Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Current Review

http://dx.doi.org/10.5415/apallergy.2013.3.4.209
Asia Pac Allergy 2013;3:209-214

What Taiwan contributes to the world of allergy and clinical immunology?

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In commemorate the 9th Asia Pacific Congress of Allergy, Asthma, and Clinical Immunology (APCAACI) in Taipei, Taiwan in November this year, some of the seminar works and contributions by the researchers from Taiwan to the advance in the field of allergy and clinical immunology, such as DNA vaccine, traditional Chinese medicine, anti-IgE antibody, and personalized medicine for severe drug allergic reaction, are summarized in this special review.

Key words: Allergy; Taiwan; Anti-IgE antibody; Severe drug reaction

Allergy, asthma, and clinical immunology in Asia Pacific-coming of age

This year is the 24th year since the Asian Pacific Association of Allergology and Clinical Immunology (APAACI; now Asia Pacific Association of Allergy, Asthma and Clinical Immunology Societies, APAAACI) was formed at a regional allergy meeting held in Bali, Indonesia, in 1989. The first Asian Pacific Congress of Allergology and Clinical Immunology (APCACI) was held in 1992 in Bangkok, and subsequent congresses have been held every two to three years in Taipei (1995), Manila (1998), Sydney (2000), Seoul (2002), Tokyo (2004), Bangkok (2007), and Singapore (2010). The meetings in Sydney (2000) and Bangkok (2007) were held in conjunction with World Allergy Organization (WAO)'s World Allergy Congress of those years. In fact, APAAACI became a regional society member of the WAO in 2000, which provide platform for the global communication and collaboration between our region and the rest of the world [1]. The 9th APAAACI congress will be held again in Taipei in November 14–17, 2013. On behalf of local organization community, we are much honored to be host society to commemorate the most important allergy and clinical immunology meeting of Asia Pacific in this year. In this review, I will briefly summarize the contributions for the advancing in the field of allergy and clinical immunology by Taiwan research scientists and allergists in recent decades.

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Received: October 12, 2013
Accepted: October 16, 2013

The prevalence studies of childhood allergy diseases in Taiwan

Asthma, allergic rhinitis, and atopic dermatitis are very common allergic diseases in Taiwan. Despite a short history, scientific research by a handful Taiwan clinical researchers, now only 300 plus board certificated allergists and clinical immunologists, has expanded quantitatively and qualitatively over the last three decades since the publication of the first prevalence survey of childhood asthma was conducted by Professor Hsieh, Kue-Hsiung in 1984 (Fig. 1). According to Hsieh and Shen [2], the prevalence of childhood asthma in Taipei, Taiwan was 1.3% in 1974 and 5.0% in 1985. Using the International Society for Augmentative and Alternative Communication (ISAAC) questionnaire in 1994 and 2002 in 6- to 7-year-old schoolchildren in the same place, an increasing trend was observed for asthma prevalence in 1994, but a leveling trend was detected for the period between 1994 and 2002 [3, 4]. However, a phase III study conducted by Yan et al. [5] in 2002 in 13- to 14-year-old schoolchildren in Taipei showed an increasing prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema. Recently, Wu et al. [6] showed that, from a total population of 24,999 first-grade students from 153 elementary schools in Taipei who completed the questionnaire, the proportion of children who have experienced wheezing and nocturnal cough in the past 12 months was significantly increased in 2007 compared with results for 1994 and 2002. In contrast, no significant differences were detected in the prevalence of current wheeze or physician-diagnosed asthma. The prevalence of severe wheezing symptoms in the past 12 months (four or more attacks of wheezing, 1 night of sleep disturbance due to wheezing per week, wheezing that limits speech, and exercise-induced wheezing) also decreased significantly. Alarmingly, the prevalence and severity of rhinitis symptoms increased significantly during the 13-year period that was analyzed. The prevalence of eczema symptoms, defined as recurrent itchy rash and typical atopic eczema distribution in the past 12 months, also increased. From a survey for 2,240 six- to seven-year-old children, 47.7% suffered from rhinitis, but only 10.7% of them were not troubled by it in their daily activities. As for physician-diagnosed allergic diseases, the prevalence was 24.6% for rhinitis and 18.0% for eczema, respectively. The authors noted that increases in the prevalence and severity of allergic rhinitis and atopic eczema but not in asthma are multifactorial and need to be explored further.

The burden of allergy diseases in Taiwan using National Health Insurance Database

The burden of asthma, particularly in children, have been greater more than ever to patients and their families as well as to governments and health-care systems despite efforts advocated by Global Initiative for Asthma (GINA) for total asthma controls. Using Taiwan National Health Insurance Research Database (NHIRD), the population-based prospective studies showed the costs and health care utilization, the prescription patterns of anti-

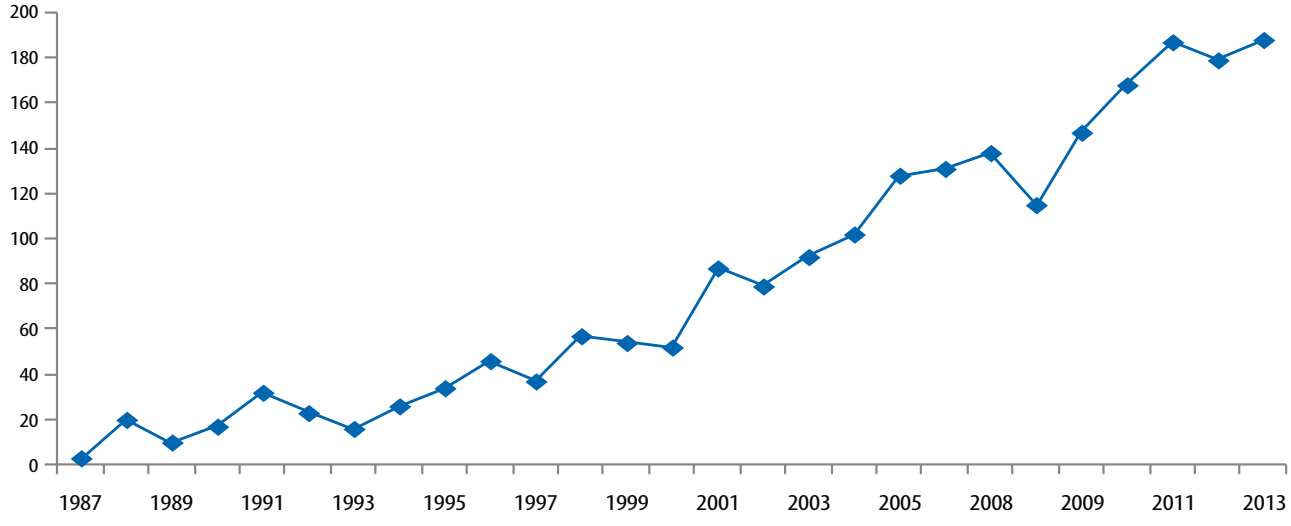

Fig. 1. Growth of Taiwan allergy Science Citation Index papers. These data were obtained from a PubMed search—(allergy or asthma or hypersensitivity) and affiliation [Taiwan].

http://dx.doi.org/10.5415/apallergy.2013.3.4.209

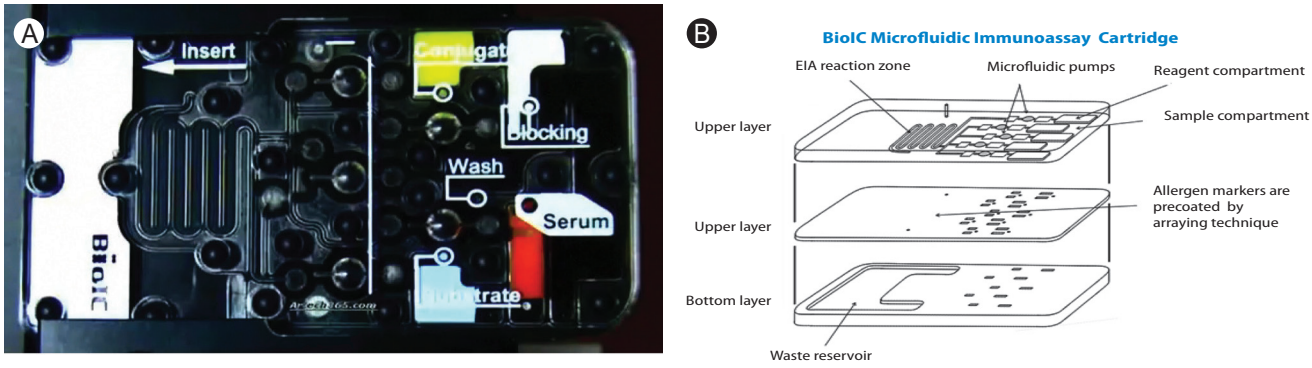

Fig. 2. A microfluidic-based, advanced screening technology for protein microarray analysis in diagnostic applications is shown. Utilizing microfluidic pumps and valves in a disposable cartridge, automated immunoassays can be carried out with equipment smaller than a personal computer and require only minimal user intervention (A). Low sample and reagent volumes reduce costs and allow multiplexed screening using serum obtained from capillary blood draws. In most cases, assays are completed within 30 minutes due to increased surface to volume ratios coupled with high sensitivity chemi-luminescence detection (B).

asthmatic medications among physician in different discipline, the appropriateness of combinational therapy of inhaled corticosteroid and long-acting beta agonist for moderate to severe childhood asthma were far from satisfaction [7-9]. Recently, from two birth cohorts obtained from NHIRD, we and other researchers provide suggestive evidence that temporal effect of exposure to acetaminophen and/or antibiotics in the first year of life influences the development of common allergic diseases in later childhood, i.e. increase the risk of asthma, allergic rhinitis, and atopic dermatitis to nearly two folds in general population of Taiwan [10]. Therefore, in the real-world situation, asthmatic patients as well as medical professions who take care of asthmatic children still have much space for their symptoms controls and knowledge improvement to reduce the burden of asthma. From the experience of care and management of childhood asthma in Taiwan, it may reveal same problems of childhood asthma care in the similar cultural and ecological environments of Asian pacific countries [11], and suggest government-sponsored outpatient based disease management program for patients with asthma [12], and nurse-led management program for pediatric asthma [13] may also have significant impact aimed at improving the care of patients with asthma.

Advances in the research field of allergy in Taiwan

Despite a short history and small research community in Taiwan [14], scientific publications in allergy-related field has expanded quantitatively and qualitatively in recent two decades since professor Hsieh, Keu-Hsiung first published his seminar paper on the changes of lymphoproliferative responses of T cell subsets to allergen and mitogen after hyposensitization in asthmatic children at the Journal of Allergy and Clinical Immunology (JACI) in the year 1984 [15]. In the following years of his short academic life (deceased in 1998), professor Hsieh had published more than 10 distinguished research papers in JACI, and the most influential work, published in the year of 1995 in Nature Medicine along with late professor Chua, Kaw-Yan, was using DNA vaccine in the allergen gene-transfer to treat allergy diseases in experimental animal models [16]. After he took the helm of Department of Life Sciences, National Science Council, Taiwan, an first-of-ever interdisciplinary project was enacted for scientific studies and applications of tradition Chinese medicine (TCM) in allergy diseases. Professor Hsieh and author are the first to conduct double-blinded, randomized placebo-controlled clinical trials to evaluate three herb complexes (Fan-Chi) of TCM in 350 asthmatic children [17] and evaluate the pharmacology effect of xiao-qing-long tang in mouse model of asthma that open-up the trend for scientific research using TCM in the prevention and treatment of allergy diseases [18].

The invention of anti-IgE antibody by professor Chang, Tse-Wen

In late 1990s, professor Chang returned to his alumina Tsinghua University at Hsin-Chu, Taiwan from the United States where he and his former wife set up Tanox, a successful company that co-developed an asthma drug called Omalizumab (trade name Xolair, Roche/Genentech and Novartis), which is a humanized antibody used to reduce sensitivity to inhaled or ingested allergens, especially in the control of moderate to severe allergic asthma which does not respond to high doses of corticosteroids [19]. It

 http://dx.doi.org/10.5415/apallergy.2013.3.4.209

has been approved for use in more than 90 countries, although some countries restrict its use to patients over 12 years old. To develop a new drug for allergy and asthma deserve a lot of efforts and courage [20]. Initially, the anti-IgE therapeutic concept was not well received in the early period of the program. The scientists comprehended at that time that an ordinary anti-IgE antibody would invariably activate mast cells and basophils and cause anaphylactic shocks and probably deaths among injected persons. In order to seek funding for the anti-IgE program, the two scientist founders (all came from Taiwan) of Tanox, Nancy T. Chang and Tse-Wen Chang, visited about 25 pharmaceutical and larger biotech companies in the USA, Canada, Europe, Japan, and other countries to discuss collaboration throughout 1989. In 1991, after several rounds of pre-IND (investigational new drug) meetings with officials/scientists of the Food and Drug Administration (FDA), the FDA finally gave a nod for CGP51901 (the initial code name for Omalizumab) to be tested in human subjects. This approval of IND for an anti-IgE antibody for the first time was regarded a brave demonstration of professionalism for both the FDA officials and the Tanox/Ciba-Geigy team. In 1991–1993, researchers from Ciba-Geigy and Tanox and a leading clinical research group (headed by Stephen Holgate) in the asthma/allergy field ran a successful phase I human clinical trial of CGP51901 in Southampton, England and showed that the tested antibody is safe [21]. And the rest become history (details of the development of Omalizumab can be browsed in Wikipedia, http://en.wikipedia.org/wiki/Omalizumab). Professor Chang, now in Genomic Research Center, Academic Sinica, Taiwan, has established his historic role of develop new drug for asthma and allergy [22].

Personalized medicine for severe drug allergic reaction by Professor Chen, Yuan-Tsong

Stevens-Johnson syndrome (SJS) and its related disorder, toxic epidermal necrolysis (TEN) are life-threatening adverse reactions most often caused by drugs. They are two of the most serious drug hypersensitivity reactions which carry mortality rate as high as 40%, and are historically referred to as being unpredictable, dose-independent idiosyncratic reactions. In 2004, Dr. Chen's team in the institute of Biomedical Sciences, Academic Sinica, Taiwan, made the ground-breaking discovery of genetic basis of SJS and TEN. In a paradigm shift, Dr. Chen's team showed that these reactions are, in fact, predictable, for example, carbamazepine, a drug used to treat epilepsy and allopurinol, a widely prescribed drug for gout, are strongly associated with human leukocyte antigen (HLA)-B alleles; people having a gene for a specific human leukocyte antigen (HLA-B1502) have a 2,000-fold higher risk of developing carbamazepine-induced SJS-TEN than people lacking the antigen [23]; and people having HLA-B5801 carry 500-fold higher risk for allopurinol-induced severe adverse drug in Hans popualtion [24]. These strong genetic association suggests a direct involvement of HLA in the pathogenesis of drug hypersensitivity and this is indeed the case in which HLA molecule presents an antigenic drug and recognized by specific T cell receptor for T cell activation which leads to secretion of a cytotoxic molecule called granulysin as a key mediator for the disseminated keratinocyte death in SJS and toxic epidermal necrolysis [25]. These pharmacogenetic researches have prompted the FDA to relabeled carbamazepine with genetic information and recommend genetic screening before doctors prescribe the medication. In the case of carbamazepine, a prospective study using HLA-B1502 genotyping has effectively prevented the SJS-TEN [26] and Taiwan becomes the first country to implement the test nationwide. The screening test now becomes a standard care in clinic in Taiwan [editorial note: The allele frequency of HLA-B1502 is less than 1% in Korea and Japan, which means that HLA-B1502 may not be an adequate marker for screening in Korea. One published data by Chang et al. supports HLA-B1511 for predicting severe cutaneous reactions (also in Japan) although only one entire case with HLA-B1502 showed SJS. Debates and screening test in Taiwan, Singapore, and Hong Kong will be briefly mentioned in the other article by Bernard Thong in the same issue]. By using genetic information to guide the choice of the drug, professor Chen played a leading role in the era of personalized medicine and his research has led to safer and more effective use of drugs worldwide.

Genome-wide association study for Kawasaki diseases and nanotechnology application in vitro allergen-specific IgE detection

Other important contributions in the field of allergy and clinical immunology including recent identified association of CD40L genetic polymorphisms and Kawasaki diseases in genome-wide association study (GWAS) by the research teams from the Department of Pediatric Allergy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung and Department of Pediatrics, China Medical University, Taichung, Taiwan [27]. A microfluidic cartridge and system for multiplexed immunoassays for in vitro allergen-specific IgE diagnostics is developed applying nanotechnology spin-off from Industry Technology Research Institute in Hsinchu, and

http://dx.doi.org/10.5415/apallergy.2013.3.4.209

Department of Pediatric Allergy and Immunology, National Cheng Kung University, Tainan, Taiwan, which use 0.09 mL of patients' sera, and the results can be read out in 30 minutes [28]. The sensitivity and specificity for multiple allergens IgE detection are compatible with CAP and skin prick tests [29].

Lying ahead-a long and winding road

In less than 30 years the tiny island of Taiwan has gone from agricultural backwater to global electronics giant. Now it is turning its attention to biotechnology. But can Taiwan sustain the pace of development? This question is raised in the year 2000 by the editor of Nature in a special article regarding regional insight of Taiwan [30]. For the capacity of Taiwan, and as a member society of Asia Pacific, to rise to the challenge and find a niche in the field of allergy research, we have the glory history to create directions, but lying ahead, a long and winding road waiting to be travelled by our young generations and researchers in the year to come.

REFERENCES

1. Asia Pacific Association of Allergy, Asthma, and Clinical Immunology Societies (APAAACI). About APAAACI [Internet]. Sydney: APAAACI; 2011 [cited 2013 Oct 11]. Available from: http://www.apaaaci.org/about.php.
2. Hsieh KH, Shen JJ. Prevalence of childhood asthma in Taipei, Taiwan, and other Asian Pacific countries. J Asthma 1988;25:73-82.
3. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998;12:315-35.
4. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.
5. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL. Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. Ann Allergy Asthma Immunol 2005;95:579-85.
6. Wu WF, Wan KS, Wang SJ, Yang W, Liu WL. Prevalence, severity, and time trends of allergic conditions in 6-to-7-year-old schoolchildren in Taipei. J Investig Allergol Clin Immunol 2011;21:556-62.
7. Sun HL, Kao YH, Lu TH, Chou MC, Lue KH. Health-care utilization and costs in Taiwanese pediatric patients with asthma. Pediatr Int 2007;49:48-52.
8. Sun HL, Lue KH. Health care utilization and costs of adult asthma in Taiwan. Allergy Asthma Proc 2008;29:177-81.
9. Sun HL, Kao YH, Chou MC, Lu TH, Lue KH. Differences in the prescription patterns of anti-asthmatic medications for children by pediatricians, family physicians and physicians of other specialties. J Formos Med Assoc 2006;105:277-83.
10. Wang JY, Liu LF, Chen CY, Huang YW, Hsiung CA, Tsai HJ. Acetaminophen and/or antibiotic use in early life and the development of childhood allergic diseases. Int J Epidemiol 2013;42:1087-99.
11. Wang JY, Liu LF. Health care utilization and medical costs for childhood asthma in Taiwan: using Taiwan National Health Insurance Research Database. Asia Pac Allergy 2012;2:167-71.
12. Weng HC. Impacts of a government-sponsored outpatient-based disease management program for patients with asthma: a preliminary analysis of national data from Taiwan. Dis Manag 2005;8:48-58.
13. Weng HC, Yuan BC, Su YT, Perng DS, Chen WH, Lin LJ, Chi SC, Chou CH. Effectiveness of a nurse-led management programme for paediatric asthma in Taiwan. J Paediatr Child Health 2007;43:134-8.
14. Klaewsongkram J, Reantragoon R. Asthma research performance in Asia-Pacific: a bibliometric analysis by searching PubMed database. J Asthma 2009;46:1013-20.
15. Hsieh KH. Changes of lymphoproliferative responses of T cell subsets to allergen and mitogen after hyposensitization in asthmatic children. J Allergy Clin Immunol 1984;74:34-40.
16. Hsu CH, Chua KY, Tao MH, Lai YL, Wu HD, Huang SK, Hsieh KH. Immunoprophylaxis of allergen-induced immunoglobulin E synthesis and airway hyperresponsiveness in vivo by genetic immunization. Nat Med 1996;2:540-4.
17. Hsieh KH. Evaluation of efficacy of traditional Chinese medicines in the treatment of childhood bronchial asthma: clinical trial, immunological tests and animal study. Taiwan Asthma Study Group. Pediatr Allergy Immunol 1996;7:130-40.
18. Kao ST, Wang SD, Wang JY, Yu CK, Lei HY. The effect of Chinese herbal medicine, xiao-qing-long tang (XQLT), on allergen-induced bronchial inflammation in mite-sensitized mice. Allergy 2000;55:1127-33.
19. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med 2001;164(8 Pt 2):S6-11.
20. Chang TW, Wu PC, Hsu CL, Hung AF. Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. Adv Immunol 2007;93:63-119.

 http://dx.doi.org/10.5415/apallergy.2013.3.4.209

21. Corne J, Djukanovic R, Thomas L, Warner J, Botta L, Grandordy B, Gygax D, Heusser C, Patalano F, Richardson W, Kilchherr E, Staehelin T, Davis F, Gordon W, Sun L, Liou R, Wang G, Chang TW, Holgate S. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. J Clin Invest 1997;99:879-87.
22. Chang TW. The pharmacological basis of anti-IgE therapy. Nat Biotechnol 2000;18:157-62.
23. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
24. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, Chen YT. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134-9.
25. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, Chin SW, Chiou CC, Chu SC, Ho HC, Yang CH, Lu CF, Wu JY, Liao YD, Chen YT. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14:1343-50.
26. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, Tai CT, Wu SL, Lu CH, Hsu YC, Yu HY, Ro LS, Lu CT, Chu CC, Tsai JJ, Su YH, Lan SH, Sung SF, Lin SY, Chuang HP, Huang LC, Chen YJ, Tsai PJ, Liao HT, Lin YH, Chen CH, Chung WH, Hung SI, Wu JY, Chang CF, Chen L, Chen YT, Shen CY; Taiwan SJS Consortium. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126-33.
27. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR, Liang CD, Chi H, Huang FY, Lee ML, Huang YC, Hwang B, Chiu NC, Hwang KP, Lee PC, Chang LC, Liu YM, Chen YJ, Chen CH; Taiwan Pediatric ID Alliance, Chen YT, Tsai FJ, Wu JY. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet 2012;44:522-5.
28. Tai LW, Tseng KY, Wang ST, Chiu CC, Kow CH, Chang P, Chen C, Wang JY, Webster JR. An automated microfluidic-based immunoassay cartridge for allergen screening and other multiplexed assays. Anal Biochem 2009;391:98-105.
29. Shyur SD, Jan RL, Webster JR, Chang P, Lu YJ, Wang JY. Determination of multiple allergen-specific IgE by microfluidic immunoassay cartridge in clinical settings. Pediatr Allergy Immunol 2010;21:623-33.
30. Swinbanks D, Cyranoski D. Taiwan backs experience in quest for biotech success. Nature 2000;407:417-26.

http://dx.doi.org/10.5415/apallergy.2013.3.4.209