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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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-
Research of allergy and clinical immunology in Taiwan

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].

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).

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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 population [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
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.

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