TURKISH SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

National Institute of Allergy and Infectious Diseases

School of Medicine

The Isil Barlan Symposium on Primary Immunodeficiency in Turkey

Marmara University School of Medicine
&
Marmara University Pendik Research and Training Hospital

April 19-20, 2018
Istanbul, Turkey

Program

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TURKISH SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

The Isil Barlan Symposium on Primary Immunodeficiency in Turkey

Conference Agenda

Marmara University Medical Faculty and
Marmara University Research and Training Hospital
Istanbul, Turkey

The Isil Barlan Symposium on Primary Immunodeficiency in Turkey

The scope of the symposium is to create an international platform to gather people from various disciplines in order to open new avenues in the Turkish genomics research with the partnership of national and international actors. The objectives of the meeting include:
-To create an environment that serves for building an indigenous research and clinical operation that conducts top quality, cutting edge investigations and scholarship in collaboration with national and international partners,
- Produce a network between institutions to train future scientists in the field.

Chairs: Michael Lenardo, Helen Su, Deniz Çağdaş Ayvaz, Ahmet Özen
Organizing Committee: Michael Lenardo, Ahmet Özen, Elif Karakoç-Aydıner, Safa Barış, Helen Matthews, İsmail Öğülür
Place: Marmara University Pendik Training and Research Hospital, Kaynarca/ Pendik / Istanbul, Turkey
Dates: April 19-20, 2018.
Hosting Institution: Marmara University Medical Faculty and Marmara University Pendik Training and Research Hospital.

Topics:
Basics of Genomics Research and its applications to immune disorders.
Solving any disorders: Phases in discovery of novel diseases.
Bench to bedside: Translation of basic-research-driven data into improving health
Basic and Clinical Immunological Research in Turkey

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WHO IS PROF. DR. IŞIL BARLAN?

Professor Dr. Işıl Berat Barlan (1958-2015) was born in Trabzon. She attended Robert College in Istanbul and received her medical degree from Istanbul University Cerrahpaşa Faculty of Medicine. She completed her residency in Pediatrics at Marmara University Faculty of Medicine, Istanbul.

She trained in Allergy and Immunology first with Dr. Müjdat Başaran at Marmara University and later with Dr. Raif Geha at the Boston Children's Hospital. She went on to become the Chair of Pediatrics and the Chief of the Division of Pediatric Allergy and Immunology at Marmara University. Professor Barlan was a visionary physician-scientist who made a profound impact on the science and health care delivery in Allergy and Immunology in Turkey and beyond. She was a highly productive investigator, with more than 120 peer-reviewed papers in international and national Journals. Critically, she engaged in building a research and academic infrastructure in Allergy and Immunology in Turkey, established enduring international collaborations and mentored a large number of investigators and practitioners in the field.

Professor Barlan has made numerous key contributions to the field of Allergy and Immunology at large. In a series of highly cited papers, she established the efficacy of pharmacotherapy with intranasal steroids in allergic rhinitis and rhinosinusitis, and that of sublingual immunotherapy for allergic upper airway disease and asthma. She also pioneered combination subcutaneous and sublingual immunotherapy for allergic asthma. Professor Barlan made critical contributions in the field of primary immunodeficiencies (PID). Professor Barlan actively engaged in national and international collaborations on the investigation, diagnosis and management of primary immunodeficiency diseases. She played a critical role in studies that led to the identification of DOCK8 deficiency as the underlying cause of the autosomal recessive form of the hyper IgE syndrome as well as other novel immunodeficiencies.

The ambitious scope of Professor Barlan's studies was enabled by her creation of productive research and training programs and community outreach efforts. She established the first Jeffrey Modell Center for Primary Immunodeficiency and the first International Patient Organization for Primary Immunodeficiencies chapter in Turkey, both placed at Marmara University. A critical achievement of Dr. Barlan was her training of a large number of academic physician-scientists in Allergy/Immunology, with many of her trainees assuming leadership positions in Turkey and abroad. Professor Barlan had a particular interest in women advancement in science, an issue that she strongly advocated for in both national and international forums. She trained several women physician-scientists, who went on to lead their own programs in Allergy and Immunology.

Professor Barlan was a member of the AAAAI, and an active participant and speaker at its annual meetings. She served on the executive committee of the European Academy of Allergy and Clinical Immunology (EAACI). She was the recipient of a number of awards, including the highly prestigious Sedat Simavi Prize in Turkey for her scientific contributions in the field of immunotherapy, as well as multiple prizes by the Turkish Society of Pediatrics, Marmara University Medical Faculty and Istanbul Provincial Directorate for her medical research and clinical excellence.

The American Academy of Allergy, Asthma & Immunology has honored outstanding individuals who have contributed to this field as leaders and teachers by the establishment of Annual Meeting lectureships. Professor Işıl Barlan is one of the 6 individuals, whom an annual lectureship is assigned, named as The Isil Berat Barlan Memorial Lectureship. We are honored to be commemorating our dearest mentor Prof. Barlan with the attendance of world- famous scientists and physicians who have dedicated their lives to improve care of children with PIDs.

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THE KEYNOTE SPEAKER: PROF. MICHAEL LENARDO, MD

We are thrilled to announce that the keynote speech of the symposium will be given by Prof. Michael Lenardo from National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA. Dr Lenardo has discovered the molecular, cellular, and immunological basis of a variety of monogenic forms of infectious, auto-immune, and malignant diseases. His research is focused on understanding the regulation of T lymphocytes in the healthy and diseased immune system especially using genomic approaches in individuals with congenital immune disorders. A notable example is the analysis of individuals with mutations in the MagT1 magnesium transporter which led to a novel role for Mg2+ as a second messenger for TCR signals that is crucial for activation of phospholipase C and downstream pathways. They showed that TCR mediated flux of Mg2+ as well as free basal Mg2+ are crucial for normal immune responses, especially anti-viral immunity. These studies have followed on earlier observations on how the TCR both promotes and inhibits T cell activation, showing that IL-2 could program T cells to undergo apoptosis in addition to its well known role in inducing proliferation. In studies of human genetic diseases, Dr. Lenardo defined the critical components of this pathway, including TNF receptor family molecules, providing the first demonstration that these immune regulatory receptors required a pre-association domain in order to bind ligand, and caspase-8. These studies shed light on basic aspects of cell fate control during immune responses. Also, these observations are leading to novel diagnostic and therapeutic approaches for immune diseases and lymphoid malignancies. As a Section Chief in the NIAID intramural research program for over 28 years, he has been mentoring over 110 trainees, with the majority of trainees moving on to academic positions.

Most significant contributions to science:

1 - Discovery of antigen-induced T cell apoptosis (reference #1). This discovery revealed a new mechanism of peripheral tolerance that could also be used as a type of reverse vaccination to decrease pathogenic T cells and autoimmune disease (reference #2).

2 - Discovery of the Autoimmune Lymphoproliferative Syndrome (ALPS, reference #3). This was the first Mendelian genetic disorder of apoptosis and autoimmunity. Multiple genes were found to result in this syndrome and thousands of cases have been identified around the world. As the product of an ongoing clinical protocol at the NIH clinical Center, we have just published the 20 year follow-up in which improved diagnosis, treatment, and clinical management have been documented for ALPS patients.

3 - Discovery of the pre-ligand assembly domain in the tumor necrosis factor receptor superfamily (reference #6). The researchers show that a critical structural feature of receptors such as Fas that are in the tumor necrosis factor receptor superfamily is the existence of a pre-ligand assembly domain which is important for the oligomerization of the receptor and the ability of like and to bind and signal. This domain is a potential target for therapeutics in this family of receptors (reference #9).

4 - Discovery of magnesium as an immune signaling ion (reference #14). As described more completely above, this investigation revealed the molecular basis of a primary immunodeficiency termed XMEN disease and described a new step in T cell receptor signaling. Furthermore, this has led to the use of magnesium as an oral therapy for this immunodeficiency (reference #16).

Selected Peer-reviewed Publications (Selected from 234 peer-reviewed publications)

1 - Lenardo, M.J.: Interleukin-2 programs mature alpha beta T cells for apoptosis. Nature 353: 858-861, 1991.

2 - Critchfield, J.M., Racke, M.K., Zuniga-Pflucker, J.C., Cannella, B., Raine, C.S., Goverman, J., and Lenardo, M.J.: T cell deletion in high antigen dose therapy of autoimmune encephalomyelitis. Science 263: 1139-1143, 1994.

3 - Fisher, G.H., Rosenberg, F.J., Straus, S.E., Dale, J.K., Middelton, L.A., Lin, A.Y., Strober, W., Lenardo, M.J., and Puck, J.: Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome (ALPS). Cell 81: 935-946, 1995.

4 - Combadiere, B., Reis e Sousa, C., Trageser, C., Kim, C.R., and Lenardo, M.J.: Differential TCR signaling regulates apoptosis and immunopathology during antigen responses in vivo. Immunity, 9: 305-313, 1998.

5 - Wang, J., Zheng, L., Lobito, A., Chan, F.K., Dale, J., Sneller, M., Yao, Y., Puck, J.M., Straus, S.E., and Lenardo, M.J.: Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell, 98: 47-58, 1999.

6 - Siegel, R. M., Frederiksen, J. K., Zacharias, D. A., Chan, F. K., Johnson, M., Lynch, D.,Tsien, R. Y., and Lenardo, M. J.: Fas preassociation required for apoptosis signaling and dominant inhibition by pathogenic mutations. Science, 288: 2354-2357, 2000.

7 - Chun, H. J., Zheng, L., Ahmad, M., Wang, J., Speirs, C. K., Siegel, R. M., Dale, J. K., Puck, J., Davis, J., Hall, C. G., Sgota-Smith, S., Atkinson, T. P., Straus, S. E., and Lenardo, M. J.: Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. Nature 419: 395-399, 2002.

8 - Su,H., Bidere, N., Zheng, L., Cubre, A., Sakai, K., Dale, J., Salmena, L., Hakem, R., Straus, S., and Lenardo, M.: Requirement for caspase-8 in NF-κB activation by antigen receptor. Science 307: 1465-1468, 2005.

9 - Chun, H. J., Ali, Z. A., Kojima, Y., Kundu, R. K., Sheikh, A. Y., Agrawal, R., Zheng, L., Keeper, N. J., Pearl, N. E., Patterson, A. J., Anderson, J. P., Tsao, P. S., Lenardo, M. J., Ashley, E. A., and Quertermous, T.: Apelin signaling antagonizes Ang II effects in mouse models of atherosclerosis. J. Clin. Invest. 118: 3343-3354, 2008.

10 - Bidère N, Ngo VN, Lee J, Collins C, Zheng L, Wan F, Davis RE, Lenz G, Anderson DE, Arnoult D, Vazquez A, Sakai K, Zhang J, Meng Z, Veenstra TD, Staudt LM, Lenardo MJ: Casein kinase 1alpha governs antigen-receptor-induced NF-kappaB activation and human lymphoma cell survival. Nature. 458(7234):92-6, 2009.

11 - Snow, A.L., Xiao, W., Stinson, J.R., Lu, W., Chaigne-Delalande, B., Zheng, L., Pittaluga, S., Matthews, H.F., Schmitz, R., Jhavar, S., Kuchen, S., Kardava, L., Wang, W., Lamborn, I.T., Jing, H., Raffeld, M., Moir, S., Fleisher, T.A., Staudt, L.M., Su, H.C., Lenardo, M.J.: Congenital B cell lymphocytosis explained by novel germline CARD11 mutations. J Exp Med. 2012 Nov 19;209(12):2247-61.

12 - Chaigne-Delalande, B., Li, F.Y., O'Connor, G. M., Lukacs, M.J., Jiang, P., Zheng, L., Shatzer, A., Biancalana, M., Pittaluga, S., Matthews, H.F., Jancel, T.J., Bleesing, J.J., Marsh, Rebecca A., Kuipjers, T.W., Nichols, K.E., Lucas, C.L., Nagpal, S., Mehmet, H., Su, H.C., Cohen, J.I., Uzel, G., Lenardo, M.J.: Mg^{2}+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D, Science 341:186-91, 2013.

13 - Lo, B., Zhang, K., Lu, W., Zheng, L., Zhang Q., Kanellopoulou, C., Zhang, Y., Liu, Z., Fritz, J.M., Marsh, R., Husami, A., Kissell, D., Nortman, S., Chaturvedi, V., Haines, H., Young, L. R., Mo, J., Filipovich, A.H., Bleesing, J.J., Mustillo, P., Stephens, M., Rueda, C.M., Chougnet, C.A., Hoebe, K., McElwee, J., Hughes, J.D., Karakoc-Aydiner, E., Matthews, H.F., Price, S., Su, H.C., Rao, V.K., Lenardo, M.J., Jordan, M.B.: AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 349:436-40, 2015.

14 - Majri SS, Fritz JM, Villarino AV, Zheng L, Kanellopoulou C, Chaigne-Delalande B, Grönholm J, Niemela JE, Afzali B, Biancalana M, Pittaluga S, Sun A, Cohen JL, Holland SM, O'Shea JJ, Uzel G, Lenardo MJ., STAT5B: A Differential Regulator of the Life and Death of CD4+ Effector Memory T Cells. J Immunol. 2018 Jan 1;200(1):110-118. doi: 10.4049/jimmunol.1701133.

15 - Rao VK, Webster S, Dalm VASH, Šedivá A, van Hagen PM, Holland S, Rosenzweig SD, Christ AD, Sloth B, Cabanski M, Joshi AD, de Buck S, Doucet J, Guerini D, Kalis C, Pylvaenaeinen I, Soldermann N, Kashyap A, Uzel G, Lenardo MJ, Patel DD, Lucas CL, Burkhart C., Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib. Blood. 2017 Nov 23;130(21):2307-2316. doi: 10.1182/blood-2017-08-801191.

16 - Ozen A, Comrie WA, Ardy RC, Domínguez Conde C, Dalgic B, Beser ÖF, Morawski AR, Karakoc-Aydiner E, Tutar E, Baris S, Ozcay F, Serwas NK, Zhang Y, Matthews HF, Pittaluga S, Folio LR, Unlusoy Aksu A, McElwee JJ, Krolo A, Kiykim A, Baris Z, Gulsan M, Ogulur I, Snapper SB, Houwen RHJ, Leavis HL, Ertem D, Kain R, Sari S, Erkan T, Su HC, Boztug K, Lenardo MJ., CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis. N Engl J Med. 2017 Jul 6;377(1):52-61. doi: 10.1056/NEJMoa1615887.

17 - Afzali B, Grönholm J, Vandrovcova J, O'Brien C, Sun HW, Vanderleyden I, Davis FP, Khoder A, Zhang Y, Hegazy AN, Villarino AV, Palmer IW, Kaufman J, Watts NR, Kazemian M, Kamenyeva O, Keith J, Sayed A, Kasperaviciute D, Mueller M, Hughes JD, Fuss IJ, Sadiyah MF, Montgomery-Recht K, McElwee J, Restifo NP, Strober W, Linterman MA, Wingfield PT, Uhlig HH, Roychoudhuri R, Aitman TJ, Kelleher P, Lenardo MJ, O'Shea JJ, Cooper N, Laurence ADJ., BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. Nat Immunol. 2017 Jul;18(7):813-823. doi: 10.1038/ni.3753.

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12:30 - 13:00 **Opening Remarks and Welcome**

The Legacy of Dr. Isil Barlan
***Ahmet Ozen**, Marmara University*

13:00 - 13:45 **Keynote Address**

Chairs: ***Yıldız Camcıoğlu, Feyzullah Çetinkaya***

NIH/Turkish Clinical Genomics Program, Milestones and Future Discoveries
***Michael J. Lenardo,** MD, NIH*

13:45 - 14:15

TÜSEB: A New Funding Agency for Health Research & Technology in Turkey
Fahrettin Keleştemur

14:15 - 15:15

Chairs: ***Şebnem Kılıç, Günnur Deniz***

Germline Genomics for Disorders of the Immune System
***Magdalena Walkiewicz,** NIH*

Human Genomics in Primary Immunodeficiency Diseases
***Yu Zhang,** PhD, NIH*

Investigations into the genomes of patients with suspected monogenic IBD or IBD-like disease.
***Bernice Lo,** Sidra University*

15:15 - 15:30 **Coffee Break**

15:30 - 15:50

International Cooperation Opportunities in Life Sciences
***Jale Şahin,** PhD The Scientific and Technological Research Council of Turkey, Directorate for International Cooperation, Bilateral and Multilateral Relations Department*

15:50 -16:50

Chairs: ***Michael Lenardo, Reha Cengizlier***

CD55 deficiency, early-onset protein-losing enteropathy, and thrombosis
Drew Comrie*, NIH*

From bench to the bed side: Therapeutic modulation of complement in CHAPLE disease
Ahmet Ozen, *Marmara University*

Plasma extracellular vesicles along with TLR and inflammasome signaling impact severity of CHAPLE syndrome
İhsan Gürsel, *Bilkent University*

16:50 - 17:00 **Coffee Break**

17:00 - 18:00

Chairs: ***İlhan Tezcan, Helen Su***

Combined Immunodeficiency: The Middle East Experience
Waleed Al-Herz, *MD, Kuwait University*

Hematopoietic Stem Cell Transplantation in Combined Immune Deficiencies: Characteristics and Outcome
Aydan İkincioğulları, *MD, Ankara University*

Accurate molecular diagnosis translates into better treatment in PIDs, Marmara experience
Elif Karakoc Aydıner, *MD, Marmara University*

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08:00 - 09:20

Chairs: ***Mehmet Kılıç, Michael Lenardo***

Bioinformatics Approach to Disorders of the Immune System
Celine Hong, *NIH*

Irhom2 Deficiency Associated With Hyper-Ige, Recurrent Infections, and Cavitary Lung Lesions
Hayley Raquer, *BS, NIH,* ***Jill Fritz,*** *PhD, NIH*

Structure and Function of Btb Domain Transcription Factors
Batu Erman, *PhD, Sabanci University*

Characterization of Genetic Defects in GHRHR-GH-GHR axis causing Growth Hormone Deficiency
Ahmet Arman, *PhD, Marmara University*

09:20 - 10:20

Chairs: ***Helen Su, Mehmet Kılıç***

Immunodeficiency and Immune Dysregulation in DOCK8 Deficiency: Clinical and Mechanistic Studies in a defined Patient Cohort
Sevgi Keleş, *MD, Necmettin Erbakan University*

Group 3 Innate Lymphoid Cells in DOCK8 Deficiency: From Mice to Human
Ahmet Eken, *PhD, Erciyes University*

Genetically Modified Antigen-specific Natural Killer Cells
Tolga Sütlü, *PhD*

10:20 - 10:40 **Coffee Break**

10:40 - 11:40

Chairs: ***Figen Doğu, Güher Saruhan Direskeneli***

Viral Susceptibility and Immune Deficiency
Helen Su, *MD, PhD, NIH*

Stat1 Gain of Function Mutations: Marmara University Experience
Safa Barış, *MD, Marmara University*

The Role Of Type I Interferons And Neutrophils In Primary Immune Deficiencies
Mayda Gürsel, *PhD, Middle East Technical University*

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TURKISH SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

11:45 - 12:30

Research & Development Activities In Marmara Research Center (MRC) Genetic Engineering & Biotechnology Institute
Şaban Tekin, *PhD, TUBITAK Marmara Research Center, GEBI*

Turkish Genome Project & Biotechnology Projects of TÜSEB
Ali Osman Kılıç, *MD, Health Institutes of Turkey (TÜSEB)*

12:30 -12:40

Consenting Patients and Perfecting paperwork
Helen Matthews, RN, BSN, NIH

12:40 - 14:00 **Lunch**

14:00 - 15:15

Chairs: ***Gülderen Yanıkkaya Demirel, Öner Özdemir***

Molecular diagnostics of PID in Istanbul; from NGS to KREC/TREC anaylsis
Yuk Yin (Peter) *Ng, PhD, Istanbul Bilgi University*

NIAID Genomic Research Integration System (GRIS)
Andrew Oler, *PhD, NIH*

Mapping Intracellular Immune Responses Against Lentiviral Vectors in NK Cells Using Genome-Scale CRISPR- Knockout Libraries
Aydan Saraç, *PhD, MAM GMBE*

Mesenchymal stem cells and cellular therapy
Tunç Akkoç, *PhD, Marmara University*

15:15 - 16:15

Chairs: ***Uğur Muşabak, Figen Doğu***

Ege University experience in the diagnosis of PIDS: comparison of pre and post- NGS era
Güzide Aksu, *MD, Ege University*

Investigation of Genetic Defects in Severe Combined Immunodeficiency Patients from Turkey by Targeted Sequencing
Baran Erman, *PhD, Koç University*

Communicating Genomic Research Results To Patients And Families: Les Sons From The Us Experience
Leila Jamal, *ScM, PhD, CGC*

16:15 - 16:30 **Coffee Break**

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16:30 - 17:30

Chairs: ***Dilara Kocacık Uygun, Güzide Aksu***

DCLRE1C (ARTEMIS) mutations causing different phenotypes of immunodeficiency
Şükrü Nail Güner, *MD, Necmettin Erbakan University*

ADA deficiency: Management and outcome in Turkey
Deniz Çağdaş Ayvaz, *MD, Hacettepe University*

HSCT Experience in NIK Defect
Sevgi Köstel-Bal, *MD, Ankara University*

17:30 - 18:00 ***Closing Remarks***
Deniz Çağdaş Ayvaz, *MD, Hacettepe University*

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Bilimsel Sekreterya

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