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Peptides against autoimmune neurodegeneration

Stepanov A., Lomakin Y., Gabibov A., Belogurov A.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 Bentham Science Publishers. The mammalian immune system is a nearly perfect defensive system polished by a hundred million years of evolution. Unique flexibility and adaptivity have created a virtually impenetrable barrier to numerous exogenous pathogens that are assaulting us every moment. Unfortunately, triggers that remain mostly enigmatic will sometimes persuade the immune system to retarget against self-antigens. This civil war remains underway, showing no mercy and taking no captives, eventually leading to irreversible pathological changes in the human body. Research that has emerged during the last two decades has given us hope that we may have a chance to overcome autoimmune diseases using a variety of techniques to "reset" the immune system. In this report, we summarize recent advances in utilizing short polypeptides - mostly fragments of autoantigens - in the treatment of autoimmune neurodegeneration.

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Keywords

Autoantibodies, Autoreactive B cell elimination, Cross-reactivity, Immunotoxins, Liposomes, Multiple sclerosis, Specific allergen immunotherapy, Tolerance

References

[1] Cho, J.H.; Feldman, M. Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies. Nat. Med., 2015, 21(7), 730-738.

[2] Ransohoff, R.M.; Hafler, D.A.; Lucchinetti, C.F. Multiple sclerosis-a quiet revolution. Nat. Rev. Neurol., 2015, 11(3), 134-142.

[3] Noon, L. Prophylactic inoculation against hay fever. Lancet., 1911, i, 1572-1573.

[4] Critchfield, J.M.; Racke, M.K.; Zuniga-Pflucker, J.C.; Cannella, B.; Raine, C.S.; Goverman, J.; Lenardo, M.J. T cell deletion in high antigen dose therapy of autoimmune encephalomyelitis. Science., 1994, 263(5150), 1139-1143.

[5] Koch-Henriksen, N.; Sorensen, P.S. The changing demographic pattern of multiple sclerosis epidemiology. Lancet. Neurol., 2010, 9(5), 520-532.

[6] Arnon, R.; Teitelbaum, D.; Sela, M. Suppression of experimental allergic encephalomyelitis by COP1-relevance to multiple sclerosis. Isr. J. Med. Sci., 1989, 25(12), 686-689.

[7] Fridkis-Hareli, M.; Teitelbaum, D.; Pecht, I.; Arnon, R.; Sela, M. Binding of copolymer 1 and myelin basic protein leads to clustering of class II MHC molecules on antigen-presenting cells. Int. Immunol., 1997, 9(7), 925-934.

[8] Duda, P.W.; Schmied, M.C.; Cook, S.L.; Krieger, J.I.; Hafler, D.A. Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. J. Clin. Invest., 2000, 105(7), 967-976.

[9] Aharoni, R.; Teitelbaum, D.; Leitner, O.; Meshorer, A.; Sela, M.; Arnon, R. Specific Th2 cells accumulate in the central nervous system of mice protected against experimental autoimmune encephalomyelitis by copolymer 1. Proc. Natl. Acad. Sci. U. S. A., 2000, 97(21), 11472-11477.

[10] Hong, J.; Li, N.; Zhang, X.; Zheng, B.; Zhang, J.Z. Induction of CD4+CD25+ regulatory T cells by copolymer-I through activation of transcription factor Foxp3. Proc. Natl. Acad. Sci. U. S. A., 2005, 102(18), 6449-6454.

[11] Aharoni, R.; Kayhan, B.; Eilam, R.; Sela, M.; Arnon, R. Glatiramer acetate-specific T cells in the brain express T helper 2/3 cytokines and brain-derived neurotrophic factor in situ. Proc. Natl. Acad. Sci. U. S. A., 2003, 100(24), 14157-14162.

[12] Fridkis-Hareli, M.; Strominger, J.L. Promiscuous binding of synthetic copolymer 1 to purified HLA-DR molecules. J. Immunol., 1998, 160(9), 4386-4397.

[13] Johnson, K.P.; Brooks, B.R.; Cohen, J.A.; Ford, C.C.; Goldstein, J.; Lisak, R.P.; Myers, L.W.; Panitch, H.S.; Rose, J.W.; Schiffer, R.B. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology., 1995, 45(7), 1268-1276.

[14] La Mantia, L.; Di Pietrantonj, C.; Rovaris, M.; Rigon, G.; Frau, S.; Berardo, F.; Gandini, A.; Longobardi, A.; Weinstock-Guttman, B.; Vaona, A. Comparative efficacy of interferon beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. J. Neurol. Neurosurg. Psychiatry., 2015, 86(9), 1016-1020.

[15] Kalincik, T.; Jokubaitis, V.; Izquierdo, G.; Duquette, P.; Girard, M.; Grammond, P.; Lugaresi, A.; Oreja-Guevara, C.; Bergamaschi, R.; Hupperts, R.; Grand'Maison, F.; Pucci, E.; Van Pesch, V.; Boz, C.; Iuliano, G.; Fernandez-Bolanos, R.; Flechter, S.; Spitaleri, D.; Cristiano, E.; Verheul, F.; Lechner-Scott, J.; Amato, M.P.; Cabrera-Gomez, J.A.; Saladino, M.L.; Slee, M.; Moore, F.; Gray, O.; Paine, M.; Barnett, M.; Havrdova, E.; Horakova, D.; Spelman, T.; Trojano, M.; Butzkueven, H.; Group, M.S.S. Comparative effectiveness of glatiramer acetate and interferon beta formulations in relapsing-remitting multiple sclerosis. Mult. Scler., 2015, 21(9), 1159-1171.

[16] Palace, J.; Duddy, M.; Bregenzer, T.; Lawton, M.; Zhu, F.; Boggild, M.; Piske, B.; Robertson, N.P.; Oger, J.; Tremlett, H.; Tilling, K.; Ben-Shlomo, Y.; Dobson, C. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. Lancet. Neurol., 2015, 14(5), 497-505.

[17] Munari, L.; Lovati, R.; Boiko, A. Therapy with glatiramer acetate for multiple sclerosis. Cochrane. Database. Syst. Rev., 2004(1), CD004678.

[18] Ford, C.; Goodman, A.D.; Johnson, K.; Kachuck, N.; Lindsey, J.W.; Lisak, R.; Luzzio, C.; Myers, L.; Panitch, H.; Preiningerova, J.; Pruitt, A.; Rose, J.; Rus, H.; Wolinsky, J. Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. Mult. Scler., 2010, 16(3), 342-350.

[19] Ziemssen, T.; Bajenaru, O.A.; Carra, A.; de Klippel, N.; de Sa, J.C.; Edland, A.; Frederiksen, J.L.; Heinzlef, O.; Karageorgiou, K.E.; Lander Delgado, R.H.; Landtblom, A.M.; Macias Islas, M.A.; Tubridy, N.; Gilgun-Sherki, Y. A 2-year observational study of patients with relapsing-remitting multiple sclerosis converting to glatiramer acetate from other disease-modifying therapies: the COPTIMIZE trial. J. Neurol., 2014, 261(11), 2101-2111.

[20] Comi, G.; Martinelli, V.; Rodegher, M.; Moiola, L.; Leocani, L.; Bajenaru, O.; Carra, A.; Elovaara, I.; Fazekas, F.; Hartung, H.P.; Hillert, J.; King, J.; Komoly, S.; Lubetzki, C.; Montalban, X.; Myhr, K.M.; Preziosa, P.; Ravnborg, M.; Rieckmann, P.; Rocca, M.A.; Wynn, D.; Young, C.; Filippi, M. Effects of early treatment with glatiramer acetate in patients with clinically isolated syndrome. Mult. Scler., 2013, 19(8), 1074-1083.

[21] Belogurov, A.A. Jr.; Kurkova, I.N.; Friboulet, A.; Thomas, D.; Misikov, V.K.; Zakharova, M.Y.; Suchkov, S.V.; Kotov, S.V.; Alehin, A.I.; Avalle, B.; Souslova, E.A.; Morse, H.C. 3rd; Gabibov, A.G.; Ponomarenko, N.A. Recognition and degradation of myelin basic protein peptides by serum autoantibodies: novel biomarker for multiple sclerosis. J. Immunol., 2008, 180(2), 1258-1267.

[22] Ponomarenko, N.A.; Durova, O.M.; Vorobiev, II; Belogurov, A.A. Jr.; Kurkova, I.N.; Petrenko, A.G.; Telegin, G.B.; Suchkov, S.V.; Kiselev, S.L.; Lagarkova, M.A.; Govorun, V.M.; Serebryakova, M.V.; Avalle, B.; Tornatore, P.; Karavanov, A.; Morse, H.C. 3rd; Thomas, D.; Friboulet, A.; Gabibov, A.G. Autoantibodies to myelin basic protein catalyze site-specific degradation of their antigen. Proc. Natl. Acad. Sci. U. S. A., 2006, 103(2), 281-286.

[23] Fridkis-Hareli, M.; Stern, J.N.; Fugger, L.; Strominger, J.L. Synthetic peptides that inhibit binding of the myelin basic protein 85-99 epitope to multiple sclerosis-associated HLA-DR2 molecules and MBP-specific T-cell responses. Hum. Immunol., 2001, 62(8), 753-763.

[24] Fridkis-Hareli, M.; Santambrogio, L.; Stern, J.N.; Fugger, L.; Brosnan, C.; Strominger, J.L. Novel synthetic amino acid copolymers that inhibit autoantigen-specific T cell responses and suppress experimental autoimmune encepha-lomyelitis. J. Clin. Invest., 2002, 109(12), 1635-1643.

[25] Illes, Z.; Stern, J.N.; Reddy, J.; Waldner, H.; Mycko, M.P.; Brosnan, C.F.; Ellmerich, S.; Altmann, D.M.; Santam-brogio, L.; Strominger, J.L.; Kuchroo, V.K. Modified amino acid copolymers suppress myelin basic protein 85-99-induced encephalomyelitis in humanized mice through different effects on T cells. Proc. Natl. Acad. Sci. U. S. A., 2004, 101(32), 11749-11754.

[26] Stern, J.N.; Illes, Z.; Reddy, J.; Keskin, D.B.; Fridkis-Hareli, M.; Kuchroo, V.K.; Strominger, J.L. Peptide 15-mers of defined sequence that substitute for random amino acid copolymers in amelioration of experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A., 2005, 102(5), 1620-1625.

[27] Stern, J.N.; Keskin, D.B.; Zhang, H.; Lv, H.; Kato, Z.; Strominger, J.L. Amino acid copolymer-specific IL-1--secreting regulatory T cells that ameliorate autoimmune diseases in mice. Proc. Natl. Acad. Sci. U. S. A., 2008, 105(13), 5172-5176.

[28] Kawamoto, N.; Ohnishi, H.; Kondo, N.; Strominger, J.L. The role of dendritic cells in the generation of CD4(+) CD25(HI) Foxp3(+) T cells induced by amino acid copolymers. Int. Immunol., 2013, 25(1), 53-65.

[29] Koenig, P.A.; Spooner, E.; Kawamoto, N.; Strominger, J.L.; Ploegh, H.L. Amino acid copolymers that alleviate experimental autoimmune encephalomyelitis in. vivo interact with heparan sulfates and glycoprotein 96 in APCs. J. Immunol., 2013, 191(1), 208-216.

[30] Vandenbark, A.A.; Hashim, G.; Offner, H. Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis. Nature., 1989, 341(6242), 541-544.

[31] Offner, H.; Hashim, G.A.; Vandenbark, A.A. T cell receptor peptide therapy triggers autoregulation of experimental encephalomyelitis. Science., 1991, 251(4992), 430-432.

[32] Howell, M.D.; Winters, S.T.; Olee, T.; Powell, H.C.; Carlo, D.J.; Brostoff, S.W. Vaccination against experimental allergic encephalomyelitis with T cell receptor peptides. Science., 1989, 246(4930), 668-670.

[33] Buenafe, A.C.; Andrew, S.; Afentoulis, M.; Offner, H.; Vandenbark, A.A. Prevention and treatment of experimental autoimmune encephalomyelitis with clonotypic CDR3 peptides: CD4(+) Foxp3(+) T-regulatory cells suppress interleukin-2-dependent expansion of myelin basic protein-specific T cells. Immunology., 2010, 130(1), 114-124.

[34] Marini, J.C.; Jameson, B.A.; Lublin, F.D.; Korngold, R. A CD4-CDR3 peptide analog inhibits both primary and secondary autoreactive CD4+ T cell responses in experimental allergic encephalomyelitis. J. Immunol., 1996, 157(8), 3706-3715.

[35] Edling, A.E.; Choksi, S.; Huang, Z.; Korngold, R. Effect of a cyclic heptapeptide based on the human CD4 domain 1 CC' loop region on murine experimental allergic encepha-lomyelitis: inhibition of both primary and secondary responses. J. Neuroimmunol., 2001, 112(1-2), 115-128.

[36] Srinivasan, M.; Gienapp, I.E.; Stuckman, S.S.; Rogers, C.J.; Jewell, S.D.; Kaumaya, P.T.; Whitacre, C.C. Suppression of experimental autoimmune encephalomyelitis using peptide mimics of CD28. J. Immunol., 2002, 169(4), 2180-2188.

[37] Garren, H.; Robinson, W.H.; Krasulova, E.; Havrdova, E.; Nadj, C.; Selmaj, K.; Losy, J.; Nadj, I.; Radue, E.W.; Kidd, B.A.; Gianettoni, J.; Tersini, K.; Utz, P.J.; Valone, F.; Steinman, L.; Group, B.H.T.S. Phase 2 trial of a DNA vaccine encoding myelin basic protein for multiple sclerosis. Ann. Neurol., 2008, 63(5), 611-620.

[38] Katsara, M.; Deraos, G.; Tselios, T.; Matsoukas, M.T.; Friligou, I.; Matsoukas, J.; Apostolopoulos, V. Design and synthesis of a cyclic double mutant peptide (cyclo(87-99)[A91,A96]MBP87-99) induces altered responses in mice after conjugation to mannan: implications in the immuno-therapy of multiple sclerosis. J. Med. Chem., 2009, 52(1), 214-218.

[39] Katsara, M.; Yuriev, E.; Ramsland, P.A.; Deraos, G.; Tselios, T.; Matsoukas, J.; Apostolopoulos, V. A double mutation of MBP(83-99) peptide induces IL-4 responses and antagonizes IFN-gamma responses. J. Neuroimmunol., 2008, 200(1-2), 77-89.

[40] Peschl, P.; Reindl, M.; Schanda, K.; Sospedra, M.; Martin, R.; Lutterotti, A. Antibody responses following induction of antigen-specific tolerance with antigen-coupled cells. Mult. Scler., 2015, 21(5), 651-655.

[41] Lutterotti, A.; Yousef, S.; Sputtek, A.; Sturner, K.H.; Stellmann, J.P.; Breiden, P.; Reinhardt, S.; Schulze, C.; Bester, M.; Heesen, C.; Schippling, S.; Miller, S.D.; Sospedra, M.; Martin, R. Antigen-specific tolerance by autologous myelin peptide-coupled cells: a phase 1 trial in multiple sclerosis. Sci. Transl. Med., 2013, 5(188), 188ra175.

[42] Liu, X.; Ciumas, C.; Huang, Y.M.; Steffensen, K.R.; Lian, H.; Link, H.; Xiao, B.G. Autoantigen-pulsed dendritic cells constitute a beneficial cytokine and growth factor network in ameliorating experimental allergic encephalomyelitis. Mult. Scler., 2005, 11(4), 381-389.

[43] Crowe, P.D.; Qin, Y.; Conlon, P.J.; Antel, J.P. NBI-5788, an altered MBP83-99 peptide, induces a T-helper 2-like immune response in multiple sclerosis patients. Ann. Neurol., 2000, 48(5), 758-765.

[44] Kappos, L.; Comi, G.; Panitch, H.; Oger, J.; Antel, J.; Conlon, P.; Steinman, L. Induction of a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. The Altered Peptide Ligand in Relapsing MS Study Group. Nat. Med., 2000, 6(10), 1176-1182.

[45] Bielekova, B.; Goodwin, B.; Richert, N.; Cortese, I.; Kondo, T.; Afshar, G.; Gran, B.; Eaton, J.; Antel, J.; Frank, J.A.; McFarland, H.F.; Martin, R. Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. Nat. Med., 2000, 6(10), 1167-1175.

[46] Ruiz, P.J.; Garren, H.; Hirschberg, D.L.; Langer-Gould, A.M.; Levite, M.; Karpuj, M.V.; Southwood, S.; Sette, A.; Conlon, P.; Steinman, L. Microbial epitopes act as altered peptide ligands to prevent experimental autoimmune encephalomyelitis. J. Exp. Med., 1999, 189(8), 1275-1284.

[47] Yeste, A.; Nadeau, M.; Burns, E.J.; Weiner, H.L.; Quintana, F.J. Nanoparticle-mediated codelivery of myelin antigen and a tolerogenic small molecule suppresses experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A., 2012, 109(28), 11270-11275.

[48] Tselios, T.; Aggelidakis, M.; Tapeinou, A.; Tseveleki, V.; Kanistras, I.; Gatos, D.; Matsoukas, J. Rational design and synthesis of altered peptide ligands based on human myelin oligodendrocyte glycoprotein 35-55 epitope: inhibition of chronic experimental autoimmune encephalomyelitis in mice. Molecules., 2014, 19(11), 17968-17984.

[49] Nicholson, L.B.; Greer, J.M.; Sobel, R.A.; Lees, M.B.; Kuchroo, V.K. An altered peptide ligand mediates immune deviation and prevents autoimmune encephalomyelitis. Immunity., 1995, 3(4), 397-405.

[50] Nicholson, L.B.; Murtaza, A.; Hafler, B.P.; Sette, A.; Kuchroo, V.K. A T cell receptor antagonist peptide induces T cells that mediate bystander suppression and prevent autoimmune encephalomyelitis induced with multiple myelin antigens. Proc. Natl. Acad. Sci. U. S. A., 1997, 94(17), 9279-9284.

[51] Young, D.A.; Lowe, L.D.; Booth, S.S.; Whitters, M.J.; Nicholson, L.; Kuchroo, V.K.; Collins, M. IL-4, IL-10, IL-13, and TGF-beta from an altered peptide ligand-specific Th2 cell clone down-regulate adoptive transfer of experimental autoimmune encephalomyelitis. J. Immunol., 2000, 164(7), 3563-3572.

[52] Kuchroo, V.K.; Greer, J.M.; Kaul, D.; Ishioka, G.; Franco, A.; Sette, A.; Sobel, R.A.; Lees, M.B. A single TCR antagonist peptide inhibits experimental allergic encephalomyelitis mediated by a diverse T cell repertoire. J. Immunol., 1994, 153(7), 3326-3336.

[53] Franco, A.; Southwood, S.; Arrhenius, T.; Kuchroo, V.K.; Grey, H.M.; Sette, A.; Ishioka, G.Y. T cell receptor antagonist peptides are highly effective inhibitors of experimental allergic encephalomyelitis. Eur. J. Immunol., 1994, 24(4), 940-946.

[54] Hunter, Z.; McCarthy, D.P.; Yap, W.T.; Harp, C.T.; Getts, D.R.; Shea, L.D.; Miller, S.D. A biodegradable nanoparticle platform for the induction of antigen-specific immune tolerance for treatment of autoimmune disease. ACS. Nano., 2014, 8(3), 2148-2160.

[55] Kobayashi, N.; Kobayashi, H.; Gu, L.; Malefyt, T.; Siahaan, T.J. Antigen-specific suppression of experimental autoimmune encephalomyelitis by a novel bifunctional peptide inhibitor. J. Pharmacol. Exp. Ther., 2007, 322(2), 879-886.

[56] Hecker, M.; Fitzner, B.; Wendt, M.; Lorenz, P.; Flechtner, K.; Steinbeck, F.; Schroder, I.; Thiesen, H.J.; Zettl, U.K. High-Density Peptide Microarray Analysis of IgG Autoantibody Reactivities in Serum and Cerebrospinal Fluid of Multiple Sclerosis Patients. Mol. Cell. Proteomics., 2016, 15(4), 1360-1380.

[57] Belogurov, A.A. Jr.; Zargarova, T.A.; Turobov, V.I.; Novikova, N.I.; Favorova, O.O.; Ponomarenko, N.A.; Gabibov, A.G. Suppression of ongoing experimental allergic encephalomyelitis in DA rats by novel peptide drug, structural part of human myelin basic protein 46-62. Autoimmunity., 2009, 42(4), 362-364.

[58] Belogurov, A. Jr.; Kuzina, E.; Kudriaeva, A.; Kononikhin, A.; Kovalchuk, S.; Surina, Y.; Smirnov, I.; Lomakin, Y.; Bacheva, A.; Stepanov, A.; Karpova, Y.; Lyupina, Y.; Kharybin, O.; Melamed, D.; Ponomarenko, N.; Sharova, N.; Nikolaev, E.; Gabibov, A. Ubiquitin-independent proteosomal degradation of myelin basic protein contributes to development of neurodegenerative autoimmunity. FASEB. J., 2015, 29(5), 1901-1913.

[59] Kuzina, E.S.; Chernolovskaya, E.L.; Kudriaeva, A.A.; Zenkova, M.A.; Knorre, V.D.; Surina, E.A.; Ponomarenko, N.A.; Bobik, T.V.; Smirnov, I.V.; Bacheva, A.V.; Belogurov, A.A.; Gabibov, A.G.; Vlasov, V.V. Immunoproteasome enhances intracellular proteolysis of myelin basic protein. Dokl. Biochem. Biophys., 2013, 453, 300-303.

[60] Belogurov, A. Jr.; Kudriaeva, A.; Kuzina, E.; Smirnov, I.; Bobik, T.; Ponomarenko, N.; Kravtsova-Ivantsiv, Y.; Ciechanover, A.; Gabibov, A. Multiple sclerosis autoantigen myelin basic protein escapes control by ubiquitination during proteasomal degradation. J. Biol. Chem., 2014, 289(25), 17758-17766.

[61] Belogurov, A.A. Jr.; Stepanov, A.V.; Smirnov, I.V.; Melamed, D.; Bacon, A.; Mamedov, A.E.; Boitsov, V.M.; Sashchenko, L.P.; Ponomarenko, N.A.; Sharanova, S.N.; Boyko, A.N.; Dubina, M.V.; Friboulet, A.; Genkin, D.D.; Gabibov, A.G. Liposome-encapsulated peptides protect against experimental allergic encephalitis. FASEB. J., 2013, 27(1), 222-231.

[62] Tseveleki, V.; Tselios, T.; Kanistras, I.; Koutsoni, O.; Karamita, M.; Vamvakas, S.S.; Apostolopoulos, V.; Dotsika, E.; Matsoukas, J.; Lassmann, H.; Probert, L. Mannanconjugated myelin peptides prime non-pathogenic Th1 and Th17 cells and ameliorate experimental autoimmune encephalomyelitis. Exp. Neurol., 2015, 267, 254-267.

[63] Belogurov, A. Jr.; Zakharov, K.; Lomakin, Y.; Surkov, K.; Avtushenko, S.; Kruglyakov, P.; Smirnov, I.; Makshakov, G.; Lockshin, C.; Gregoriadis, G.; Genkin, D.; Gabibov, A.; Evdoshenko, E. CD206-Targeted Liposomal Myelin Basic Protein Peptides in Patients with Multiple Sclerosis Resistant to First-Line Disease-Modifying Therapies: A First-in Human, Proof-of-Concept Dose-Escalation Study. Neurotherapeutics., 2016.

[64] Grewal, I.S.; Flavell, R.A. CD40 and CD154 in cellmediated immunity. Annu. Rev. Immunol., 1998, 16, 111-135.

[65] Lomakin, Y.; Belogurov, A. Jr.; Glagoleva, I.; Stepanov, A.; Zakharov, K.; Okunola, J.; Smirnov, I.; Genkin, D.; Gabibov, A. Administration of Myelin Basic Protein Peptides Encapsulated in Mannosylated Liposomes Normalizes Level of Serum TNF-alpha and IL-2 and Chemoattractants CCL2 and CCL4 in Multiple Sclerosis Patients. Mediators. Inflamm., 2016, 2016, 2847232.

[66] Cahalan, M.D.; Chandy, K.G. The functional network of ion channels in T lymphocytes. Immunol. Rev., 2009, 231(1), 59-87.

[67] Beeton, C.; Wulff, H.; Standifer, N.E.; Azam, P.; Mullen, K.M.; Pennington, M.W.; Kolski-Andreaco, A.; Wei, E.; Grino, A.; Counts, D.R.; Wang, P.H.; LeeHealey, C.J.; B, S.A.; Sankaranarayanan, A.; Homerick, D.; Roeck, W.W.; Tehranzadeh, J.; Stanhope, K.L.; Zimin, P.; Havel, P.J.; Griffey, S.; Knaus, H.G.; Nepom, G.T.; Gutman, G.A.; Calabresi, P.A.; Chandy, K.G. Kv1.3 channels are a therapeutic target for T cell-mediated autoimmune diseases. Proc. Natl. Acad. Sci. U. S. A., 2006, 103(46), 17414-17419.

[68] Chhabra, S.; Chang, S.C.; Nguyen, H.M.; Huq, R.; Tanner, M.R.; Londono, L.M.; Estrada, R.; Dhawan, V.; Chauhan, S.; Upadhyay, S.K.; Gindin, M.; Hotez, P.J.; Valenzuela, J.G.; Mohanty, B.; Swarbrick, J.D.; Wulff, H.; Iadonato, S.P.; Gutman, G.A.; Beeton, C.; Pennington, M.W.; Norton, R.S.; Chandy, K.G. Kv1.3 channel-blocking immunomodulatory peptides from parasitic worms: implications for autoimmune diseases. FASEB. J., 2014, 28(9), 3952-3964.

[69] Weinstock, J.V. Autoimmunity: The worm returns. Nature., 2012, 491(7423), 183-185.

[70] Correale, J.; Farez, M. Association between parasite infection and immune responses in multiple sclerosis. Ann. Neurol., 2007, 61(2), 97-108.

[71] Belogurov, A. Jr.; Smirnov, I.; Ponomarenko, N.; Gabibov, A. Antibody-antigen pair probed by combinatorial approach and rational design: bringing together structural insights, directed evolution, and novel functionality. FEBS. Lett., 2012, 586(18), 2966-2973.

[72] Elliott, C.; Lindner, M.; Arthur, A.; Brennan, K.; Jarius, S.; Hussey, J.; Chan, A.; Stroet, A.; Olsson, T.; Willison, H.; Barnett, S.C.; Meinl, E.; Linington, C. Functional identification of pathogenic autoantibody responses in patients with multiple sclerosis. Brain., 2012, 135(Pt 6), 1819-1833.

[73] Meinl, E. Untapped targets in multiple sclerosis. J. Neurol. Sci., 2011, 311. Suppl. 1, S12-15.

[74] Chamczuk, A.J.; Ursell, M.; O'Connor, P.; Jackowski, G.; Moscarello, M.A. A rapid ELISA-based serum assay for myelin basic protein in multiple sclerosis. J. Immunol. Methods, 2002, 262(1-2), 21-27.

[75] Reindl, M.; Linington, C.; Brehm, U.; Egg, R.; Dilitz, E.; Deisenhammer, F.; Poewe, W.; Berger, T. Antibodies against the myelin oligodendrocyte glycoprotein and the myelin basic protein in multiple sclerosis and other neurological diseases: a comparative study. Brain., 1999, 122. (Pt. 11), 2047-2056.

[76] Sun, X.; Bakhti, M.; Fitzner, D.; Schnaars, M.; Kruse, N.; Coskun, U.; Kremser, C.; Willecke, K.; Kappos, L.; Kuhle, J.; Simons, M. Quantified CSF antibody reactivity against myelin in multiple sclerosis. Ann. Clin. Transl. Neurol., 2015, 2(12), 1116-1123.

[77] Quintana, F.J.; Farez, M.F.; Izquierdo, G.; Lucas, M.; Cohen, I.R.; Weiner, H.L. Antigen microarrays identify CNS-produced autoantibodies in RRMS. Neurology., 2012, 78(8), 532-539.

[78] Genain, C.P. MR imaging investigations in a non-human primate model of multiple sclerosis. AJNR. Am. J. Neuroradiol., 1999, 20(6), 955-957.

[79] Berger, T.; Rubner, P.; Schautzer, F.; Egg, R.; Ulmer, H.; Mayringer, I.; Dilitz, E.; Deisenhammer, F.; Reindl, M. Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N. Engl. J. Med., 2003, 349(2), 139-145.

[80] Zouali, M. Tweaking the B lymphocyte compartment in autoimmune diseases. Nat. Immunol., 2014, 15(3), 209-212.

[81] Goodnow, C.C.; Vinuesa, C.G.; Randall, K.L.; Mackay, F.; Brink, R. Control systems and decision making for antibody production. Nat. Immunol., 2010, 11(8), 681-688.

[82] Halverson, R.; Torres, R.M.; Pelanda, R. Receptor editing is the main mechanism of B cell tolerance toward membrane antigens. Nat. Immunol., 2004, 5(6), 645-650.

[83] Wardemann, H.; Yurasov, S.; Schaefer, A.; Young, J.W.; Meffre, E.; Nussenzweig, M.C. Predominant autoantibody production by early human B cell precursors. Science., 2003, 301(5638), 1374-1377.

[84] Pelanda, R.; Torres, R.M. Central B-cell tolerance: where selection begins. Cold. Spring. Harb. Perspect. Biol., 2012, 4(4), a007146.

[85] Martin, F.; Chan, A.C. B cell immunobiology in disease: evolving concepts from the clinic. Annu. Rev. Immunol., 2006, 24, 467-496.

[86] Li, Y.; Chen, F.; Putt, M.; Koo, Y.K.; Madaio, M.; Cambier, J.C.; Cohen, P.L.; Eisenberg, R.A. B cell depletion with anti-CD79 mAbs ameliorates autoimmune disease in MRL/lpr mice. J. Immunol., 2008, 181(5), 2961-2972.

[87] Dorner, T.; Burmester, G.R. New approaches of B-cell-directed therapy: beyond rituximab. Curr. Opin. Rheumatol., 2008, 20(3), 263-268.

[88] Salzer, J.; Svenningsson, R.; Alping, P.; Novakova, L.; Bjorck, A.; Fink, K.; Islam-Jakobsson, P.; Malmestrom, C.; Axelsson, M.; Vagberg, M.; Sundstrom, P.; Lycke, J.; Piehl, F.; Svenningsson, A. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. Neurology., 2016, 87(20), 2074-2081.

[89] Sorensen, P.S.; Lisby, S.; Grove, R.; Derosier, F.; Shackelford, S.; Havrdova, E.; Drulovic, J.; Filippi, M. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology., 2014, 82(7), 573-581.

[90] Kappos, L.; Li, D.; Calabresi, P.A.; O'Connor, P.; Bar-Or, A.; Barkhof, F.; Yin, M.; Leppert, D.; Glanzman, R.; Tinbergen, J.; Hauser, S.L. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet., 2011, 378(9805), 1779-1787.

[91] Matsushita, T.; Yanaba, K.; Bouaziz, J.D.; Fujimoto, M.; Tedder, T.F. Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression. J. Clin. Invest., 2008, 118(10), 3420-3430.

[92] Goetz, M.; Atreya, R.; Ghalibafian, M.; Galle, P.R.; Neurath, M.F. Exacerbation of ulcerative colitis after rituximab salvage therapy. Inflamm. Bowel. Dis., 2007, 13(11), 1365-1368.

[93] Zhang, L.; French, R.R.; Chan, H.T.; O'Keefe, T.L.; Cragg, M.S.; Power, M.J.; Glennie, M.J. The development of anti-CD79 monoclonal antibodies for treatment of B-cell neo-plastic disease. Ther. Immunol., 1995, 2(4), 191-202.

[94] Ouarzane, M.; Zouali, M. Novel opportunities for therapeutic targeting in systemic autoimmune diseases. Methods. Mol. Biol., 2007, 361, 285-297.

[95] Cohen, S.B. Updates from B Cell Trials: Efficacy. J. Rheumatol. Suppl., 2006, 77, 12-17.

[96] Kaveri, S.V.; Lacroix-Desmazes, S.; Bayry, J. The antiin-flammatory IgG. N. Engl. J. Med., 2008, 359(3), 307-309.

[97] Yu, X.; Gilden, D.H.; Ritchie, A.M.; Burgoon, M.P.; Keays, K.M.; Owens, G.P. Specificity of recombinant antibodies generated from multiple sclerosis cerebrospinal fluid probed with a random peptide library. J. Neuroimmunol., 2006, 172(1-2), 121-131.

[98] von Budingen, H.C.; Harrer, M.D.; Kuenzle, S.; Meier, M.; Goebels, N. Clonally expanded plasma cells in the cerebro-spinal fluid of MS patients produce myelin-specific antibodies. Eur. J. Immunol., 2008, 38(7), 2014-2023.

[99] Lambracht-Washington, D.; O'Connor, K.C.; Cameron, E.M.; Jowdry, A.; Ward, E.S.; Frohman, E.; Racke, M.K.; Monson, N.L. Antigen specificity of clonally expanded and receptor edited cerebrospinal fluid B cells from patients with relapsing remitting MS. J. Neuroimmunol., 2007, 186(1-2), 164-176.

[100] Yu, X.; Gilden, D.; Schambers, L.; Barmina, O.; Burgoon, M.; Bennett, J.; Owens, G. Peptide reactivity between multiple sclerosis (MS) CSF IgG and recombinant antibodies generated from clonally expanded plasma cells in MS CSF. J. Neuroimmunol., 2011, 233(1-2), 192-203.

[101] Gabibov, A.G.; Belogurov, A.A. Jr.; Lomakin, Y.A.; Zakharova, M.Y.; Avakyan, M.E.; Dubrovskaya, V.V.; Smirnov, I.V.; Ivanov, A.S.; Molnar, A.A.; Gurtsevitch, V.E.; Diduk, S.V.; Smirnova, K.V.; Avalle, B.; Sharanova, S.N.; Tramontano, A.; Friboulet, A.; Boyko, A.N.; Ponomarenko, N.A.; Tikunova, N.V. Combinatorial antibody library from multiple sclerosis patients reveals antibodies that cross-react with myelin basic protein and EBV antigen. FASEB. J., 2011, 25(12), 4211-4221.

[102] Owens, G.P.; Gilden, D.; Burgoon, M.P.; Yu, X.; Bennett, J.L. Viruses and multiple sclerosis. Neuroscientist., 2011, 17(6), 659-676.

[103] Lomakin, Y.A.; Zakharova, M.Y.; Stepanov, A.V.; Dronina, M.A.; Smirnov, I.V.; Bobik, T.V.; Pyrkov, A.Y.; Tikunova, N.V.; Sharanova, S.N.; Boitsov, V.M.; Vyazmin, S.Y.; Kabilov, M.R.; Tupikin, A.E.; Krasnov, A.N.; Bykova, N.A.; Medvedeva, Y.A.; Fridman, M.V.; Favorov, A.V.; Ponomarenko, N.A.; Dubina, M.V.; Boyko, A.N.; Vlassov, V.V.; Belogurov, A.A. Jr.; Gabibov, A.G. Heavy-light chain interrelations of MS-associated immunoglobulins probed by deep sequencing and rational variation. Mol. Immunol., 2014, 62(2), 305-314.

[104] Lomakin, Y.A.; Zakharova, M.Y.; Belogurov, A.A.; Bykova, N.A.; Dronina, M.A.; Tupikin, A.E.; Knorre, V.D.; Boyko, A.N.; Favorov, A.V.; Kabilov, M.R.; Ponomarenko, N.A.; Gabibov, G. Polyreactive monoclonal autoantibodies in multiple sclerosis: functional selection from phage display library and characterization by deep sequencing analysis. Acta. Naturae., 2013, 5(4), 94-104.

[105] Lomakin, Y.; Shmidt, A.; Glagoleva, I.; Okunola, J.; Vaskina, M.; Belogurov, A. Jr.; Gabibov A. Myelin-Reactive Monoclonal Antibodies from Multiple Sclerosis Patients Cross-React with Nucleoproteins in HEp-2 Lysate. BioNanoSci., 2016, 6(4), 322-324.

[106] Larman, H.B.; Zhao, Z.; Laserson, U.; Li, M.Z.; Ciccia, A.; Gakidis, M.A.; Church, G.M.; Kesari, S.; Leproust, E.M.; Solimini, N.L.; Elledge, S.J. Autoantigen discovery with a synthetic human peptidome. Nat. Biotechnol., 2011, 29(6), 535-541.

[107] Larman, H.B.; Laserson, U.; Querol, L.; Verhaeghen, K.; Solimini, N.L.; Xu, G.J.; Klarenbeek, P.L.; Church, G.M.; Hafler, D.A.; Plenge, R.M.; Nigrovic, P.A.; De Jager, P.L.; Weets, I.; Martens, G.A.; O'Connor, K.C.; Elledge, S.J. PhIP-Seq characterization of autoantibodies from patients with multiple sclerosis, type 1 diabetes and rheumatoid arthritis. J. Autoimmun., 2013, 43, 1-9.

[108] Madhumathi, J.; Verma, R.S. Therapeutic targets and recent advances in protein immunotoxins. Curr. Opin. Microbiol., 2012, 15(3), 300-309.

[109] Stepanov, A.V.; Belogurov, A.A. Jr.; Ponomarenko, N.A.; Stremovskiy, O.A.; Kozlov, L.V.; Bichucher, A.M.; Dmitriev, S.E.; Smirnov, I.V.; Shamborant, O.G.; Balabashin, D.S.; Sashchenko, L.P.; Tonevitsky, A.G.; Friboulet, A.; Gabibov, A.G.; Deyev, S.M. Design of targeted B cell killing agents. PLoS. One., 2011, 6(6), e20991.

[110] Stepanov, A.V.; Belogurov, A.A. Jr.; Kothapalli, P.; Shamborant, O.G.; Knorre, V.D.; Telegin, G.B.; Ovsepyan, A.A.; Ponomarenko, N.A.; Deyev, S.M.; Kaveri, S.V.; Gabibov, A.G. Specific Depletion of Myelin-Reactive B Cells via BCR-Targeting. Acta. Naturae., 2015, 7(2), 74-79.

[111] Zocher, M.; Baeuerle, P.A.; Dreier, T.; Iglesias, A. Specific depletion of autoreactive B lymphocytes by a recombinant fusion protein in. vitro and in. vivo. Int. Immunol., 2003, 15(7), 789-796.

[112] Nachreiner, T.; Kampmeier, F.; Thepen, T.; Fischer, R.; Barth, S.; Stocker, M. Depletion of autoreactive B-lymphocytes by a recombinant myelin oligodendrocyte gly-coprotein-based immunotoxin. J. Neuroimmunol., 2008, 195(1-2), 28-35.

[113] Stepanov, A.; Belyy, A.; Kasheverov, I.; Rybinets, A.; Dronina, M.; Dyachenko, I.; Murashev, A.; Knorre, V.; Sakharov, D.; Ponomarenko, N.; Tsetlin, V.; Tonevitsky, A.; Deyev, S.; Belogurov, A. Jr.; Gabibov, A. Development of a recombinant immunotoxin for the immunotherapy of autoreactive lymphocytes expressing MOG-specific BCRs. Biotechnol. Lett., 2016, 38(7), 1173-1180.

[114] Olsen, E.; Duvic, M.; Frankel, A.; Kim, Y.; Martin, A.; Vonderheid, E.; Jegasothy, B.; Wood, G.; Gordon, M.; Heald, P.; Oseroff, A.; Pinter-Brown, L.; Bowen, G.; Kuzel, T.; Fivenson, D.; Foss, F.; Glode, M.; Molina, A.; Knobler, E.; Stewart, S.; Cooper, K.; Stevens, S.; Craig, F.; Reuben, J.; Bacha, P.; Nichols, J. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J. Clin. Oncol., 2001, 19(2), 376-388.

[115] Smith, C.E.; Eagar, T.N.; Strominger, J.L.; Miller, S.D. Differential induction of IgE-mediated anaphylaxis after soluble vs. cell-bound tolerogenic peptide therapy of autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A., 2005, 102(27), 9595-9600.

[116] Pedotti, R.; Mitchell, D.; Wedemeyer, J.; Karpuj, M.; Chabas, D.; Hattab, E.M.; Tsai, M.; Galli, S.J.; Steinman, L. An unexpected version of horror autotoxicus: anaphylactic shock to a self-peptide. Nat. Immunol., 2001, 2(3), 216-222.

[117] Miller, S.D.; Turley, D.M.; Podojil, J.R. Antigen-specific tolerance strategies for the prevention and treatment of autoimmune disease. Nat. Rev. Immunol., 2007, 7(9), 665-677.

[118] Sabatos-Peyton, C.A.; Verhagen, J.; Wraith, D.C. Antigen-specific immunotherapy of autoimmune and allergic diseases. Curr. Opin. Immunol., 2010, 22(5), 609-615.

[119] Gharagozloo, M.; Majewski, S.; Foldvari, M. Therapeutic applications of nanomedicine in autoimmune diseases: from immunosuppression to tolerance induction. Nanomedicine, 2015, 11(4), 1003-1018.