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## **Autoantibodies in patients with asthma: is there a link between asthma and autoimmunity?**

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### **Theocharis G. Konstantinidis\***

Regional Public Health Laboratory (East Macedonia-Thrace),  
Andronikou 36, Alexandroupolis 68100, Greece  
Fax: +302551025488  
E-mail: [tkonsta@med.duth.gr](mailto:tkonsta@med.duth.gr)  
E-mail: [theoxari\\_ko@yahoo.gr](mailto:theoxari_ko@yahoo.gr)  
\*Corresponding author

### **Christina Tsigalou**

Immunology Department of Microbiology Laboratory,  
University General Hospital of Alexandroupolis,  
Dragana, Alexandroupolis 68100, Greece  
E-mail: [xtsigalou@yahoo.gr](mailto:xtsigalou@yahoo.gr)

### **Alexandros Bisiklis**

Microbiology Laboratory 'analysis',  
Orpheus 9, Komotini 69100, Greece  
E-mail: [alexbisiklis@gmail.com](mailto:alexbisiklis@gmail.com)

### **Gioulia Romanidou**

General Hospital 'Sismanoglio' Komotini,  
Sismanoglou 45, Komotini 69100, Greece  
E-mail: [dr\\_giouliarom@yahoo.gr](mailto:dr_giouliarom@yahoo.gr)

### **Eleni Konstantinidou**

Immunology Department of Microbiology Laboratory,  
University General Hospital of Alexandroupolis,  
Dragana, Alexandroupolis 68100, Greece  
E-mail: [dr\\_konsteleni@yahoo.gr](mailto:dr_konsteleni@yahoo.gr)

### **Theodore Parasidis**

Regional Public Health Laboratory (East Macedonia-Thrace),  
Andronikou 36, Alexandroupolis 68100, Greece  
E-mail: [tparasid@med.duth.gr](mailto:tparasid@med.duth.gr)

## Theodora Gioka and Georgia Kampouromiti

Immunology Department of Microbiology Laboratory,  
University General Hospital of Alexandroupolis,  
Dragana, Alexandroupolis 68100, Greece  
E-mail: tgioka@pgna.gr  
E-mail: g.kabouromiti@yahoo.gr

## Theodore C. Constantinidis

Laboratory of Hygiene and  
Environmental Protection in Medical School,  
Democritus University of Thrace,  
Dragana, Alexandroupolis 68100, Greece  
E-mail: tconstan@med.duth.gr

## Dimitrios C. Cassimos

Paediatric Department,  
Medical School,  
Democritus University of Thrace,  
Dragana, Alexandroupolis 68100, Greece  
E-mail: dkasimos@med.duth.gr

**Abstract:** The objective of this study was to measure autoantibodies and the mean individual immune reactivity (IR) in children with asthma. The study group consisted of ten children with asthma and the control group of ten age-matched healthy subjects. In all patients IR and 24 autoantibodies (aAb) type G were measured by ELISA (Immunculus, Russia). The IR in asthmatics was 42% and was statistically significantly higher than this of control group 9% ( $p < 0.005$ ). The level of aAbs (LuM, LuS, CoM and dsDNA) was also raised in the asthmatics. Anti-Adr aAbs was higher in one patient who required intense treatment for asthma with frequent use of corticosteroids. Anti-HMMP, insulin and IR aAbs were significantly lower in comparison to the control group ( $p < 0.05$ ). This study confirms the high level of immunological activation in patients with asthma. The presence of autoantibodies implies that autoimmunity might have a role in the pathogenesis of asthma.

**Keywords:** immunoregulation; autoantibodies; immunoglobulin E; asthma; children; immune reactivity.

**Reference** to this paper should be made as follows: Konstantinidis, T.G., Tsigalou, C., Bisiklis, A., Romanidou, G., Konstantinidou, E., Parasidis, T., Gioka, T., Kampouromiti, G., Constantinidis, T.C. and Cassimos, D.C. (2012) 'Autoantibodies in patients with asthma: is there a link between asthma and autoimmunity?', *Int. J. Immunological Studies*, Vol. 1, No. 4, pp.376–387.

**Biographical notes:** Theocharis G. Konstantinidis is a medical doctor. He graduated from the Kuban State Medical Academy of Krasnodar, Russia in 1998. He completed his Master from Medical School of Democritus University of Thrace. He is a PhD student in Immunology at Medical School of Democritus University of Thrace. His research areas of interest are prevention medicine, allergy, inflammation, immunology and autoimmunity. Since 2009, he has been a member of Regional Public Health Laboratories (East Macedonia – Thrace Region) of Hellenic Centre for Diseases Control and Prevention.

Christina Tsigalou is a medical doctor. She graduated from Democritus University of Thrace in 1992. She completed her PhD from Laboratory of Microbiology in Medical School of Democritus University of Thrace. She works as a consultant since 1999 in General University Hospital of Alexandroupolis. Her areas of interest are all kind of biochemical and immunological fields.

Alexandros Bisiklis graduated from the Medicine School of Aristotelian University of Thessaloniki. He completed his specialty in biopathology from AHEPA University Hospital of Thessaloniki. He was awarded with PhD from Aristotelian University. He has published several research papers and presented at national and international level. Now, he is working as a doctor in Greek Army.

Gioulia Romanidou is a medical doctor. She graduated from the Voronez State Medical Academy, Russia in 2001. She works as an Internship in Internal Medicine at the General Hospital of Komotini. Her main fields of interest include emergency medicine, immunology.

Eleni Konstantinidou is a medical doctor. She graduated from the Kuban State Medical Academy of Krasnodar, Russia in 1998. She works as an Internship in Laboratory Medicine at the General University Hospital of Alexandroupolis. Her main fields of interest include laboratory medicine, immunology and microbiology.

Theodore A. Parasidis studied biology at the University of Patras in Greece. He completed his PhD in Public Health from Laboratory of Hygiene and Environmental Protection in Medical School of Democritus University of Thrace. His research areas of interest are virology and molecular techniques such as real time PCR and sequencing analysis. His current position is Biologist at Regional Public Health Laboratories of East Macedonia – Thrace Region of Hellenic Centre for Diseases Control and Prevention.

Theodora M. Gioka is a medical doctor with specialisation in microbiology. She graduated from University of Bologna in Italy in 1984. She is the Director of the Laboratory of Microbiology in the General University Hospital of Alexandroupolis. Apart from having expertise in flow cytometry, she also deals with other area of interest such as the allergy field, the inflammation, and the immunology and autoimmunity field. She is the President of Committee of Hospital Infections. In the region East Macedonia Thrace. She also holds the place of the Vice President of the Medical Association.

Georgia Kampouromiti is a medical doctor. She graduated from Aristotle University of Thessalonica in 1978. She is the Head of Clinical Biochemistry and Immunology Department of the General University Hospital of Alexandroupolis (last 11 yrs). Her areas of interest are all kind of biochemical and immunological fields, quality procedures and laboratory administration.

Theodoros C. Constantinidis is Associate Professor and Director of Laboratory of Hygiene and Environmental Protection in Medical School of Democritus University of Thrace. He has published several papers in international and local journals and supervised many MSc and PhD thesis. His research areas of interest are occupational diseases, risk assessment, biostatistics, and epidemiology.

Dimitrios C. Cassimos is an Assistant Professor in Paediatric Department of Democritus University of Thrace. He obtained his MD and PhD at Medical School of Athens. He obtained his diploma of GPs in 1991 after vocational training and degree of Specialty in Paediatrics in 1998. He completed his post-graduate training in immunology-allergology at Great Ormond Street Hospital and St. Mary's Hospitals UK (1997–1998), Aglaia Kyriakou and Aghia Sophia Children's Hospitals in Greece (1999–2001). He has published several papers in medical journals in immunology and allergology. His research areas of interest are allergology, immunology, infectious diseases and nutrition in children.

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## **1 Introduction**

Asthma is a universal health problem and the most common chronic inflammatory disorder of the respiratory system in children. The prevalence of this has increased dramatically over the last 40 years, something that has been associated with the western way of living (Masoli et al., 2004). Asthma is thought to be the subsequent result of an interactive process of multiple factors and mechanisms controlling. Despite intensive efforts and acquired knowledge in molecular biology and genetics, it is not fully understood the genetic background of the disease. On the other hand, the aggregation of the disease within family members, according to Burke et al. (2003) are in favour for the effect of shared genes. Epidemiological studies have linked infection with the development and severity of asthma, in both children and adults via defects in innate immunity at the airway epithelium (Holgate et al., 2009). Several *in vitro* studies have shown that microbial components or synthetic adjuvant can directly act on innate immune cells such as DC and NK cells triggering the production of IL-12, thus sensitised T cells for secreted less IFN- $\gamma$ , but enhanced IL-5, characteristic of Th2 (Koski et al., 2004; Parronchi et al., 1999). *In vivo*, studies have also demonstrated that stimulation of innate immune cells with microbial or synthetic compounds hamper the development of allergic diseases by promoting Th1 phenotypes.

Also, viral infections are well recognised as significant triggers of acute exacerbations of asthma in children and adults (Mazmanian et al., 2005). The mechanisms by which infections influence asthma are not fully recognised. It is not clear if viral respiratory infections are causative of asthma or indicative of a predisposition to the development of asthma (Cassimos et al., 2008). Numerous immune mechanisms and more specifically of autoimmune origin are related in the pathogenesis – development of asthma (Rottem and Shoenfeld, 2003; Rottem et al., 2002; Zweiman, 2007; Dietert and Zelikoff, 2010). ‘The autoimmune hypothesis’ about the pathogenesis of asthma emerges from the presence of autoantibodies against different antigens such as alpha-enolase protein (Nahm et al., 2006), antinuclear antibodies – ANA (Agache et al., 2009), rheumatoid factor (Kobayashi et al., 2004) and the response to medical regimes used for systemic autoimmune diseases such as corticosteroids, anti-TNF, etc. (Quintero et al., 1966; Cox, 2008; Holgate, 2004). Several studies evaluated the relationship between specific cytokines and asthma. Lewis et al. (2009) sought to clarify the role of IL-4 and IL-13 in the pathogenesis of asthma. Kanda et al. (2009) reported a surprising link between eosinophils and IFN- $\gamma$  in a murine model (Kanda et al., 2009; Lewis et al., 2009).

However, there is no consistent evidence to support a specific mechanism connecting autoimmunity response with the development of asthma.

In the present study, we measured IgG autoantibodies against different autoantigens in the serum of patients with severe asthma in order to examine the impact of autoimmune reaction in such subject.

## 2 Materials and methods

We used serum samples from ten children with severe asthma and ten age-matched healthy controls. Asthma control was defined by the paediatric allergist based on symptoms such as cough and/or wheeze and measurements of lung function by spirometry (forced expiratory volume in 1 second-FEV1 and forced vital capacity-FVC) according to GINA guidelines (GINA, 2011). All the patients with severe asthma, included in the study group had similar clinical characteristics and one of them required frequent administrations of oral corticosteroids for the control of symptoms. The characteristics of the study population are presented in Table 1.

**Table 1** Characteristics of the study population

	<i>Asthma (n = 10)</i>	<i>Healthy controls (= 10)</i>
Gender M/F	5/5	4/6
Age (years)	8	7
Corticosteroid (n)	1	0
Serum IgE ng/ml	470.98	22.1

We measured 24 autoantibodies (a-Abs), type IgG, and the mean individual immune reactivity, by ELISA (ELI viscero 24 test, Immunculus, Russia Table 2).

This kit is for the semi-quantitative evaluation of a panel of autoantibodies (a-Abs) against antigens of the main human organs (heart, lungs, liver, etc.), as well as to antigens characterising the state of the immune system (dsDNA) in the blood serum. Blood samples from patients and control subjects were drawn into a vacutainer tube without anticoagulant and were centrifuged for 15 min at a speed of 1,000–2,000 RCF, as suggested by manufacturer. Thereafter, samples were stored at –20°C until the tests were performed. Before running the test we kept the kit's components in room temperature for more than 60 min. The serum samples were diluted 1:200 in 0.05% Tween-20 phosphate-buffered saline and were placed into wells preliminary coated with the selected antigens. The standard enzyme-linked immunosorbent assay (ELISA) protocol has been followed. The level for each aAb was calculated in conditional units (CU) to an internal standard optical density using the following equation:

$$IR = \frac{OD_{p(AGn)} \times 100}{OD_{st}} - 100$$

where  $OD_{p(AGn)}$  is the optical density of patient's sera with antigen (AGn) and  $OD_{st}$  is the optical density of an internal standard with the same antigen (AGn). All analysed samples and the control samples were tested twice.

**Table 2** ELI viscera test auto-Abs profile

<i>Interpretations</i>	<i>Abbreviations</i>
dsDNA	DNA
Fc-fragment of immunoglobulins IgG	Fc
Beta2-glycoprotein I	b2 GPI
Membrane antigen of lung	LuM
Cytoplasmic antigen of lung	LuS
Cytoplasmic antigen of kidney	KiS
Membrane antigen of kidney	KiM
Membrane antigen of stomach	GaM
Membrane antigen of small intestine	ItM
Cytoplasmic antigen of liver	HeS
Antigen of liver mitochondria	HMMP
b-adrenoreceptors	bAR
Membrane antigen of myocardial cells	CoM
Membrane antigen of platelets	TrM
Anionic antigen of endothelium	ANCA
Thyroglobulin	TG
Receptor of TSH	TSH-R
Insulin	Ins
Insulin receptors	Ins-R
Membrane antigen of adrenal gland	Adr
Membranous antigen of prostate/spermatozoids	Spr
Protein S100	S100
Protein of intercurrent astrocytes' filaments	GFAP
Myelin basic protein	MBP

It is well known that, inflammatory diseases, acute infections, as well as septic conditions are accompanied by a generalised (polyclonal) activation of lymphocytes which leads to the transitory elevation of different type a-Abs. Patients with acute infection were excluded from this study in order to avoid bias that could lead to misinterpretation.

In all patients, we also determined serum IgE concentration by electrochemeluminescent method (Roche Elecsys). An IgE level  $\geq 90$  IU/mL in four to nine years old patients was considered significantly elevated.

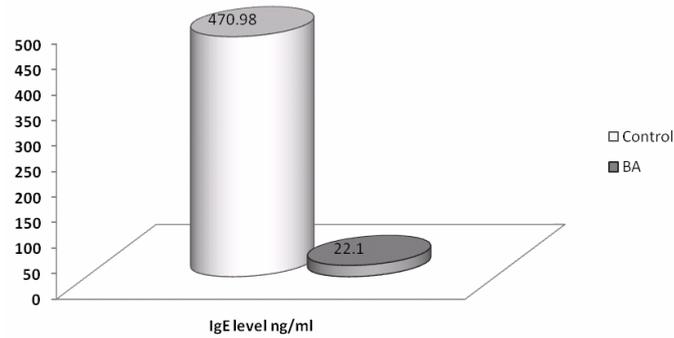
The statistical evaluation was performed using a software program (SPSS; Inc, Chicago, IL). A  $p$  value  $< 0.05$  was set to determine level of significant difference.

### 3 Results

The mean level of total IgE was 470.98 ng/ml (132.9–914.7 ng/ml) in patients and 22.1 ng/ml (3.93–55.67 ng/ml) in control group (Figure 1). Asthmatic patients presented a significantly higher immune reactivity in comparison to control subjects with a mean individual immune reactivity 42% and 9% respectively ( $p < 0.005$ ). The level of aAbs against LuM, LuS, CoM and dsDNA in the study group were significantly increased, in

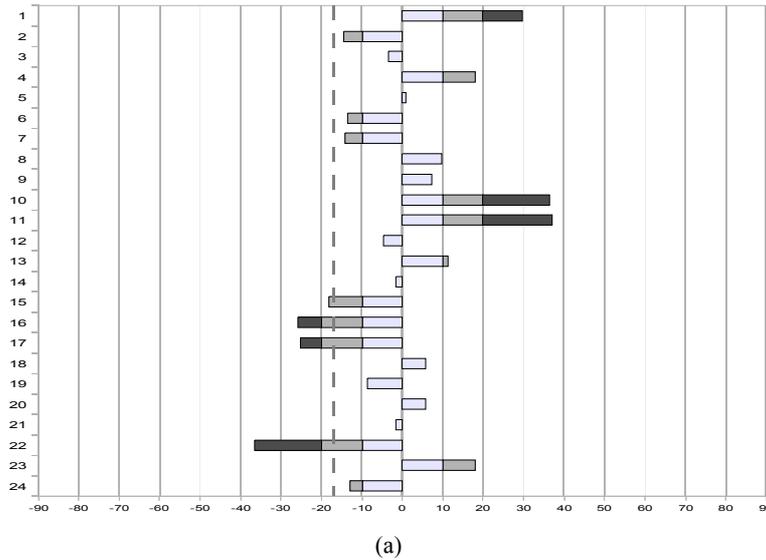
comparison to the control group (Figure 2). Anti-Adr a-Abs was higher in one patient which required frequent administration of oral corticosteroids for control of asthma (Figure 3). Anti-HMMP, Insulin and IR aAbs were inversely associated with asthma ( $p < 0.05$ ).

**Figure 1** IgE serum level



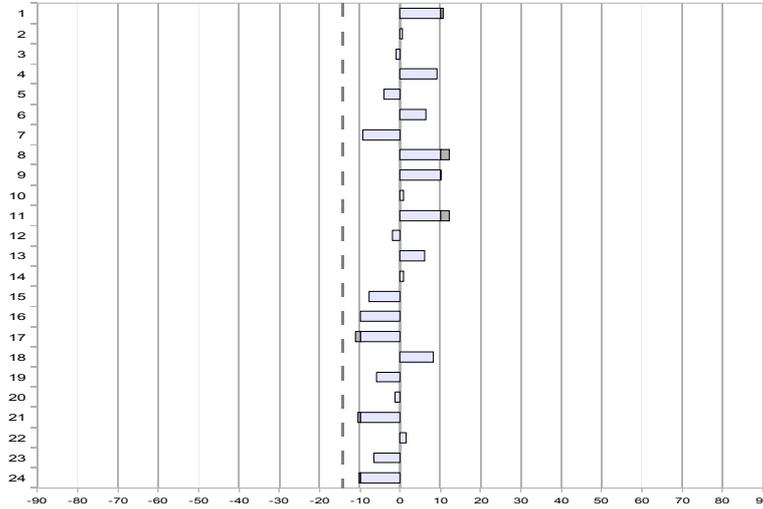
Note: BA-patients with bronchial asthma control – control group.

**Figure 2** ELI 24 viscero test, (a) patients with asthma (b) controls (see online version for colours)



Notes: 1 – dsDNA, 2 – beta2-glycoprotein I, 3 – Fc-fragment of immunoglobulins IgG, 4 – membrane antigen of myocardial cells, 5 – b-adrenoreceptors, 6 – membrane antigen of platelets, 7 – ANCA, 8 – membrane antigen of kidney, 9 – cytoplasmic antigen of kidney, 10 – membrane antigen of lung, 11 – cytoplasmic antigen of lung, 12 – membrane antigen of stomach, 13 – membrane antigen of small intestine, 14 – cytoplasmic antigen of liver, 15 – antigen of liver mitochondria, 16 – insulin, 17 – insulin receptors, 18 – thyroglobulin, 19 – receptor of TSH, 20 – membrane antigen of adrenal gland, 21 – membranous antigen of prostate/spermatozoids, 22 – protein S100, 23 – GFAP, 24 – myelin basic protein.

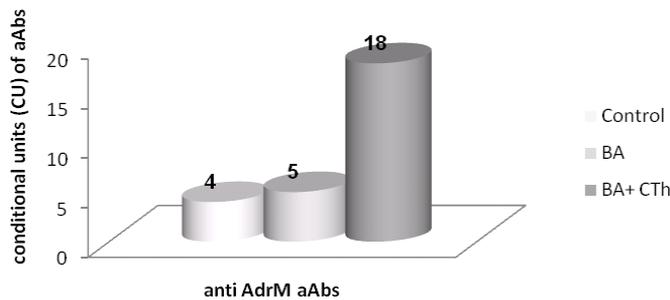
**Figure 2** ELI 24 viscero test, (a) patients with asthma (b) controls (continued) (see online version for colours)



(b)

Notes: 1 – dsDNA, 2 – beta2-glycoprotein I, 3 – Fc-fragment of immunoglobulins IgG, 4 – membrane antigen of myocardial cells, 5 – b-adrenoreceptors, 6 – membrane antigen of platelets, 7 – ANCA, 8 – membrane antigen of kidney, 9 – cytoplasmic antigen of kidney, 10 – membrane antigen of lung, 11 – cytoplasmic antigen of lung, 12 – membrane antigen of stomach, 13 – membrane antigen of small intestine, 14 – cytoplasmic antigen of liver, 15 – antigen of liver mitochondria, 16 – insulin, 17 – insulin receptors, 18 – thyroglobulin, 19 – receptor of TSH, 20 – membrane antigen of adrenal gland, 21 – membranous antigen of prostate/spermatozoids, 22 – protein S100, 23 – GFAP, 24 – myelin basic protein.

**Figure 3** Serum levels of anti AdrM auto-Abs



Note: BA-patients with bronchial asthma, BA+CTh patient with bronchial asthma under oral corticosteroids administrations, control – control group

#### 4 Discussion

The possible involvement of autoimmunity in the pathogenesis of asthma has been postulated in previous study (Szczeplik et al., 1995). In the present study we focused on the analysis of autoantibodies in serum samples by multiplex system in the search for new non-invasive biomarkers for asthma. The generation of a-Abs against self-antigens is a common phenomenon in humans. Elevated levels of a-Abs have been associated exclusively with the pathogenesis-diagnosis of autoimmune diseases. Nevertheless, it has been recognised that the level of some a-Abs can be increased and in other diseases, not within the spectrum of autoimmunity, like stroke, cancer, etc. (Poletaev, 2006; Belousov et al., 2008; Backes et al., 2011; Poletaev and Churilov, 2010). Furthermore, it has been demonstrated that natural a-Abs, IgG and IgM, against different self-antigens can be found in the serum of healthy individuals. It seems that the production and secretion of natural a-Abs are regulated directly in relation to quantity/availability of the respective antigens and in a feed-back mode (Poletaev and Osipenko, 2003; Poletaev and Boura, 2011).

In this study, we found that the mean individual immune reactivity in asthmatics was significantly higher than in the control subjects. The level of the pulmonotropic autoantibodies (LuM, LuS) were significantly higher in asthmatic patients in comparison to control subjects, 36% vs. 4% and 38 vs. 11% respectively ( $p < 0.001$ ). Skurydin et al. (2004) support the use of pulmonotropic autoantibodies as early markers of pulmonary parenchymatic lesions.

We also found that asthmatic patients had higher level of anti dsDNA a-Abs (Figure 2), something that could be considered as another non-specific indicator of a generalised immune activation (Poletaev and Arapov, 2006).

In this study anti insulin a-Abs and anti Insulin receptor a-Abs were inversely associated with asthma (–26% vs. –10% and –25% vs. –11%,  $p < 0.001$ ). This finding is in accordance to previous studies that presented also an inverse negative correlation of atopic manifestations' (such as bronchial reactivity, asthma and atopic dermatitis) and IDDM (Tzeng et al., 2007; Cakir et al., 2008). The EURODIAB (2000a, 2000b) – a multicentre, population-based case control study – found a decreased prevalence of atopic diseases, in particular asthma, in children with IDDM. Cardwell et al. (2003) performed a metaanalysis summarising the association between IDDM and atopic diseases (asthma, eczema, allergic rhinitis) in children. The analysis suggests that there is a small but significant reduction in the prevalence of asthma in children with IDDM. In contrary to the most accepted perception about the inverse association of atopy with autoimmunity some investigators have demonstrated that autoimmune Th1 diseases such as thyroiditis, IDDM, celiac, psoriasis and rheumatoid arthritis in both adults and children can coexist with Th2-mediated diseases, suggesting that the Th1/Th2 equities is oversimplified (Duran et al., 2008; Simpson et al., 2002). Furthermore, the increasing prevalence of atopic diseases worldwide is accompanied by a simultaneous rise in autoimmune Th1-mediated diseases such as IDDM.

We also found that serum level of anti S100 a-Abs were inversely associated with asthma. In previous studies it has been demonstrated that asthmatic patients had higher level of S 100 proteins (Hofmann et al., 2011; Yang et al., 2007; Yin et al., 2010). In accordance to the above, it is possible that a-Abs cannot be detected because they form complexes with antigens which are in excess in patients with asthma. The production and

concentration of serum a-Abs is regulated in a feed-back a mode according to the level of the relevant autoantigens (Cohen and Young, 1991).

As this is a first study that used multiplex system to measure autoantibodies, the number of subjects studied was kept small. This is a limitation of this study. These considerations warrant caution in interpreting the above results and suggest further evaluation with new studies to assess the role of autoantibodies in asthma.

In conclusion, changes in the production of a-Abs may play an important homeostatic role in various disorders as in asthma. The linkage between autoimmune response and the pathogenesis of asthma needs to be further explored.

It seems clear, that a better understanding of the dialectics of a-Abs, now often regarded as a theoretical matter, in the future may provide significant tools for the diagnosis and treatment of asthma.

### Acknowledgements

We would like to thank the Medical Research Centre (MRC), 'Immunculus' and their distributors in Greece 'ISYS Diagnostics' for providing with the ELI viscera 24 kit. We also like to thank Prof. Poletaev A.B. for his support interpreting of ELI 24 viscera test.

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