

Less Travelled Roads in Clinical Immunology and Allergy: Drug Reactions and the Environmental Influence

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Abstract Allergy and clinical immunology are examples of areas of knowledge in which working hypotheses are dominant over mechanistic understanding. As such, sometimes scientific efforts follow major streams and overlook some epidemiologically prevalent conditions that thus become underestimated by the research community. For this reason, we welcome the present issue of *Clinical Reviews in Allergy and Immunology* that is dedicated to uncommon themes in clinical immunology and allergy. First, comprehensive discussions are provided for allergy phenomena of large potential impact in clinical practice such as reactions to cephalosporins or aspirin-induced asthma and in everyday life such as allergies to food additives or legumes. Further, the issue addresses other uncommon themes such as urticaria and angioedema, cercarial dermatitis, or late-onset inflammation to soft tissue fillers. Last, there will be discussion on transversal issues such as olfactory defects in autoimmunity, interleukin 1 beta pathway, and the search for new serological markers in chronic inflammation. As a result, we are convinced that this issue will be of help to clinicians involved in internal medicine as well as to allergists and clinical immunologists. More importantly, we are convinced that these discussions will be of interest also to basic scientists for the numerous translational implications.

Key words Drug hypersensitivity · Antibiotics · Food additive · Legume · Systemic lupus erythematosus

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In the past decades, the epidemiological impact of allergies has steadily increased and this has significantly changed our approach to this multidisciplinary area of clinical practice. In parallel, clinical immunology has expanded its influence to numerous previously unsuspected symptoms and conditions. As a result, these disciplines have rapidly grown in importance, as well illustrated by the latest issues of this journal [1–16]. Nevertheless, immunology and allergy both follow mainstream directions and this explains the exponential growth in our understanding of major areas of interest. These are well exemplified in the past years by the hundreds of articles on microRNA and proinflammatory cytokines in immune-mediated diseases [17–24], with the obvious therapeutic implications in terms of cytokine and miRNA antagonists currently being developed. The present issue is intended to address and briefly discuss four major areas in this growing field.

First, adverse reactions to common drugs (ADR) are a major concern to clinicians worldwide; the main decision is whether to stop the drug and/or whether a rechallenge is recommended. ADR occur in 15 % or more of senior patients presenting to offices, hospitals, and extended care facilities but, more importantly, these events are potentially preventable up to 50 % of the time [25]. Common serious manifestations include falls, orthostatic hypotension, heart failure, and delirium; the most frequent causes of death are gastrointestinal or intracranial bleeding and renal failure [26]. Antithrombotic and antidiabetic medications, diuretics, and nonsteroidal anti-inflammatory drugs cause most of the preventable hospital admissions due to ADR [27–29]. In some cases, these are serious and constitute absolute contraindications, whereas others are mild and may or may not occur on subsequent exposure. The mechanism of the ADR may be helpful in risk assessment and drug allergies frequently have immunological mechanisms. Drug side-effects are more common and predictable, vary in severity, and depend on the drug's pharmacological action [30]. The decision to prescribe a drug where there is a history of a previous ADR

requires careful assessment of the risks and potential benefits. Strategies to reduce the risk of ADRs include discontinuing medications, prescribing new drugs sparingly, reducing the number of prescribers, and frequently reconciling medications. The Beers, STOPP (screening tool of older persons' potentially inappropriate prescriptions), and START (screening tool to alert doctors to right treatment) criteria can help identify medications causing adverse drug events [31]. Unfortunately, not all potentially inappropriate medications can be avoided, as in the case of cephalosporins which are largely utilized for community-acquired infections and led to the development of numerous bacterial resistant strains [32–34]. Using the European Surveillance of Antimicrobial Consumption and the Surveillance System of Antibiotic use and Bacterial Resistance in Intensive Care Units—a method of surveillance in use in Germany—Meyer et al. described that the burden of third generation-resistant *Escherichia coli* and *Klebsiella pneumoniae* more than quintupled (up to 2.6 and 1.2, respectively) and was followed by a threefold increase in the use of carbapenems and correlated with quinolone and third-generation cephalosporin use; they detected that the strongest correlation for third-generation cephalosporin pathogens was seen with carbapenem use which is clearly a result as first line treatment for extended-spectrum β -lactamase-producing enterobacteria infections [35]. Understanding the chemical structure of bacterial-resistant strains allows to identify the allergenic determinants for penicillin; however, the exact allergenic determinants of cephalosporins are not as well understood. Accordingly, standardized diagnostic skin testing is not available for cephalosporins as it is for penicillin but skin testing to the cephalosporin in question, using a nonirritating concentration, may provide additional information which may guide the management of a patient suspected of having an allergy. Together, the history and the skin test results can assist the allergist in the decision to recommend continued drug avoidance or to perform a graded challenge versus an induction of tolerance procedure [32].

In a complementary fashion, the idiosyncratic effect of aspirin on asthma-susceptible individuals is not related with an IgE mechanism but shares an abnormal metabolism of the lipoxygenase and cyclooxygenase pathways [36, 37]. Nowadays, a diagnosis of aspirin sensitivity can be established only by provocative aspirin challenge, which represents a potential risk for the patient. In a recent study, authors suggest that the non-allergic feature of the inflammatory process in aspirin-intolerant asthma can consider the participation of the Th1 and Th2 cytokines and to their regulatory mechanisms; for example the inhibition of IL-4 and a decrease of the nuclear translocation of NF- κ B by aspirin have opened a great deal of speculations [38]. Another study led in mice revealed that aspirin can inhibit the Th17 response and favor a Th2

inflammatory process [39]. Following this road, we hopefully think that biomarkers may represent a powerful, noninvasive tool in the diagnosis of aspirin sensitivity; moreover, they could provide a new way to classify asthma phenotypes.

The second issue described in the journal is represented by food allergies which constitute a large fraction of common allergies and sometimes may constitute a life-threatening emergency. While allergies to nuts and shellfish are well understood and widely investigated, allergies to legumes are rapidly becoming prevalent while remaining poorly understood [40]. Legumes comprise a large group of foods consumed worldwide; several legumes are allergenic, and peanut is surely the most important. Legumes like lupin, fenugreek, soy, lentils, and others also have the ability to induce clinical allergy [41–43] and there is extensive serological cross-reactivity among legumes. This cross-reactivity has traditionally been regarded to have limited clinical relevance [44] but the introduction of novel legumes to Western countries may have changed this pattern; in some studies, cross-allergy to lupin has been reported in more than 60 % of peanut-allergic patients [44–46]. The prevalence of legume allergy differs according to different dietary habits and environmental factors around the world [47]. In the beginning, the major part of the reported cases was caused by a cross-allergic reaction in peanut allergic patients, but a study in 2010 revealed as many cases caused by primary lupin allergy as cases caused by cross-allergy [48]. A serological cross-reactivity in vitro to several legumes is common in humans even though this will not necessarily lead to clinical relevance.

Data derived from the Norwegian Food Allergy Register [49] regarding legumes indicate that peanut is the allergen giving the highest allergen-specific IgE concentration while lupin and fenugreek give intermediary levels, and green pea and soy give the lowest concentration. A recent work investigated cross-allergic mechanisms using serum mouse mast cell protease-1, antibody responses, immunoblotting, and ex vivo production of cytokines by spleen cells; results demonstrated that cross-allergy did not reveal any signs of mast cell activation; in fact, it has been demonstrated that food-induced anaphylaxis may depend more on macrophages and basophils than on mast cells [50]. Vinje et al. concluded that differences in serological responses between primary allergy and cross-allergy might be due to mediation through different immune mechanisms or reflect different epitope affinity to IgE [51].

An additionally overlooked cause for food allergy is related to additives [52] which may act as adjuvants to trigger the immune reaction. Thousands of additives, either synthetic or natural, are used worldwide and these were primarily of natural origin before synthetic additives were gradually introduced and became predominant [53]. Based on their protein content, natural additives are more likely to induce immune-mediated adverse reactions. Most of the reports of

adverse reactions attributed to additives were case reports, small series, or based on poorly controlled challenge testing. It is difficult to estimate the prevalence of these phenomena because there is lack of consensus regarding the prevalence and the clinical manifestations. In a large cohort of British patients, the estimated prevalence of self-reported symptoms to food additives was 0.01–0.23 % [54]; studies in Denmark estimated the prevalence at 1–2 % in atopic children [55].

The natural or synthetic origin of potentially allergenic substances such as lysozyme, casein, lactose, albumin, phosphatide, and aromatic essences should be clearly stated. Providing this information has two clear advantages, i.e. allergic reactions to drugs in patients with food allergy could be avoided (if the substances have a natural origin) and prescriptions would improve by not restricting drugs containing synthetic substances (which do not usually induce allergic reactions) [56]. Several types of gum are used as emulsifiers; one of the most commonly used is guar gum, derived from the guar bean and used as stabilizer and emulsifier, particularly in ice creams, ketchups, salad dressings, yogurt, and baked goods. It has been described some case reports of occupational asthma [57] and a life-threatening hypersensitivity reaction following mucosal application of a local anesthetic containing guar gum [58]. Spices are derived from plants and used as flavoring agents. Because of the presence of capsaicin in hot spices, it may be difficult to differentiate intolerance from allergy, especially in children; a French study identified that 2 % of adults with food allergy have allergy to spices [59]; spices not known to cause IgE-mediated reactions have been listed to be especially useful as alternative for spice-sensitive patients. Butylated hydroxyanisole and butylated hydroxytoluene are common antioxidants that preserve fat and slow spoilage, commonly used in butter, cereals, chewing gum, baked goods, snack foods, dehydrated potatoes, and beer; these have been identified as triggers for exacerbations in two patients with chronic urticaria [60].

Monosodium glutamate (MSG) was originally obtained from seaweed and was later synthesized for wide distribution and is frequently used as a popular flavor enhancer added to many foods, especially Asian dishes. There are reports of asthma exacerbations due to MSG but no definite link was found in double-blind MSG challenges [61] while definitive data on its role in the metabolic syndrome are awaited [62–64]. Benzoates are food preservatives commonly used in alcoholic beverages, fruit juices, sparkling drinks, and pickles and have been reported to cause asthma in a few patients [65].

Third, uncommon themes also include more rare conditions such as urticaria and angioedema [66] in which pathogenetic mechanisms recognize new therapeutic targets for monoclonal antibodies. Similarly, less well-known reactions take place against soft tissue fillers [67] or cercarial dermatitis [68]. Also, the connection between metabolic disease and autoimmunity is

a further unsuspected link that Tsuneyama et al. investigate in both patients and fatty liver mouse models [69].

Fourth and finally, themes that are shared by different conditions are of major interest and thus discussed. These include changes in the olfactory capacity in autoimmune diseases such as lupus [70] that parallel data on frequent eye manifestation. Similarly, interleukin 1 beta is crucial to autoinflammatory diseases [71] but may also be pivotal to other inflammatory conditions and point towards innate immunity in clinical immunology [72, 73]. Despite the promising data on cytokine levels, serum autoantibodies are the most widely used biomarkers for the diagnosis and management of immune diseases and this is well represented by anti-neutrophil cytoplasmic antibodies in inflammatory bowel disease [74].

Concluding remarks and future directions may be difficult to trace for these wide areas of research. Nevertheless, an interdisciplinary approach with clinical observation-driven research, new molecular techniques, and a better understanding of individual susceptibility using deep sequencing and methylome analyses could be helpful to understand the mechanisms to prevent allergy or autoimmunity [75–79].

References

1. Antico A, Tozzoli R, Giavarina D, Tonutti E, Bizzaro N (2012) Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-control study and review of the literature on the interaction of vitamin D with the immune system. *Clin Rev Allergy Immunol* 42:355–364
2. Bizzaro N, Covini G, Rosina F, Muratori P, Tonutti E, Villalta D, Pesente F, Alessio MG, Tampoia M, Antico A, Platzgummer S, Porcelli B, Terzuoli L, Liguori M, Bassetti D, Brusca I, Almasio PL, Tarantino G, Bonaguri C, Agostinis P, Bredi E, Tozzoli R, Invernizzi P, Selmi C (2012) Overcoming a “probable” diagnosis in antimitochondrial antibody negative primary biliary cirrhosis: study of 100 sera and review of the literature. *Clin Rev Allergy Immunol* 42:288–297
3. Bizzaro N, Tozzoli R, Villalta D, Fabris M, Tonutti E (2012) Cutting-edge issues in celiac disease and in gluten intolerance. *Clin Rev Allergy Immunol* 42:279–287
4. Folci M, Meda F, Gershwin ME, Selmi C (2012) Cutting-edge issues in primary biliary cirrhosis. *Clin Rev Allergy Immunol* 42:342–354
5. Hajeb P, Selamat J (2012) A contemporary review of seafood allergy. *Clin Rev Allergy Immunol* 42:365–385
6. Lerner A, Shapira Y, Agmon-Levin N, Pacht A, Ben-Ami Shor D, Lopez HM, Sanchez-Castanon M, Shoenfeld Y (2012) The clinical significance of 25OH-vitamin D status in celiac disease. *Clin Rev Allergy Immunol* 42:322–330
7. Nussinovitch U, Shoenfeld Y (2012) The diagnostic and clinical significance of anti-muscarinic receptor autoantibodies. *Clin Rev Allergy Immunol* 42:298–308
8. Rozenberg O, Lerner A, Pacht A, Grinberg M, Reginashvili D, Henig C, Barak M (2012) A novel algorithm for the diagnosis of celiac disease and a comprehensive review of celiac disease diagnostics. *Clin Rev Allergy Immunol* 42:331–341

9. Selmi C (2012) Cutting-edge issues in autoimmunity and allergy of the digestive system. *Clin Rev Allergy Immunol* 42:265–268
10. Toh BH, Chan J, Kyaw T, Alderuccio F (2012) Cutting edge issues in autoimmune gastritis. *Clin Rev Allergy Immunol* 42:269–278
11. Vergani D, Mieli-Vergani G (2012) Cutting edge issues in autoimmune hepatitis. *Clin Rev Allergy Immunol* 42:309–321
12. Maverakis E, Goodarzi H, Wehrli LN, Ono Y, Garcia MS (2012) The etiology of paraneoplastic autoimmunity. *Clin Rev Allergy Immunol* 42:135–144
13. Nakahara J, Maeda M, Aiso S, Suzuki N (2012) Current concepts in multiple sclerosis: autoimmunity versus oligodendroglialopathy. *Clin Rev Allergy Immunol* 42:26–34
14. Orbach H, Zandman-Goddard G, Boaz M, Agmon-Levin N, Amital H, Szekanecz Z, Szucs G, Rovinsky J, Kiss E, Doria A, Ghirardello A, Gomez-Arbesu J, Stojanovich L, Ingegnoli F, Meroni PL, Rozman B, Blank M, Shoenfeld Y (2012) Prolactin and autoimmunity: hyperprolactinemia correlates with serositis and anemia in SLE patients. *Clin Rev Allergy Immunol* 42:189–198
15. Pontikaki I, Shahi E, Frasin LA, Gianotti R, Gelmetti C, Gerloni V, Meroni PL (2012) Skin manifestations induced by TNF-alpha inhibitors in juvenile idiopathic arthritis. *Clin Rev Allergy Immunol* 42:131–134
16. Rook GA (2012) Hygiene hypothesis and autoimmune diseases. *Clin Rev Allergy Immunol* 42:5–15
17. Sammiceli S, Ruffin N, Lantto R, Vivar N, Chiodi F, Rethi B (2012) IL-7 modulates b cells survival and activation by inducing BAFF and CD70 expression in T cells. *J Autoimmun* 38:304–314
18. Sharma R, Sung SS, Gaskin F, Fu SM, Ju ST (2012) A novel function of IL-2: chemokine/chemoattractant/retention receptor genes induction in Th subsets for skin and lung inflammation. *J Autoimmun* 38:322–331
19. Singh N, Cohen PL (2012) The T cell in Sjogren's syndrome: force majeure, not spectateur. *J Autoimmun* 39:229–233
20. van Wanrooij RL, Zwiers A, Kraal G, Bouma G (2012) Genetic variations in interleukin-12 related genes in immune-mediated diseases. *J Autoimmun* 39:359–368
21. Yan Y, Wang YH, Diamond B (2012) IL-6 contributes to an immune tolerance checkpoint in post germinal center B cells. *J Autoimmun* 38:1–9
22. Zhang J, Huang Z, Sun R, Tian Z, Wei H (2012) IFN-gamma induced by IL-12 administration prevents diabetes by inhibiting pathogenic IL-17 production in NOD mice. *J Autoimmun* 38:20–28
23. Dias PM, Banerjee G (2013) The role of Th17/IL-17 on eosinophilic inflammation. *J Autoimmun* 40:9–20
24. Jin JO, Han X, Yu Q (2013) Interleukin-6 induces the generation of IL-10-producing Tr1 cells and suppresses autoimmune tissue inflammation. *J Autoimmun* 40:28–44
25. Pretorius RW, Gataric G, Swedlund SK, Miller JR (2013) Reducing the risk of adverse drug events in older adults. *Am Fam Physician* 87:331–336
26. Acheampong P, Doig JC, Doshi M (2012) Prevalence, seriousness and effect of previous adverse drug reactions on prescribing during acute medical admission. *Int J Clin Pharm* 34:871–875
27. Junqueira DR, Carvalho M, Perini E (2013) Heparin-induced thrombocytopenia: a review of concepts regarding a dangerous adverse drug reaction. *Rev Assoc Med Bras* 59:161–166
28. Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G (2013) Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review. *Euro Rev Med Pharm Sci* 17(Suppl 1):45–49
29. White AA, Stevenson DD, Woessner KM, Simon RA (2013) Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies. *Allergy Asthma Proc: Off J Reg State Allergy Soc* 34:138–142
30. Smith W (2013) Adverse drug reactions—allergy? side-effect? intolerance? *Aust Fam Physician* 42:12–16
31. Lam MP, Cheung BM (2012) The use of STOPP/START criteria as a screening tool for assessing the appropriateness of medications in the elderly population. *Expert Rev Clin Pharmacol* 5:187–197
32. S.D. Dickson, K.C. Salazar. (2013) Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. *Clin Rev Allergy Immunol*. doi:10.1007/s12016-013-8367-x
33. Klausner JD, Kerndt P (2013) Cephalosporin resistance in neisseria gonorrhoeae infections. *JAMA*. doi:10.1001/jama.2013.4078
34. Shahada F, Chuma T, Kosugi G, Kusumoto M, Iwata T, Akiba M (2013) Distribution of extended-spectrum cephalosporin resistance determinants in *Salmonella enterica* and *Escherichia coli* isolated from broilers in southern Japan. *Poult Sci* 92:1641–1649
35. Meyer P, Gastmeier M, Deja FS (2013) Antibiotic consumption and resistance: data from Europe and Germany. *Int J Med Microbiol*. doi:10.1016/j.ijmm.2013.04.004
36. Babu KS, Salvi SS (2000) Aspirin and asthma. *Chest* 118:1470–1476
37. Szczeklik A, Stevenson DD (2003) Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 111:913–921, quiz 922
38. J.R. Velazquez, L.M. Teran. (2012) Aspirin-intolerant asthma: a comprehensive review of biomarkers and pathophysiology. *Clin Rev Allergy Immunol*
39. Moon HG, Tae YM, Kim YS, Gyu Jeon S, Oh SY, Song Gho Y, Zhu Z, Kim YK (2010) Conversion of Th17-type into Th2-type inflammation by acetyl salicylic acid via the adenosine and uric acid pathway in the lung. *Allergy* 65:1093–1103
40. Verma AK, Kumar S, Das M, Dwivedi PD (2012) A comprehensive review of legume allergy. *Clin Rev Allergy Immunol*
41. Patil SP, Niphadkar PV, Bapat MM (1997) Allergy to fenugreek (*Trigonella foenum graecum*). *Ann Allergy Asthma Immunol* 78:297–300
42. Martinez San Ireneo M, Ibanez MD, Fernandez-Caldas E, Carnes J (2008) In vitro and in vivo cross-reactivity studies of legume allergy in a Mediterranean population. *Int Arch Allergy Immunol* 147:222–230
43. Matheu V, de Barrio M, Sierra Z, Gracia-Bara MT, Tornero P, Baeza ML (1999) Lupine-induced anaphylaxis. *Ann Allergy Asthma Immunol* 83:406–408
44. Moneret-Vautrin DA, Guerin L, Kanny G, Flabbee J, Fremont S, Morisset M (1999) Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J Allergy Clin Immunol* 104:883–888
45. Peeters KA, Koppelman SJ, Penninks AH, Lebens A, Bruijnzeel-Koomen CA, Hefle SL, Taylor SL, van Hoffen E, Knulst AC (2009) Clinical relevance of sensitization to lupine in peanut-sensitized adults. *Allergy* 64:549–555
46. Shaw J, Roberts G, Grimshaw K, White S, Hourihane J (2008) Lupin allergy in peanut-allergic children and teenagers. *Allergy* 63:370–373
47. Martinez San Ireneo M, Ibanez Sandin MD, Fernandez-Caldas E (2000) Hypersensitivity to members of the botanical order fabales (legumes). *J Investig Allergol Clin Immunol* 10:187–199
48. Jappe U, Vieths S (2010) Lupine, a source of new as well as hidden food allergens. *Mol Nutr Food Res* 54:113–126
49. Namork E, Faeste CK, Stensby BA, Egeas E, Lovik M (2011) Severe allergic reactions to food in Norway: a ten year survey of cases reported to the food allergy register. *Int J Env Res Public Health* 8:3144–3155
50. Khodoun M, Strait R, Orekov T, Hogan S, Karasuyama H, Herbert DR, Kohl J, Finkelman FD (2009) Peanuts can contribute to anaphylactic shock by activating complement. *J Allergy Clin Immunol* 123:342–351
51. Vinje NE, Namork E, Lovik M (2012) Cross-allergic reactions to legumes in lupin and fenugreek-sensitized mice. *Scand J Immunol* 76:387–397

52. F. Gultekin, D.K. Doguc. (2012) Allergic and immunologic reactions to food additives. *Clin Rev Allergy Immunol*
53. Randhawa S, Bahna SL (2009) Hypersensitivity reactions to food additives. *Curr Opin Allergy Clin Immunol* 9:278–283
54. Young E, Patel S, Stoneham M, Rona R, Wilkinson JD (1987) The prevalence of reaction to food additives in a survey population. *J R Coll Physicians Lond* 21:241–247
55. Fuglsang G, Madsen C, Saval P, Osterballe O (1993) Prevalence of intolerance to food additives among Danish school children. *Pediatr Allergy Immunol* 4:123–129
56. Audicana Berasategui MT, Barasona Villarejo MJ, Corominas Sanchez M, De Barrio Fernandez M, Garcia Aviles MC, Garcia Robaina JC, Gastaminza Lasarte G, Laguna Martinez JJ, Lobera Labairu T, Lopez San Martin M, Martin Lazaro J, Moreno Rodilla E, Ortega Rodriguez N, Torres Jaen MJ (2011) Potential hypersensitivity due to the food or food additive content of medicinal products in Spain. *J Investig Allergol Clin Immunol* 21:496–506
57. Lemiere C, Cartier A, Malo JL, Lehrer SB (2000) Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med* 162:976–980
58. Roesch A, Haegele T, Vogt T, Babilas P, Landthaler M, Szeimies RM (2005) Severe contact urticaria to guar gum included as gelling agent in a local anaesthetic. *Contact dermatitis* 52:307–308
59. Moneret-Vautrin DA, Morisset M, Lemerdy P, Croizier A, Kanny G (2002) Food allergy and IgE sensitization caused by spices: CICBAA data (based on 589 cases of food allergy). *Allergie Immunologie* 34:135–140
60. Goodman DL, McDonnell JT, Nelson HS, Vaughan TR, Weber RW (1990) Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol* 86:570–575
61. Woods RK, Weiner JM, Thien F, Abramson M, Walters EH (1998) The effects of monosodium glutamate in adults with asthma who perceive themselves to be monosodium glutamate-intolerant. *J Allergy Clin Immunol* 101:762–771
62. Insawang C, Selmi U, Cha'on S, Pethlert P, Yongvanit P, Areejitranusorn P, Boonsiri T, Khampitak R, Tangrassameeprasert C, Pinitsoontorn V, Prasongwattana ME, Gershwin BDH (2012) Monosodium glutamate (MSG) intake is associated with the prevalence of metabolic syndrome in a rural Thai population. *Nutr Metab (Lond)* 9(1):50
63. Fujimoto M, Tsuneyama K, Fujimoto T, Selmi C, Gershwin ME, Shimada Y (2012) Spirulina improves non-alcoholic steatohepatitis, visceral fat macrophage aggregation, and serum leptin in a mouse model of metabolic syndrome. *Dig Liver Dis* 44:767–774
64. Nakanishi Y, Tsuneyama K, Fujimoto M, Salunga TL, Nomoto K, An JL, Takano Y, Iizuka S, Nagata M, Suzuki W, Shimada T, Aburada M, Nakano M, Selmi C, Gershwin ME (2008) Monosodium glutamate (MSG): a villain and promoter of liver inflammation and dysplasia. *J Autoimmun* 30:42–50
65. Pacor ML, Di Lorenzo G, Martinelli N, Mansueto P, Rini GB, Corrocher R (2004) Monosodium benzoate hypersensitivity in subjects with persistent rhinitis. *Allergy* 59:192–197
66. K. Altman, C. Chang. (2012) Pathogenic intracellular and autoimmune mechanisms in urticaria and angioedema. *Clin Rev Allergy Immunol*
67. J. Alijotas-Reig, M.T. Fernandez-Figueras, L. Puig. (2013) Late-onset inflammatory adverse reactions related to soft tissue filler injections. *Clin Rev Allergy Immunol*
68. L. Kolarova, P. Horak, K. Skirnisson, H. Mareckova, M. Doenhoff. (2012) Cercarial dermatitis, a neglected allergic disease. *Clin Rev Allergy Immunol*
69. K. Tsuneyama, H. Baba, K. Kikuchi, T. Nishida, K. Nomoto, S. Hayashi, S. Miwa, T. Nakajima, Y. Nakanishi, S. Masuda, M. Terada, J. Imura. (2013) Autoimmune features in metabolic liver disease: a single-center experience and review of the literature. *Clin Rev Allergy Immunol* 45 (in press).
70. C. Perricone, N. Shoenfeld, N. Agmon-Levin, C. de Carolis, R. Perricone, Y. Shoenfeld. (2012) Smell and autoimmunity: a comprehensive review. *Clin Rev Allergy Immunol*
71. Soriano, E. Verecchia, A. Afeltra, R. Landolfi, R. Manna. (2013) IL-1 β biological treatment of familial Mediterranean fever. *Clin Rev Allergy Immunol*
72. Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, Rose NR, Gershwin ME (2012) Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences Expert Panel workshop. *J Autoimmun* 39:272–284
73. Tian Z, Gershwin ME, Zhang C (2012) Regulatory NK cells in autoimmune disease. *J Autoimmun* 39:206–215
74. M.T. Arias-Loste, G. Bonilla, I. Moraleja, M. Mahler, M.A. Mieses, B. Castro, M. Rivero, J. Crespo, M. Lopez-Hoyos. (2013) Presence of anti-proteinase 3 antineutrophil cytoplasmic antibodies (anti-PR3 ANCA) as serologic markers in inflammatory bowel disease. *Clin Rev Allergy Immunol*
75. Germolec D, Kono DH, Pfau JC, Pollard KM (2012) Animal models used to examine the role of the environment in the development of autoimmune disease: findings from an NIEHS Expert Panel workshop. *J Autoimmun* 39:285–293
76. Miller FW, Pollard KM, Parks CG, Germolec DR, Leung PS, Selmi C, Humble MC, Rose NR (2012) Criteria for environmentally associated autoimmune diseases. *J Autoimmun* 39:253–258
77. Pollard KM (2012) Gender differences in autoimmunity associated with exposure to environmental factors. *J Autoimmun* 38:J177–J186
78. Sawalha AH, Wang L, Nadig A, Somers EC, McCune WJ, Hughes T, Merrill JT, Scofield RH, Strickland FM, Richardson B (2012) Sex-specific differences in the relationship between genetic susceptibility, T cell DNA demethylation and lupus flare severity. *J Autoimmun* 38:J216–J222
79. Selmi C, Lu Q, Humble MC (2012) Heritability versus the role of the environment in autoimmunity. *J Autoimmun* 39:249–252