1994;153(10):4349–56.

271. Iglesias A, Bauer J, Litzenburger T, Schubart A, Linington C. T- and B-cell responses to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis and multiple sclerosis. Glia. 2001;36(2):220–34.

272. Singh RP, Blossey R, Cleri F. Structure and Mechanical Characterization of DNA i-Motif Nanowires by Molecular Dynamics Simulation. Biophys J. 2013;105(12):2820–31.

273. Su Z-Y, Wang Y-T. A Molecular Dynamics Simulation of the Human Lysozyme – Camelid VHH HL6 Antibody System. Int J Mol Sci. 2009;10(4):1719–27.

274. Hanasaki I, Haga T, Kawano S. The antigen–antibody unbinding process through steered molecular dynamics of a complex of an Fv fragment and lysozyme. J Phys: Condens Matter. 2008;20(25):255238.

275. Garcia PS, Moreau ALD, Ierich JCM, Vig ACA, Higa AM, Oliveira GS, et al. A Nanobiosensor Based on 4-Hydroxyphenylpyruvate Dioxygenase Enzyme for Mesotrione Detection. IEEE Sensors Journal. 2015;15(4):2106–13.

276. Coen MC, Lehmann R, Gröning P, Bielmann M, Galli C, Schlapbach L. Adsorption and Bioactivity of Protein A on Silicon Surfaces Studied by AFM and XPS. J Colloid Interface Sci. 2001;233(2):180–9.

277. Sotriffer CA, Rode BM, Varga JM, Liedl KR. Elbow flexibility and ligand-induced domain rearrangements in antibody Fab NC6.8: large effects of a small hapten. Biophys J. 2000;79(2):614–28.

278. Zhang X, Zhang L, Tong H, Peng B, Rames MJ, Zhang S, et al. 3D Structural Fluctuation of IgG1 Antibody Revealed by Individual Particle Electron Tomography. Sci Rep. 2015;5:9803.

279. Janda A, Bowen A, Greenspan NS, Casadevall A. Ig Constant Region Effects on Variable Region Structure and Function. Front Microbiol. 2016;7.

280. Takahashi T. Significant role of electrostatic interactions for stabilization of protein assemblies. Adv Biophys. 1997;34:41–54.

281. Petukhov M, Rychkov G, Firsov L, Serrano L. H-bonding in protein hydration revisited. Protein Sci. 2004;13(8):2120–9.

282. Bosshard HR, Marti DN, Jelesarov I. Protein stabilization by salt bridges: concepts, experimental approaches and clarification of some misunderstandings. J Mol Recognit. 2004;17(1):1–16.

283. HyunJoong Joh N, Min A, Faham S, Whitelegge JP, Yang D, Woods VL, et al. Modest stabilization by most hydrogen-bonded side-chain interactions in membrane proteins. Nature. 2008;453(7199):1266–70.

284. Xie N-Z, Du Q-S, Li J-X, Huang R-B. Exploring Strong Interactions in Proteins with Quantum Chemistry and Examples of Their Applications in Drug Design. PLoS One. 2015;10(9).

285. Franca EF, Leite FL, Cunha RA, Oliveira Jr. ON, Freitas LCG. Designing an enzyme-based nanobiosensor using molecular modeling techniques. Phys Chem Chem Phys. 2011;13(19):8894–9.

286. Kerlero de Rosbo N, Hoffman M, Mendel I, Yust I, Kaye J, Bakimer R, et al. Predominance of the autoimmune response to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis: reactivity to the extracellular domain of MOG is directed against three main regions. Eur J Immunol. 1997;27(11):3059–69.

287. Blanchfield JL, Evavold BD. MOG35-55, not NFM15-35, is the critical autoantigen for inducing demyelinating autoimmune disease. J Immunol. 2017;198(1 Supplement):156.28-156.28.

288. Yannakakis MP, Tzoupis H, Michailidou E, Mantzourani E, Simal C, Tselios T. Molecular dynamics at the receptor level of immunodominant myelin oligodendrocyte glycoprotein 35-55 epitope implicated in multiple sclerosis. J Mol Graph Model. 2016;68:78–86.

289. Zhang Z, Witham S, Alexov E. On the role of electrostatics on protein-protein interactions. Phys Biol. 2011;8(3):035001.

290. Sinha N, Smith-Gill SJ. Electrostatics in protein binding and function. Curr Protein Pept Sci. 2002;3(6):601–14.

291. Martin AR. Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Kontermann R, Dübel S, organizadores. Antibody Engineering. Heidelberg: Springer; 2010. p. 33–51.

292. Venclovas C. Methods for Sequence–Structure Alignment. In: Orry AJW, Abagyan R, organizadores. Homology Modeling: Methods and Protocols. New York: Springer; 2012. p. 55–82.

293. Wucherpfennig KW, Sette A, Southwood S, Oseroff C, Matsui M, Strominger JL, et al. Structural requirements for binding of an immunodominant myelin basic protein peptide to DR2 isotypes and for its recognition by human T cell clones. J Exp Med. 1994;179(1):279–90.

294. Wucherpfennig KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell. 1995;80(5):695–705.

295. Li Y, Li H, Martin R, Mariuzza RA. Structural basis for the binding of an immunodominant peptide from myelin basic protein in different registers by two HLA-DR2 proteins. J Mol Biol. 2000;304(2):177–88.

296. Krogsgaard M, Wucherpfennig KW, Cannella B, Hansen BE, Svejgaard A, Pyrdol J, et al. Visualization of myelin basic protein (MBP) T cell epitopes in multiple sclerosis lesions using a monoclonal antibody specific for the human histocompatibility leukocyte antigen (HLA)-DR2-MBP 85-99 complex. J Exp Med. 2000;191(8):1395–412.

297. Lang HLE, Jacobsen H, Ikemizu S, Andersson C, Harlos K, Madsen L, et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nat Immunol. 2002;3(10):940–3.

298. Wucherpfennig KW, Catz I, Hausmann S, Strominger JL, Steinman L, Warren KG. Recognition of the immunodominant myelin basic protein peptide by autoantibodies and HLA-DR2-restricted T cell clones from multiple sclerosis patients. Identity of key contact residues in the B-cell and T-cell epitopes. J Clin Invest. 1997;100(5):1114–22.

299. Fukunishi H, Shimada J, Shiraishi K. Antigen-antibody interactions and structural flexibility of a femtomolar-affinity antibody. Biochemistry. 2012;51(12):2597–605.

300. Yang J, Wang Q, Qiao C, Lin Z, Li X, Huang Y, et al. Potent anti-angiogenesis and anti-tumor activity of a novel human anti-VEGF antibody, MIL60. Cell Mol Immunol. 2014;11(3):285–93.

301. Potocnakova L, Bhide M, Pulzova LB. An Introduction to B-Cell Epitope Mapping and In Silico Epitope Prediction. J Immunol Res. 2016;2016.

302. Morfill J, Neumann J, Blank K, Steinbach U, Puchner EM, Gottschalk K-E, et al. Force-based analysis of multidimensional energy landscapes: application of dynamic force spectroscopy and steered molecular dynamics simulations to an antibody fragment-peptide complex. J Mol Biol. 2008;381(5):1253–66.

303. Moraes A de S, Moreau AL, Hausen M, Rossi IT, Higa AM, Peroni LA, et al. Atrazine Detection in Liquid Using a Nanoimmunosensor Based on Chemically Modified Atomic Force Microscopy Tips. Sensor Letters. 2016;14(5):508–14.

304. Rodrigues LF, Ierich JCM, Andrade MA, Hausen MA, Leite FL, Moreau ALD, et al. Nanomechanical Cantilever-Based Sensor: An Efficient Tool to Measure the Binding Between the Herbicide Mesotrione and 4-Hydroxyphenylpyruvate Dioxygenase. Nano. 2017;12(07):1750079.

305. Bates IR, Harauz G. Molecular dynamics exposes alpha-helices in myelin basic protein. J Mol Model. 2003;9(5):290–7.

306. Tzakos AG, Fuchs P, Nuland NAJ van, Troganis A, Tselios T, Deraos S, et al. NMR and molecular dynamics studies of an autoimmune myelin basic protein peptide and its antagonist. Eur J Biochem. 2004;271(16):3399–413.

307. Mantzourani ED, Blokar K, Tselios TV, Matsoukas JM, Platts JA, Mavromoustakos TM, et al. A combined NMR and molecular dynamics simulation study to determine the conformational properties of agonists and antagonists against experimental autoimmune encephalomyelitis. Bioorganic Med Chem. 2008;16(5):2171–82.

308. Deraos G, Chatzantoni K, Matsoukas M-T, Tselios T, Deraos S, Katsara M, et al. Citrullination of Linear and Cyclic Altered Peptide Ligands from Myelin Basic Protein (MBP87−99) Epitope Elicits a Th1 Polarized Response by T Cells Isolated from Multiple Sclerosis Patients: Implications in Triggering Disease. J Med Chem. 2008;51(24):7834–42.

309. Stadler AM, Stingaciu L, Radulescu A, Holderer O, Monkenbusch M, Biehl R, et al. Internal nanosecond dynamics in the intrinsically disordered myelin basic protein. J Am Chem Soc. 2014;136(19):6987–94.

310. Alberga D, Trisciuzzi D, Lattanzi G, Bennett JL, Verkman AS, Mangiatordi GF, et al. Comparative molecular dynamics study of neuromyelitis optica-immunoglobulin G binding to aquaporin-4 extracellular domains. Biochim Biophys Acta. 2017;1859(8):1326–34.

311. Amarante AM, Oliveira GS, Bueno CC, Cunha RA, Ierich JCM, Freitas LCG, et al. Modeling the coverage of an AFM tip by enzymes and its application in nanobiosensors. J Mol Graph Model. 2014;53:100–4.

312. Bueno CC, Amarante AM, Oliveira GS, Deda DK, Teschke O, Franca EF, et al. Nanobiosensor for diclofop detection based on chemically modified AFM probes. IEEE Sens J. 2014;14(2):1467–75.