

The Future of Autoimmunity

Yehuda Shoenfeld

© Springer Science+Business Media, LLC 2011

Abstract There have been enormous strides in our understanding of autoimmunity. These strides have come under the umbrellas of epidemiology, immunological phenotype and function, disease definitions and classification and especially new therapeutic reagents. However, while these advances have been herculean, there remains enormous voids. Some of these voids include genetic susceptibility and the interaction of genes and environment. The voids include induction of tolerance in preclinical disease and definitions of host susceptibility and responses to the expensive biologic agents. The voids include the so-called clustering of human autoimmune diseases and the issues of whether the incidence is rising in our western society. Other voids include the relationships between microbiology, vaccination, gut flora, overzealous use of antibiotics, and the role of nanoparticles and environmental pollution in either the induction or the natural history of disease. One cannot even begin to address even a fraction of these issues. However, in this special issue, we are attempting to discuss clinical issues in autoimmunity that are not usually found in generic reviews. The goal is to bring to the readership provocative articles that ultimately will lead to improvement in patient care.

Keywords Autoimmunity · Biological therapy · Epidemiology

Y. Shoenfeld (✉)

The Zabłudowicz Center for Autoimmune Diseases,
Sheba Medical Center, Tel-Hashomer, Incumbent of the
Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases,
Sackler Faculty of Medicine, Tel-Aviv University,
Ramat gan, Israel
e-mail: shoenfel@post.tau.ac.il

Introduction

We are arriving into a golden period of autoimmune diseases. We can predict quite precisely the eventual development of a specific autoimmune disease in an individual [1–4], based on the presence of specific autoantibodies in combination with diverse genetic markers. Moreover, we aspired into a stage where we can recommend preventive measurements such as high dose of vitamin D [5–18] and others.

We better understand the mosaic of autoimmunity [3, 19, 20]. We may develop new vaccine against notorious infecting agent (i.e., Epstein–Barr virus) [21–23]. Furthermore, we have new data about the geoepidemiology of the various autoimmune diseases [24–63]. This means detection of geographic areas being of a higher risk to develop autoimmune diseases [64, 65].

New aspects of autoimmunity also emerged, i.e., depression and defect of smelling [66–73]. Last but not least, new syndrome was delineated, i.e., the autoimmune syndrome induced by adjuvant syndrome [74–87]. Novel therapies are developed every day entailing new biologics [88–99], peptides [100], and better use of intravenous immunoglobulin [101–108]. All these developments led to a better prognosis, prolonged survival time, and improved quality of life. Let me expand a little bit about the potential of peptides as new therapies not having significant side effects, an example of which, the Copaxone in multiple sclerosis is a representative successful drug.

Peptide-based therapy for treatment autoimmune diseases gain a vast interest during the last decade. In 1960, the Copaxone, a Food and Drug Administration-approved drug for treatment of multiple sclerosis [109]. The synthetic random amino acid copolymer Copolymer 1 (Cop 1, Copaxone, glatiramer acetate) was the first drug based on four amino acids (L-alanine, L-lysine, L-glutamic acid, and L lysine) which were

arbitrarily chosen from myelin basic protein (MBP) tertiary structure to construct a polymer composed of the four amino acids at different ratio. Cop-1 suppresses experimental autoimmune encephalomyelitis (EAE), slows the progression of disability, and reduces relapse rate in multiple sclerosis (MS). Cop 1 binds to various class II major histocompatibility complex molecules and inhibits the T cell responses to several myelin antigens, shift Th1 response to Th2 and upregulated T regulatory cells expression. Later, it was proved that Cop-1 cause demyelination arrest and remyelination induced when given to EAE mice [110]. At 2010, the income of Teva company sales of Copaxone reached 2.2 billion US \$.

Altered peptide ligand molecules A change in some amino acids may convert an immunogenic peptide into an inhibitory one. For example: in MS, at the site of demyelination, there is evidence that peptides encompassing the immunodominant epitope of myelin basic protein, amino acids 83–99 (MBP_{83–99}), are bound to the DR2 molecule expressed on inflammatory cells [109]. A single amino acid substitution of Ala for Lys at position 91 in the core sequence of MBP_{83–99}, called NBI 5788, changes the cellular response to MBP and protect from the development of EAE and even reversed established paralytic disease due to inhibition of proinflammatory cytokines mainly tumor necrosis factor α and interferon γ . A successful phase II clinical study with NBI 5788 was reported [111]. Substitution of MBP A97 to alanine induce activation-induced cell death of MBP_{87–99} T reactive cells [112]. Thus, single amino acid changes at different positions in the same peptide epitope can lead to altered peptide ligand peptide which may prevent the development of by different mechanisms [113].

Ligand interacting peptides Synthetic peptides which imitates the antigen–ligand binding site, thus preventing auto-antigen receptor binding. For example: peptide composed of phospholipid and membrane binding sites, prevented the binding of beta-2-glycoprotein-I (β 2GPI) to endothelial cells, thus decreased the potential of β 2GPI-anti- β 2GPI complex activation of the cells. Furthermore, this peptide penetrated to endothelial cells, upregulated phosphorylation of the cells to produce tissue factor and procoagulation state of the endothelial vascular bed [100].

Neutralizing peptides Using peptide phage display libraries, many scientists found peptides capable of neutralization of pathogenic autoantibodies. For example, in antiphospholipid syndrome, several groups were employing random peptide phage display libraries to identify target epitope on the β 2GPI for anti- β 2GPI Abs. The epitopes identified by several groups were spread all over the molecule and each patient have their own Ab signature for anti- β 2GPI-targeted epitopes [114]. Some of the peptides are used for

diagnosis of the disease and some are in the stage of development for therapy.

In silico prediction of peptides Addressing antigenic “hot spots” on molecule may introduce predictive antigenic epitopes which were the basis of development synthetic peptides based on prediction, using diverse computer programs. For example: *in silico* approach was employed by several groups which tried to develop predicted synthetic peptides which will prevent desmoglein–T cell epitope interaction that will lead to prevention of acantolysis in patients with pemphigus vulgaris. Tong et al. found extracellular DRBI*402 specific immunological (T cell epitope) “hot spot” which served as a basis for development of synthetic peptides capable of reducing acantolysis [115].

Conclusions

For more extensive literature, I refer to the recent publications on the epidemiology of autoimmune disease, published as a special symposia of the Congress of Autoimmunity [64, 98, 99, 116–161]. Thus it seems that we enter into *annus mirabilis* with a better hope for patients with autoimmune diseases. This dedicated issue stems from literature and papers presented at the Congress of Autoimmunity and is meant as an update of literature and dedicated subjects presented earlier in this journal [162–189]. This is also exemplified in the articles presented in this issue.

References

1. Shepselovitch D, Shoenfeld Y (2005) Prediction and prevention of autoimmune diseases—additional aspects of the mosaic of autoimmunity. *Lupus* 15:183–190
2. Shoenfeld Y, Carp HJA, Molina V, Blank M, Cervera R, Balasch J, Tincani A, Faden D, Lojaco A, Doria A, Konova E, Meroni PL (2006) Autoantibodies and prediction of reproductive failure. *Amer J of Reproduct Immunol* 56:337–344
3. Shoenfeld Y, Blank M, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, Bizzaro N, Gilburd B, Zandman-Goddard G, Katz U, Krause I, Langevitz P, Mackay IR, Orbach H, Ram M, Sherer Y, Toubi E, Gershwin ME (2008) The mosaic of autoimmunity: prediction, autoantibodies, and therapy in autoimmune diseases—2008. *IMAJ* 10:13–19
4. Agmon-Levin N, Shoenfeld Y (2008) Prediction and prevention of autoimmune skin disorders. *Arch Dermatol Res* 301:57–64
5. Arnsen Y, Amital H, Shoenfeld Y (2007) Vitamin D and autoimmunity: new etiological and therapeutic considerations. *Ann Rheum Dis* 66:1137–1142
6. Carvalho ZF, Blank M, Kiss E, Tarr T, Amital H, Shoenfeld Y (2007) Anti-vitamin D, vitamin D in SLE preliminary results. *Ann NY Acad Sci* 1109:550–557
7. Orbach H, Zandman-Goddard G, Amital H, Barak B, Szekaneecz Z, Szucs G, Danko K, Nagy E, Csepany T, Carvalho JF, Doria A,

- Shoenfeld Y (2007) Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D and TPA levels in autoimmune diseases. *Ann NY Acad Sci* 1109:385–400
8. Shoenfeld N, Amital H, Shoenfeld Y (2009) The effect of melatonin and vitamin D synthesis on the incidence of autoimmune disease. *Nature Rheumatol* 5:99–105
 9. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) *Mycobacterium tuberculosis*, autoimmunity, and vitamin D. *Clin Rev Allerg Immunol* 38:169–177
 10. Amital H, Szekanecz Z, Szűcs G, Dankó K, Nagy E, Csépanyi T, Kiss E, Doria A, Corocher N, Agmon-Levin N, Orbach H, Barak V, Zandman-Goddard G, Shoenfeld Y (2010) Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? *Ann Rheum Dis* 69:1155–1157
 11. Toubi E, Shoenfeld Y (2010) The role of vitamin D in regulating immune responses. *Isr Med Assoc J* 12:174–5
 12. Souberbielle J-C, Body J-J, Laappe JM, Plebani M, Shoenfeld Y, Wang TJ, Bischoff-Ferrari A, Cavalier E, Ebeling PR, Fardellone P, Gandini S, Gruson D, Guerin AP, Heickendorff L, Hollis BW, Ish-Shalom S, Gullaume J, von Landenberg P, Largura A, Olsson T, Pierrot-Deseilligny C, Pilz S, Tincani A, Valcour A, Zittermann A (2010) Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* 9:709–715
 13. Agmon-Levin N, Blank M, Zandman-Goddard G, Orbach H, Meroni PL, Tincani A, Doria A, Cervera R, Miesbach W, Stojanovich L, Barak V, Porat-Katz BS, Amital H, Shoenfeld Y (2011) Vitamin D: an instrumental factor in the antiphospholipid syndrome by inhibition of tissue factor expression. *Ann Rheum Dis* 20:145–150
 14. Oren Y, Shapira Y, Agmon-Levin N, Kivity S, Zafrir Y, Altman A, Lerner A, Shoenfeld Y (2010) Vitamin D insufficiency in a sunny environment: a demographic and seasonal analysis. *IMAJ* 12:751–756
 15. Arnson Y, Amital H, Agmon-Levin N, Alon D, Sanchez-Castanon M, Lopez-Hoyos M, Matucci-Cerinic M, Szucs G, Shapira Y, Szekanecz Z, Shoenfeld Y (2011) Serum 25-OH vitamin D concentrations are linked with various clinical aspects in patients with systemic sclerosis: a retrospective cohort study and review of the literature. *Autoimmun Rev* 10:490–494
 16. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Danko K, Szekanecz Z, Langevitz P, Shoenfeld Y (2011) Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol* 8:243–7
 17. Lerner A, Shapira Y, Agmon-Levin N, Pacht A, Ben-Ami Shor D, Lopez HM, Sanchez-Castanon M, Shoenfeld Y (2011) The clinical significance of 25OH-vitamin D status in Celiac disease. *Clin Rev Allergy Immunol*. doi:10.1007/s12016-010-8237-8.
 18. Hajas A, Sandor J, Casathy L, Csipo I, Barath S, Paragh G, Seres I, Szegedi G, Shoenfeld Y, Bodolay E (2011) Vitamin D insufficiency in a large MCTD population. *Autoimmun Rev* 10:317–24
 19. Shoenfeld Y, Gilburd B, Abu-Shakra M, Amital H, Barzilai O, Berkun Y, Blank M, Zandman-Goddard G, Katz U, Krause I, Langevitz P, Levy Y, Orbach H, Pordeus V, Ram M, Sherer Y, Toubi E, Tomer Y (2008) The mosaic of autoimmunity: genetic factors involved in autoimmune diseases—2008. *IMAJ* 10:3–7
 20. Shoenfeld Y, Zandman-Goddard G, Stojanovich L, Cutolo M, Amital H, Levy Y, Abu-Shakra M, Barzilai O, Berkun Y, Blank M, de Carvalho JF, Doria A, Gilburd B, Katz U, Krause I, Langevitz P, Orbach H, Pordeus V, Ram M, Toubi E, Sherer Y (2008) The mosaic of autoimmunity: hormonal and environmental factors involved in autoimmune diseases—2008. *IMAJ* 10:8–12
 21. Barzilai O, Sherer Y, Ram M, Izhaky D, Anaya JM, Shoenfeld Y (2007) Epstein-Barr virus and cytomegalovirus in autoimmune diseases are they truly notorious? a preliminary report. *Ann NY Acad Sci* 1108:567–577
 22. Zandman-Goddard G, Berkun Y, Barzilai O, Boaz M, Blank M, Ram M, Sherer Y, Anaya JM, Shoenfeld Y (2009) Exposure to Epstein-Barr virus infection is associated with mild systemic lupus erythematosus disease. *Ann NY Acad Sci* 1173:658–663
 23. Pender MP (2009) Preventing and curing multiple sclerosis by controlling Epstein-Barr virus infection. *Autoimmun Rev* 8:563–8
 24. Youinou P, Pers JO, Gershwin ME, Shoenfeld Y (2010) Geoepidemiology and autoimmunity. *J Autoimmunity* 34:J163–J167, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 25. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* 34:J168–J177, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 26. Hoffmann MH, Trembleau S, Muller S, Steiner G (2010) Nucleic acid-autoantigens: pathogenic involvement and therapeutic potential. *J Autoimmun* 34:J178–J206, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 27. Brooks WH, Dantec CL, Pers JO (2010) Epigenetics and autoimmunity. *J Autoimmun* 34:J207–J219, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 28. JL Rou d, OwConnell RM, Mazmanian SK (2010) Coordination of tolerogenic immune responses by the commensal microbiota. *J Autoimmun* 34:J220–J225, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 29. Powel JJ, Faeia N, Thomas-Mckay E, Pele LC (2010) Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract. *J Autoimmun* 34:J226–J233, Published in book: Shoenfeld Y, Youinou P, Gershwin EM. (Guest Editors). *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 30. Chang C (2010) The immune effects of naturally occurring and synthetic nanoparticles. *J Autoimmun* 34:J224–J246, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 31. Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H (2010) Light, including ultraviolet. *J Autoimmun* 34:J247–J257, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 32. Arnson Y, Shoenfeld Y, Amital H (2010) Effects of tobacco on immunity, inflammation and autoimmunity. *J Autoimmun* 34:J258–J265, Published in Book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) *The environment geoepidemiology and autoimmune diseases*. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 33. Chang C, Gershwin ME (2010) Drugs and autoimmunity—a contemporary review and mechanistic approach. *J Autoimmun*

- 34:J266–J275, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
34. Chen M, Daha MR, Kallenberg CGM (2010) The complement system in systemic autoimmune disease. *J Autoimmun* 34:276–J286, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 35. Borchers AT, Maguwa SM, Keen CL, Gershwin ME (2010) The implications of autoimmunity and pregnancy. *J Autoimmun* 34: J287–J299, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 36. Invernizzi P (2010) Geoepidemiology of autoimmune liver diseases. *J Autoimmun* 34:J300–J306, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 37. Hemminki K, Li X, Sundquist J, Sundquist K (2010) The epidemiology of Graves' disease: evidence of a genetic and an environmental contribution. *J Autoimmun* 34:J307–J313, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 38. Chandran V, Raycheudhuri SP (2010) Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *J Autoimmun* 34:J314–J321, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 39. Tomer Y (2010) Hepatitis C and interferon induced thyroiditis. *J Autoimmun* 34:J322–J326, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 40. Zeki AA, Schivo M, Chan AL, Hardin KA, Kenyon NJ, Albertson TE, Rosenquist GL, Louie S (2010) Geoepidemiology of COPD and idiopathic pulmonary fibrosis. *J Autoimmun* 34:J327–J338, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 41. Selmi C (2010) The worldwide gradient of autoimmune conditions. *Autoimmun Rev* 9:A247–A250, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 42. Mackay IR (2010) Travels and travails of autoimmunity: A historical journey from discovery to rediscovery. *Autoimmun Rev* 9:A251–A258, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 43. Lleo A, Invernizzi P, Gao B, Podda M, Gershwin ME (2010) Definition of human autoimmunity—autoantibodies versus autoimmune disease. *Autoimmun Rev* 9:A259–A266, Published in book: Shoenfeld Y, Youinou P, Gershwin EM. (Guest Editors). The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 44. Selmi C, Tsuneyama K (2010) Nutrition geoepidemiology, and autoimmunity. *Autoimmun Rev* 9:A267–A270, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors). The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 45. Stojanovich L (2010) Stress and autoimmunity. *Autoimmun Rev* 9:A271–A276, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 46. Tobon GJ, Youinou P, Saraux A (2010) The environment, geoepidemiology, and autoimmune disease: rheumatoid arthritis. *Autoimmun Rev* 9:A288–A292, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors). The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 47. Chen M, Kallenberg CGM (2010) The environment, geoepidemiology and ANCA-associated vasculitides. *Autoimmun Rev* 9: A293–A298, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 48. Biggioggero M, Meroni PL (2010) The geoepidemiology of the antiphospholipid antibody syndrome. *Autoimmun Rev* 9:A299–A304, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 49. Mavragani CP, Moutsopoulos HM (2010) The geoepidemiology of Sjogren's syndrome. *Autoimmun Rev* 9:A305–A310, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 50. Ranque B, Mouthon L (2010) Geoepidemiology of systemic sclerosis. *Autoimmun Rev* 9:A311–A318, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 51. Berkun Y, Padeh S (2010) Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. *Autoimmun Rev* 9:A319–A324, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 52. Ehrenfeld M (2010) Geoepidemiology: the environment and spondyloarthropathies. *Autoimmun Rev* 9:A325–A329, Published in book: Shoenfeld Y, Youinou P, Gershwin EM. (Guest Editors). The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 53. Prieto S, Grau JM (2010) The geoepidemiology of autoimmune muscle disease. *Autoimmun Rev* 9:A330–A334, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 54. Sands J, Tusciano JM (2010) Geoepidemiology and autoimmune manifestations of lymphoproliferative disorders. *Autoimmun Rev* 9:A335–A341, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoepidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 55. Deane S, Teuber SS, Gershwin ME (2010) The geoepidemiology of immune thrombocytopenic purpura. *Autoimmun Rev* 9:A342–A349, Published in book: Shoenfeld Y, Youinou P, Gershwin EM

- (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
56. Lambert JF, Nydegger UE (2010) Geoeidemiology of autoimmune hemolytic anemia. *Autoimmun Rev* 9:A350–A354, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 57. Borchers AT, Uibo R, Gershwin ME (2010) The epidemiology of type 1 diabetes. *Autoimmun Rev* 9:A355–A365, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors). The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 58. Segelmark M, Hellmark T (2010) Autoimmune kidney disease. *Autoimmun Rev* 9:A366–A371, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 59. Logan I, Bowls CL (2010) The geoeidemiology of autoimmune intestinal disease. *Autoimmun Rev* 9:A372–A378, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 60. Meyer N, Misery L (2010) Geoeidemiologic consideration of auto-immune pemphigus. *Autoimmun Rev* 9:A379–A382, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 61. Meyer A, Levy Y (2010) Chapter 33: geoeidemiology of myasthenia gravis. *Autoimmun Rev* 9:A383–A386, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors) The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 62. Milo R, Kahana E (2010) Multiple sclerosis: geoeidemiology, genetics and the environment. *Autoimmun Rev* 9:A387–A394, Published in book: Shoenfeld Y, Youinou P, Gershwin EM (guest editors). The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 63. Bhat A, Naguwa S, Cheema G, Gershwin ME (2010) The epidemiology of transverse myelitis. *Autoimmun Rev* 9:A395–A399, Published in book: Shoenfeld Y, Youinou P, Gershwin EM. (guest editors). The environment geoeidemiology and autoimmune diseases. Elsevier, Amsterdam, The Netherlands. Printed in the UK and The Netherlands
 64. Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME (2010) The geoeidemiology of systemic lupus erythematosus. *Autoimmun Rev* 9:A277–A287
 65. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Geoeidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 6:468–476
 66. To smell the immune system (2006) Olfaction, autoimmunity and brain involvement. *Autoimmune Rev* 6:54–60
 67. Katzav A, Solodov I, Brodsky O, Chapman J, Pick CG, Blank M, Zhang W, Reichlin M, Shoenfeld Y (2007) Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arth Rheum* 56:938–948
 68. Shoenfeld Y (2007) To smell autoimmunity: anti-P-Ribosomal autoantibodies, depression, and the olfactory system. *J Autoimmunity* 28:165–169
 69. Blank M, Beinglass I, Shoenfeld Y (2007) The therapeutic potential of targeting anti-ribosomal-P antibody in treating SLE patients with depression. *Expert Opin Biol Ther* 7:1283–1285
 70. Katzav A, Ben-Ziv T, Chapman J, Blank M, Reichlin M, Shoenfeld Y (2008) Anti-P ribosomal antibodies induce defect in smell capability in a model of CNS-SLE (depression). *J Autoimmun* 31:393–398
 71. Shoenfeld N, Agmon-Levin N, Flitman-Katzevman I, Paran D, Porat Katz B, Kivity S, Langevitz P, Zandman-Goddard G, Shoenfeld Y (2009) The sense of smell in systemic lupus erythematosus. *Arth Rheum* 60(5):1484–1487
 72. Samuel-Datum M, Szyper-Kravitz M, Yehuda S (2009) Olfacto: Smell: integrating neurodegeneration and autoimmunity—a personal view. *Acta Reumatol Port* 34:190–196, Portuguese
 73. Perricone C, Agmon-Levin N, Shoenfeld N, de Carolis C, Guarino MD, Gigliucci G, Milana I, Novelli L, Valesini G, Perricone R, Shoenfeld Y (2011) Evidence of impaired sense of smell in hereditary angioedema. *Allergy* 66:149–154
 74. Agmon-Levin N, Shoenfeld Y (2008) Chronic fatigue syndrome with autoantibodies—the result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant. *Autoimmun Rev* 8:52–55
 75. Israeli E, Agmon-Levin N, Blank M, Shoenfeld Y (2009) Adjuvants and autoimmunity. *Lupus* 18:1217–1225
 76. Shoenfeld Y, Agmon-Levin N (2011) ‘ASIA’—autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 36:4–8
 77. Shoenfeld Y, Agmon-Levin N (2011) Abstract of: ‘ASIA’—autoimmune (auto-inflammatory) syndrome induced by adjuvant—a new syndrome to be defined. In: Abstracts of selected invited lectures. *Lupus* 20:340–347
 78. Shoenfeld Y (2011) Autoimmune (autoinflammatory) syndrome induced by adjuvants provides a diagnostic framework for enigmatic conditions. *The Rheumatologist* 6:26–32
 79. Perricone C, Agmon-Levin N, Valesini G, Shoenfeld Y (2011) Vaccination in patients with chronic or autoimmune rheumatic diseases: the ego, the id and the superego. *Joint Bone Spine*. doi:10.1016/j.jbspin.2011.10.006.
 80. Rosenblum H, Shoenfeld Y, Amital H (2011) The common immunogenic etiology of chronic fatigue syndrome: from infections to vaccines via adjuvants to the ASIA syndrome. *Infect Dis Clin North Am* 25:851–63
 81. Cervera R (2011) “ASIA”: q new systemic autoimmune syndrome? *Lupus* 20:665–666
 82. Carvalho JF, Barros SM, Branco JC, Fonseca JE (2011) ASIA or shoenfeld’s syndrome: highlighting different perspectives for diffuse chronic pain. *Acta Rheumatol Port* 36:10–12
 83. Barros SM, Carvalho JF (2011) Shoenfeld’s syndrome after pandemic influenza A/H1N1 vaccination. *Acta Rheumatol Port* 36:65–68
 84. Pereira JP, Barroso C, Evangelista T, Fonseca JE, Pereira da Silva JA (2011) Macrophagic myofasciitis: a case report of autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *Acta Rheumatol Port* 36:75–76
 85. Israeli E, Pardo A (2011) The sick building syndrome as a part of the autoimmune (auto-inflammatory) syndrome induced by adjuvants. *Mod Rheumatol* 21:235–239
 86. Meroni PL (2011) Autoimmune of auto-inflammatory syndrome induced by adjuvants (ASIA): old truths and a new syndrome? *J AI* 36:1–3
 87. Batista-Duharte A, Lindblad EB, Oviedo-Orta E (2011) Progress in understanding adjuvant immunotoxicity mechanisms. *Toxicol Lett* 203:97–105
 88. Bogdanos DP, Rigopoulou EL, Smyk DS, Roggenbuck D, Reinhold D, Forbes A, Laass M, Conrad K (2011) Diagnostic value, clinical utility and pathogenic significance of reactivity to the

- molecular targets of Crohn's disease specific-pancreatic autoantibodies. *Autoimmun Rev*. doi:10.1016/j.autrev.2011.09.004.
89. Lepse N, Abdulahad WH, Kallenberg CG, Heeringa P (2011) Immune regulatory in ANCA-associated vasculitides. *Autoimmun Rev*. doi:10.1016/j.autrev.2011.08.002.
 90. Murdaca G, Colombo BM, Puppo F (2011) Emerging biological drugs: a new therapeutic approach for systemic lupus erythematosus. An update upon efficacy and adverse events. *Autoimmun Rev*. doi:10.1016/j.autrev.2011.07.006.
 91. Chimenti MS, Graceffa D, Perricone R (2011) Anti-TNF α discontinuation in rheumatoid and psoriatic arthritis: is it possible after disease remission? *Autoimmun Rev* 10:636–40
 92. Laccarino L, Ghirardello A, Canova M, Zen M, Bettio S, Nalotto L, Punzi L, Doria A (2011) Anti-annexins autoantibodies: their role as biomarkers of autoimmune diseases. *Autoimmun Rev* 10:553–8
 93. Liao WW, Arthur JW (2011) Prediction peptide binding to major histocompatibility complex molecules. *Autoimmun Rev* 10:469–73
 94. Ingegnoli F, Favalli EG, Meroni PL (2011) Does polymorphism of genes coding for pro-inflammatory mediators predict the clinical response to TNF Alpha blocking agents? A review analysis of the literature. *Autoimmun Rev* 10:460–3
 95. Engel P, Gomez-Puerta JA, Ramos-Casals M, Lozano F, Bosch Z (2011) Therapeutic targeting of B cells for rheumatic autoimmune diseases. *Autoimmun Rev* 63:127–56
 96. Hemdan NY, Birkenmeier G, Wichmann G, Abu El-Saad AM, Krieger T, Conrad K, Sack U (2010) Interleukin-17 producing T helper cells in autoimmunity. *Autoimmun Rev* 9:785–92
 97. Caporali R, Sarzi-Puttini P, Atzeni F, Gorla R, Filippini M, Marchesoni A, Favalli EG, Bobbio-Pallavicini F, Montecucco C (2010) Switching TNF- α antagonists in rheumatoid arthritis: the experience of the LORHEN registry. *Autoimmun Rev* 9:465–9
 98. Leung PS, Shu SA, Kenny TP, Wu PY, Tao MH (2010) Development and validation of gene therapies in autoimmune diseases: epidemiology to animal models. *Autoimmun Rev* 9:A400–5
 99. Mackay IR (2010) Travels and travails of autoimmunity: a historical journey from discovery to rediscovery. *Autoimmun Rev* 9:A251–8
 100. Blank M, Baraam L, Eisenstein M, Fridkin M, Dardik R, Heldman Y, Katchalski-Katzir E, Shoenfeld Y (2011) β 2-Glycoprotein-I based peptide regulate endothelial-cells tissue-factor expression via negative regulation of pGSK3 β expression and reduces experimental-antiphospholipid-syndrome. *J Autoimmun* 37:8–17
 101. Shoenfeld Y, Gershwin ME (2005) Intravenous immunoglobulin new indications and mechanisms of action. *Clin Rev Allergy Immunol* 29:165–166
 102. Sapir T, Shoenfeld Y (2005) Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. *Clin Rev Allergy Immunol* 29:185–199
 103. Sapir T, Shoenfeld Y (2005) Uncovering the hidden potential of intravenous immunoglobulin as an anticancer therapy. *Clin Rev Allergy Immunol* 29:307–310
 104. Katz U, Kishner I, Magalashvili D, Shoenfeld Y, Achiron A (2006) Long term safety of IVIG therapy in multiple sclerosis: 10 years experience. *Autoimmunity* 39:513–517
 105. Kessel A, Peri R, Haj T, Snir A, Slobodin G, Sabo E, Rosner I, Shoenfeld Y, Toubi E (2011) IVIG attenuates TLR-9 Activation in B cells from SLE patients. *J Clin Immunol* 31:31–38
 106. Blank M, Shoenfeld Y (2010) Sialic acid–IVIG targeting CD22. *Blood* 116:1630–1632
 107. Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, Gomez Puerta J, Espinosa G, Bucciarelli S (2007) The role of malignancies in patients with catastrophic anti-phospholipid (Asherson's) syndrome. *Clin Rheumatol* 26:2109–2114
 108. Blank M, Anafi L, Zandman-Goddard G, Krause I, Goldman S, Shalev E, Cervera R, Font J, Fridkin M, Thiesen H-J, Shoenfeld Y (2007) The efficacy of specific IVIG anti-idiotypic antibodies in antiphospholipid syndrome (APS): trophoblast invasiveness and APS animal model. *Int Immunol* 19:857–865
 109. Sela M, Teitelbaum D (2001) Glatiramer acetate in the treatment of multiple sclerosis. *Expert Opin Pharmacother* 2:1149–65
 110. Aharoni R, Herschkovitz A, Eilam R, Blumberg-Hazan M, Sela M, Bruck W, Arnon R (2008) Demyelination arrest and remyelination induced by glatiramer acetate treatment of experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci U S A* 12 (105):11358–63
 111. Kappos L, Comi G, Panitch H, Oger J, Antel J, Conlon P, Steinman L (2000) 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* 6:1176–82
 112. Krogsgaard M, Wucherpfennig KW, Cannella B, Hansen BE, Svejgaard A, Pyrdol J, Ditzel H, Raine C, Engberg J, Fugger L (2000) Visualization of myelin basic protein [MBP] T cell epitopes in MS lesions using a monoclonal antibody specific for the human histocompatibility leukocyte antigen HLA DR2 MBP 95–99 complex. *J Exp Med* 191:1395–412
 113. Gaur A, Boehme SA, Chalmers D, Crowe PD, Pahuja A, Ling N, Brocke S, Steinman L, Conlon PJ (1997) Amelioration of relapsing experimental autoimmune encephalomyelitis with altered myelin basic protein peptides involves different cellular mechanisms. *J Neuroimmunol* 74:149–58
 114. Blank M, Shoenfeld Y, Cabilly S, Heldman Y, Fridkin M, Katchalski-Katzir E (1999) Prevention of experimental antiphospholipid syndrome and endothelial cell activation by synthetic peptides. *Proc Natl Acad Sci U S A* 96:5164–8
 115. Tong JC, Sinha AA (2008) Immunological hotspots analyzed by docking simulations: evidence for a general mechanism in pemphigus vulgaris pathology and transformation. *BMC Immunol* 9:30–9
 116. Arnsom Y, Shoenfeld Y, Amital H (2010) Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 34:J258–265
 117. Berkun Y, Padeh S (2010) Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. *Autoimmun Rev* 9:A319–324
 118. Bhat A, Naguwa S, Cheema G, Gershwin ME (2010) The epidemiology of transverse myelitis. *Autoimmun Rev* 9:A395–399
 119. Biggioggero M, Meroni PL (2010) The geoepidemiology of the antiphospholipid antibody syndrome. *Autoimmun Rev* 9:A299–304
 120. Bizzaro N, Tozzoli R, Shoenfeld Y (2007) Are we at a stage to predict autoimmune rheumatic diseases? *Arthritis Rheum* 56:1736–1744
 121. Borchers AT, Naguwa SM, Keen CL, Gershwin ME (2010) The implications of autoimmunity and pregnancy. *J Autoimmun* 34:J287–299
 122. Borchers AT, Uibo R, Gershwin ME (2010) The geoepidemiology of type 1 diabetes. *Autoimmun Rev* 9:A355–365
 123. Brooks WH, Le Dantec C, Pers JO, Youinou P, Renaudineau Y (2010) Epigenetics and autoimmunity. *J Autoimmun* 34:J207–219
 124. Chandran V, Raychaudhuri SP (2010) Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *J Autoimmun* 34:J314–321
 125. Chang C (2010) The immune effects of naturally occurring and synthetic nanoparticles. *J Autoimmun* 34:J234–246
 126. Chang C, Gershwin ME (2010) Drugs and autoimmunity—a contemporary review and mechanistic approach. *J Autoimmun* 34:J266–275

127. Chen M, Daha MR, Kallenberg CG (2010) The complement system in systemic autoimmune disease. *J Autoimmun* 34: J276–286
128. Chen M, Kallenberg CG (2010) The environment, geoepidemiology and ANCA-associated vasculitides. *Autoimmun Rev* 9: A293–298
129. Deane S, Teuber SS, Gershwin ME (2010) The geoepidemiology of immune thrombocytopenic purpura. *Autoimmun Rev* 9: A342–349
130. Ehrenfeld M (2010) Geoepidemiology: the environment and spondyloarthropathies. *Autoimmun Rev* 9: A325–329
131. Gershwin ME, Goetzl EJ, Steinberg AD (1974) Cyclophosphamide: use in practice. *Ann Intern Med* 80: 531–540
132. Hemminki K, Li X, Sundquist J, Sundquist K (2010) The epidemiology of Graves' disease: evidence of a genetic and an environmental contribution. *J Autoimmun* 34: J307–313
133. Hershko AY, Naparstek Y (2006) Autoimmunity in the era of genomics and proteomics. *Autoimmun Rev* 5: 230–233
134. Hoffmann MH, Trembleau S, Muller S, Steiner G (2010) Nucleic acid-associated autoantigens: pathogenic involvement and therapeutic potential. *J Autoimmun* 34: J178–206
135. Invernizzi P (2010) Geoepidemiology of autoimmune liver diseases. *J Autoimmun* 34: J300–306
136. Lambert JF, Nydegger UE (2010) Geoepidemiology of autoimmune hemolytic anemia. *Autoimmun Rev* 9: A350–354
137. Lleo A, Invernizzi P, Gao B, Podda M, Gershwin ME (2010) Definition of human autoimmunity—autoantibodies versus autoimmune disease. *Autoimmun Rev* 9: A259–266
138. Logan I, Bowls CL (2010) The geoepidemiology of autoimmune intestinal diseases. *Autoimmun Rev* 9: A372–378
139. Mackay IR (2005) The etiopathogenesis of autoimmunity. *Semin Liver Dis* 25: 239–250
140. Martin PL, Malizia AI, Rewald E (2008) A propos time and autoimmunity. *Clin Rev Allergy Immunol* 34: 380–384
141. Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H (2010) Light, including ultraviolet. *J Autoimmun* 34: J247–257
142. Mavragani CP, Moutsopoulos HM (2010) The geoepidemiology of Sjogren's syndrome. *Autoimmun Rev* 9: A305–310
143. Meyer A, Levy Y (2010) Chapter 33: geoepidemiology of myasthenia gravis. *Autoimmun Rev* 9: A383–386
144. Meyer N, Misery L (2010) Geoepidemiologic considerations of auto-immune pemphigus. *Autoimmun Rev* 9: A379–382
145. Milo R, Kahana E (2010) Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmun Rev* 9: A387–394
146. Powell JJ, Faria N, Thomas-McKay E, Pele LC (2010) Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract. *J Autoimmun* 34: J226–233
147. Prieto S, Grau JM (2010) The geoepidemiology of autoimmune muscle disease. *Autoimmun Rev* 9: A330–334
148. Ranque B, Mouthon L (2010) Geoepidemiology of systemic sclerosis. *Autoimmun Rev* 9: A311–318
149. Round JL, O'Connell RM, Mazmanian SK (2010) Coordination of tolerogenic immune responses by the commensal microbiota. *J Autoimmun* 34: J220–225
150. Sands J, Tuscano JM (2010) Geoepidemiology and autoimmune manifestations of lymphoproliferative disorders. *Autoimmun Rev* 9: A335–341
151. Segelmark M, Hellmark T (2010) Autoimmune kidney diseases. *Autoimmun Rev* 9: A366–371
152. Selmi C (2010) The worldwide gradient of autoimmune conditions. *Autoimmun Rev* 9: A247–250
153. Selmi C, Tsuneyama K (2010) Nutrition, geoepidemiology, and autoimmunity. *Autoimmun Rev* 9: A267–270
154. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* 34: J168–177
155. Shoenfeld Y, Selmi C, Zimlichman E, Gershwin ME (2008) The autoimmunologist: geoepidemiology, a new center of gravity, and prime time for autoimmunity. *J Autoimmun* 31: 325–330
156. Stojanovich L (2010) Stress and autoimmunity. *Autoimmun Rev* 9: A271–276
157. Tobon GJ, Youinou P, Saraux A (2010) The environment, geoepidemiology, and autoimmune disease: rheumatoid arthritis. *Autoimmun Rev* 9: A288–292
158. Tomer Y (2010) Hepatitis C and interferon induced thyroiditis. *J Autoimmun* 34: J322–326
159. Tonutti E, Visentini D, Bizzaro N (2007) Interpretative comments on autoantibody tests. *Autoimmun Rev* 6: 341–346
160. Youinou P, Pers JO, Gershwin ME, Shoenfeld Y (2010) Geoepidemiology and autoimmunity. *J Autoimmun* 34: J163–167
161. Zeki AA, Schivo M, Chan AL, Hardin KA, Kenyon NJ, Albertson TE, Rosenquist GL, Louie S (2010) Geoepidemiology of COPD and idiopathic pulmonary fibrosis. *J Autoimmun* 34: J327–338
162. Zhao S, Long H, Lu Q (2010) Epigenetic perspectives in systemic lupus erythematosus: pathogenesis, biomarkers, and therapeutic potentials. *Clin Rev Allergy Immunol* 39: 3–9
163. Renaudineau Y (2010) The revolution of epigenetics in the field of autoimmunity. *Clin Rev Allergy Immunol* 39: 1–2
164. Matthias T, Pfeiffer S, Selmi C, Gershwin ME (2010) Diagnostic challenges in celiac disease and the role of the tissue transglutaminase-neo-epitope. *Clin Rev Allergy Immunol* 38: 298–301
165. Bhat A, Selmi C, Naguwa SM, Cheema GS, Gershwin ME (2010) Current concepts on the immunopathology of amyloidosis. *Clin Rev Allergy Immunol* 38: 97–106
166. Ikehara S (2010) The future of stem cell transplantation in autoimmune disease. *Clin Rev Allergy Immunol* 38: 292–297
167. Lidar M, Dori A, Levy Y, Lidar Z, Chapman J, Langevitz P (2010) Sarcoidosis presenting as “corset-like” myelopathy: a description of six cases and literature review. *Clin Rev Allergy Immunol* 38: 270–275
168. Carvalheiras G, Vita P, Marta S, Trovao R, Farinha F, Braga J, Rocha G, Almeida I, Marinho A, Mendonca T, Barbosa P, Correia J, Vasconcelos C (2010) Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. *Clin Rev Allergy Immunol* 38: 302–306
169. Kivity S, Katz U, Daniel N, Nussinovitch U, Papageorgiou N, Shoenfeld Y (2010) Evidence for the use of intravenous immunoglobulins—a review of the literature. *Clin Rev Allergy Immunol* 38: 201–269
170. Erlich JF, Paz Z (2010) Postpericardial injury syndrome: an autoimmune phenomenon. *Clin Rev Allergy Immunol* 38: 156–158
171. Ramos-Casals M, Brito-Zeron P, Perez-De-Lis M, Jimenez I, Blanco MJ, Bove A, Soto MJ, Akasbi M, Diaz C, Sentis J, Siso A (2010) Sjogren syndrome or sjogren disease? The histological and immunological bias caused by the 2002 criteria. *Clin Rev Allergy Immunol* 38: 178–185
172. Meron MK, Amital H, Shepshelovich D, Barzilai O, Ram M, Anaya JM, Gerli R, Nicola B, Shoenfeld Y (2010) Infectious aspects and the etiopathogenesis of rheumatoid arthritis. *Clin Rev Allergy Immunol* 38: 287–291
173. Emi Aikawa N, de Carvalho JF, Artur Almeida Silva C, Bonfa E (2010) Immunogenicity of anti-TNF-alpha agents in autoimmune diseases. *Clin Rev Allergy Immunol* 38: 82–89
174. Blank M, Shoenfeld Y (2010) Antiphospholipid antibody-mediated reproductive failure in antiphospholipid syndrome. *Clin Rev Allergy Immunol* 38: 141–147
175. Ambrosio P, Lermann R, Cordeiro A, Borges A, Nogueira I, Serrano F (2010) Lupus and pregnancy—15 years of experience in a tertiary center. *Clin Rev Allergy Immunol* 38: 77–81
176. De Carolis S, Botta A, Santucci S, Garofalo S, Martino C, Perrelli A, Salvi S, Ferrazzani S, Caforio L, Scambia G (2010) Predictors

- of pregnancy outcome in antiphospholipid syndrome: a review. *Clin Rev Allergy Immunol* 38:116–124
177. Ishii N, Hashimoto T, Zillikens D, Ludwig RJ (2010) High-dose intravenous immunoglobulin (IVIG) therapy in autoimmune skin blistering diseases. *Clin Rev Allergy Immunol* 38:186–195
 178. Katzav A, Shoenfeld Y, Chapman J (2010) The pathogenesis of neural injury in animal models of the antiphospholipid syndrome. *Clin Rev Allergy Immunol* 38:196–200
 179. Espirito Santo J, Gomes MF, Gomes MJ, Peixoto LC, Pereira S, Acabado A, Freitas J, de Sousa GV (2010) Intravenous immunoglobulin in lupus panniculitis. *Clin Rev Allergy Immunol* 38:307–318
 180. Matthias T, Shoenfeld Y (2010) Challenges for the autoimmunologist. *Clin Rev Allergy Immunol* 38:75–76
 181. Filippini M, Bazzani C, Favalli EG, Marchesoni A, Atzeni F, Sarzi-Puttini P, Pallavicini FB, Caporali R, Gorla R (2010) Efficacy and safety of anti-tumour necrosis factor in elderly patients with rheumatoid arthritis: an observational study. *Clin Rev Allergy Immunol* 38:90–96
 182. Thomas R, Matthias T, Witte T (2010) Leukocyte immunoglobulin-like receptors as new players in autoimmunity. *Clin Rev Allergy Immunol* 38:159–162
 183. Ribeiro FM, Szyper-Kravitz M, Klumb EM, Lannes G, Ribeiro FR, Albuquerque EM, Shoenfeld Y (2010) Can lupus flares be associated with tuberculosis infection? *Clin Rev Allergy Immunol* 38:163–168
 184. Paz Z, Shoenfeld Y (2010) Antifibrosis: to reverse the irreversible. *Clin Rev Allergy Immunol* 38:276–286
 185. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Mycobacterium tuberculosis, autoimmunity, and vitamin D. *Clin Rev Allergy Immunol* 38:169–177
 186. Holland SM (2010) Chronic granulomatous disease. *Clin Rev Allergy Immunol* 38:3–10
 187. Elhasid R, Rowe JM (2010) Hematopoietic stem cell transplantation in neutrophil disorders: severe congenital neutropenia, leukocyte adhesion deficiency and chronic granulomatous disease. *Clin Rev Allergy Immunol* 38:61–67
 188. Marks DJ, Rahman FZ, Sewell GW, Segal AW (2010) Crohn's disease: an immune deficiency state. *Clin Rev Allergy Immunol* 38:20–31
 189. Suhir H, Etzioni A (2010) The role of toll-like receptor signaling in human immunodeficiencies. *Clin Rev Allergy Immunol* 38:11–19