

## Article

# A Pioneering Clinician Scientist and a NonGovernmental Health Organization: Gunduz Gedikoglu and Our Children Leukemia Foundation - OCLF of Turkey, in Verge of Celebrating Its 30th Anniversary in 2010

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In year 2010, Turkey will celebrate its 30th anniversary of opening the first pediatric marrow transplantation unit at the “BCLV – Bizim Losemili Cocuklar Vakfi” – OCLF – Our Children Leukemia Foundation” under the patronage of the pediatric hematology professor, Dr. Gunduz Gedikoglu. The OCLF founded in 1980 has applied 1139 chemotherapies and 199 marrow / blood stem cell-transplantations until 2003 for children’s malignancies and marrow diseases. Thereafter, the foundation has focused on collecting funds for opening a dedicated hospital, which would also serve as a medical faculty for the foundation’s Halic University. Since its establishment, OCLF provided both as a health care facility in treatment of pediatric malignancies and marrow diseases and also as an education and research institution for many physicians, which had later served to establish and teach pediatric stem cell transplantation in diverse hospitals and cities throughout Turkey. Since the first brief report of proving the existence of heterochromatic regions on the human chromosomes in 1966 at the journal “Lancet”, the OCLF founder Dr. Gedikoglu published many original articles enriching Turkey’s contribution to the medical sciences. This article will briefly encompass the works of Dr. Gunduz Gedikoglu and his pioneering institution OCLF as a role model for establishing specialized non-governmental health care organizations in developing countries.

## INTRODUCTION

### Educational background of Dr. Gunduz Gedikoglu

Dr. Gedikoglu had his medical education in the Istanbul Faculty of medicine at Istanbul University. He did a residency of pediatrics at the St Paul’s Hospital and subspecialty on hematology and oncology in the Baylor University Hospital and in Wadley Research Center at Dallas, Texas. He is currently a professor of pediatric hematology and oncology, founder and president of Our Children Leukemia Foundation and president (Board of Trustee) of the Halic (Golden Horn) University.

### Studies in genetics

He was accepted into the pediatric pathology and human health division in Penarth at the Cardiff University in Wa-

les to perform research in genetics with the grant of the British council. He transferred his experience in Cardiff to perform research in Istanbul Faculty of Medicine.

### First demonstration of chromosomal heterochromasy in humans

Until 1966, existence of the heterochromatic regions in the chromosomes was well known in plants and animals, yet there was no information regarding to their presence in human chromosomes. First in 1966, Dr. Gedikoglu observed such regions in chromosomes of a 22 years old Caucasian male bearing Wilson disease independent of his disease and published these observations in Lancet Gedikoglu, 1966). (Figure 1)



Figure 1. Professor Gunduz Gedikoglu, MD

### Report of deuteranopia accompanying the Kartagener syndrome

In 1933, Kartagener described a new syndrome comprised of a symptoms trio of dextrocardia, bronchiectasis and sinusitis and therefore, this syndrome is named as Kartagener's triad or syndrome. New research confirmed that this disease phenotype may associate with multiple chromosomal regions. Most frequently, the dynein axonemal intermediate chain protein locus (9p21-p13) exerts mutations; yet 5p and 19q anomalies are also linked with the similar disease phenotypes. In 1967, Dr. Gedikoglu described new findings in a sibling born from nephew-parents with Kartagener symptoms. While documenting the existence of fibrocystic lung disease in both patients and the eosinophilic infiltration in the sinonasal epithelium as a novel finding, he also described isolated green color blindness (deuteranopia) in one of the siblings and published these novel properties in *Lancet* (Baris et al., 1967). Isolated color blindness could be the first sign of the degenerative eye diseases with progressive rod-cone injury (Mantjarvi, 1990) and one gene causing such a disease, the gene of the retinitis pigmentosa is localized also in 19q similar to the gene of Kartagener's. Recently, it is found that the motile flagellum and the immotile sensory cilia share some of their structural proteins (Whitehead et al., 1999) and in 2001 Kartagener's syndrome-accompanying retinitis pigmentosa is described (Ohga et al., 2001).

### Chromosomal abnormalities and large Y chromosomes in thalassemia major

Dr. Gedikoglu observed that abnormally large Y chromosomes are found with greater frequency in the caryotypes

of thalassemia major-bearing patients (Gedikoglu, 1969; Gedikoglu, 1973; Gedikoglu, 1972). In one thalassemia family reported by Dr. Gedikoglu, there were 2 thalassemia major cases and 1 thalassemia minor case and only the disease phenotype-carrying patients had large Y anomaly (Gedikoglu, 1972). There are no genes related to the hemoglobin metabolism and there exist many repeating nonsense sequences on that chromosome; yet novel findings revealing that the thalassemia-accompanying Y chromosome abnormalities are related with the African origin and migration pattern of the disease (Nagel, 2004) could explain this interesting association.

### Various clinical cytogenetic observations as firsts in Turkey

Klinefelter syndrome with the rare XXXXY (2n-49) chromosome-constitution as the ninth reported case at the world (Gedikoglu, 1967), Mongolism-Turner combination (Gedikoglu et al., 1968), minor deletions in the long arms of the chromosomes in Mongolism (Gedikoglu and Gurson, 1967) were detected first in Turkey with caryotype research of Dr. Gedikoglu. For the Turkish patient population, he also showed the dominance of the blood group type 0 in duodenal ulcer (Gedikoglu and Sezer, 1973), normal chromosomal patterning in the Blackfan-Diamond anemia (Gedikoglu, 1973) and the extensive chromatid breakage and achromatic regions in Fanconi anemia (Tanman et al., 1973).

### Usage of diazepam in neonatal tetanus

First in 1964, Hendrickse proposed usage of diazepam in the treatment of neonatal tetanus, yet until the middle of 1970's, the mortality ratio of neonatal tetanus remained as high as around 90%. Dr. Gedikoglu performed a research on that disease, in which he selected 2 newborn and 2 six years old patients as the investigation group and 9 newborns and 1 six years old patients as the control group. He treated intensively both the investigation and the control group patients with heterologous tetanus antitoxin + chlorpromazine + phenobarbitone + meprobamat; and added diazepam treatment (9 mg/kg) only to the therapy of the investigation group, which was at the early experimental stage for this indication on that years. Generalized spasticity, trismus, risus sardonicus, opisthotonus, sucking and swelling difficulties were at their latest stages in both groups before the treatment. The children, who were only treated with the standart treatment did not survive, yet all the investigation group children with diazepam augmentation returned to their health in 6 to 30 days (Gedikoglu et al., 1973). Dr. Gedikoglu underlined that diazepam exerted a profound inhibition on the general rigidity, spasm and convulsions, which was accompanied with a sedation and with no respiratory depression. Thus, according to his controlled study design, he proposed that diazepam acted via on motor neuron discharge and

published these results in Lancet (Gedikoglu 1973).

### **Roentgenological studies on pediatric hematologic diseases with Friedrich Reimann**

Dr. Gedikoglu joined the research of Friedrich Reimann - a world known pediatrician of Jewish descent who fled the Nazi regime and came to Turkey- on roentgen studies of pediatric diseases. Together they described the metopismus in iron deficiency anemia (Gedikoglu and Gurson, 1967) and firstly described “panzer skull” sign due to enlargement of cranial bones in compensatory hematopoiesis of thalassemia major (Reimann et al., 1979,1981).

### **Molecular and immune physiopathologic studies**

It was known that autoimmune hemolytic anemia can arise during the course of bacterial (typhus) and viral diseases (influenza-A, coxsackievirus A, measles, varicella); yet it is arousal due to vaccinations or due to different etiologies in the same patient was not well described until 1967. On that year, Dr. Gedikoglu described a 6-years old case of autoimmune hemolytic anemia (AHA) with spontaneous onset and well remission with prednisolone. In this case, the hemolytic anemia was recurred after diphtheria-tetanus-typhus vaccination and again underwent remission with prednisolone. This case demonstrated in Lancet (Gedikoglu and Cantez, 1967) was the first strong indication that vaccinations could trigger high anti-erythroid responses in AHA-prone patients, which could make Coombs test as high as 4+. Dr. Gedikoglu described the first Turkish cases of the Waardenburg syndrome (Gedikoglu et al., 1970) and the congenital leukemia (Koc et al., 1983) and established the first immune electrophoretic investigations of pediatric viral hepatitis in Turkey (Gedikoglu et al., 1970). In 1977, when the studies on vitamin E and oxidant stress theory are at the emerging stage, he described iron dependent pancreatic beta-cell damage (Koc et al., 1977) and the protective function of vitamin E against this injury (Yesilbek et al., 1977) in Turkish thalassemic patients. He published the first international report about type IV glycogenosis in Turkey (Gedikoglu et al., 1982) and performed research on ferritin-iron metabolism relations in ferropenic children and in workers of iron industry (Gedikoglu et al., 1983). He first indicated the antimicrobial function of ovalbumin (=conalbumin) in gastroenteritis (30). He first applied intravenous acyclovir prophylaxis against varicella infections in pediatric oncology patients (31), and monitored pediatric ITP cases in Turkey (32).

### **Editorial work on the translation of the “Nelson pediatrics” and preparation of the ‘Clinical Sciences’ series for the Turkish physicians**

Dr. Gedikoglu was the first to achieve the Turkish transla-

tion editions of Nelson pediatrics as 3 volumes in 1978; while working as the translation editor for all volumes, he was personally responsible to translate the sections of the area of pediatrics, hematology and convulsive diseases (Translational Editorship of Nelson Pediatrics, I., II. and III Volumes, 1978). He was one of the editors of ‘clinical sciences’ [In Turkish] series of 2940 pages published by Cerrahpasa Faculty of Medicine in 1992 and wrote the sections of pediatric growth and endocrinology, newborn diseases and pediatric hematology (Kazancigil et al., 1992).

### **Review articles and contributions to the international medical books**

Dr. Gedikoglu’s team was the first to analyze highest number of pediatric Henoch Schönlein cases (Sidal et al., 1981). The team’s original research was published in the ‘Progress in Antimicrobial and Anticancer Chemotherapy’ edited by Kuemmerle and printed in West Germany, in 1988. In this book they published anti-anti D immunoglobulin usage in the Rh incompatibility (Bilgen et al., 1988), empiric antibiotherapy for febrile neutropenia, findings of extramedullary leukemia in 214 ALL cases (Devecioglu et al., 1988), the relations of prognoses with FAB classification (Gedikoglu et al., 1988) and the chromosomal findings in leukemia (Alpay et al., 1988).

### **Establishment of the hematology – Oncology section under the pediatrics department and the achievement of the ‘tumor council’ and the ‘days of pediatrics’ as new concepts in Turkish medicine**

Dr. Gedikoglu pioneered the development of the hematology and oncology section under the pediatrics department in the Istanbul faculty of medicine and also worked as the director of the oncology institute at the Istanbul University, at this period he first achieved the establishment of the tumor council and the days of pediatrics. First in 1971, he subdivided the malignant and non-malignant blood diseases and pediatric genetic diseases into different sections at the pediatry clinics of the Istanbul faculty of medicine.

### **Establishment of the ‘Our Children Leukemia Foundation - OCLF’**

Due to the essential need of a special place for leukemia treatment, the donations of the charitable and the patients relatives were organized under the patronage of the Prime Minister Turgut Ozal in 1980. The roof of the pediatrics building was reconstructed and allocated to the ‘Our Children Leukemia Foundation’. The health establishment of “Our Children Leukemia Foundation” serviced for all pediatric diseases with special emphasis to the hematological diseases, leukemias and solid tumors of the pediatric age and it was founded in 1980. Hematolo-

gical Unit, which was founded at 1986 with 25 bed capacities, continued to give medical service at its 1000 square-meter settlement until 1989. Our Children Leukemia Foundation expanded its health service via opening the bone marrow transplantation unit at 1989 with one-patient and one-donor bed and increased its capacity to eight-patient and one-donor bed in 1994.

### **Clinical achievements of the OCLF**

Our Children Leukemia Foundation gave high quality medical service at its 2000 square-meter settlement on a 24 h/365 day and non-stop (shift) basis until 2003. OCLF continues to serve the stem cell-transplanted patients via performing their routine examinations until today. In this period, 1139 chemotherapeutical treatments and 199 marrow stem cell transplantations were achieved, including the first pediatric marrow transplantation of Turkey in 1986. The general success rate of marrow transplantations was 70%, which was a good ratio in comparison to the world standart. Between October 1988 and April 2002, OCLF was the first institution with 188 cases of marrow transplantation among the total 479 transplants in Turkey and the success rate in ALL L1G1 has reached to 89%, which is between 80 and 90% in the developed countries. Moreover, considering the cost-effectivity, both the chemotherapy and transplantation costs were lower OCLF in comparison to the developed western countries.

### **Awards given to the OCLF**

Our Children Leukemia Foundation is awarded by the directorate of the charitable funds of the Turkish government as the 'best-working foundation of the health sector' in 1998. Our Children Leukemia Foundation is awarded as 'The Foundation with the best public-communication' by the communication faculty of the Istanbul University in 1998. Our Children Leukemia Foundation has attended to the EBMT 2002, which was held in Montreux at March of 2002. Among the attended 939 abstracts, the abstract prepared by the psychologists and doctors of the 'Our Children Leukemia Foundation' has won the first prize (Peykerli et al., 2002).

### **International professors and institutions visiting OCLF and EBMT congress of 2000 under the OCLF patronage**

Prof. Donald Edward Thomas, Nobel laureate of physiology and medicine in 1972, came to OCLF for a scientific visit with the invitation of Dr. Gedikoglu and the European Bone Marrow Transplantation Society's annual congress of 2000 was established in Istanbul under the patronage of OCLF. Many other prestigious members of the international hematology community, including the inventors of the desferrioxamin (Prof. Pippard) and the gamma-globulin (Prof. Hitzick) were also among the visitors of the

OCLF.

### **Clinical research achievements of OCLF**

OCLF and Dr. Gedikoglu published experiences of Aclacinomycin-A efficacy in acute leukemia (Gedikoglu et al., 1989) the prognostic factors of acute lmyphoblastic leukemia (Gedikoglu et al., 1989), intraspinal hemorrhage in Factor XIII- deficiency (Ugur et al., 1991), efficacy of meslocillin-amikacin combination of the febrile neutropenia (Zulfikar et al., 1991) and also revealed treatment experiences in Ewing sarcoma (Zulfikar et al., 1992) and rhabdomyosarcoma (Karakas et al., 2000). Growth and puberty properties in thalassemia major-bearing children were investigated (Saka, 1995) and the first marrow transplantation results for Turkish thalassemia patients were reported (Gedikoglu et al., 2001.). The likely relations between the Ara-C and staphylococcus superantigens (Savasan et al., 1998), gingival histopathology of the leukemia (Genc et al., 1989) and the dental health care to reduce the septicemia risk in ALL (Sepet et al., 1998) were again fruits of the basic and clinical research established in OCLF. First *in vitro* chemosensitivity tests in pediatric leukemia from Turkey (Karakas et al., 1999) and reports on FLAG-IDA regime in relapsed or worse prognosis leukemia (Yalman et al., 2000) were also succeeded with the experiences of the OCLF. OCLF also provided data for international work groups to identify new gene loci related to Griscelli disease (Pastural et al., 2000). OCLF and Dr. Gedikoglu also monitored and reported rare accompanying phenomena to known diseases such as hemophagocytosis during the course of Griscelli disease in international congresses (Yalman et al., 1998). OCLF group also treated far advanced childhood malignancies with great success. A 7 years old boy with cardiac involvement of an aggressive non-Hodgkin lymphoma and cerebral stroke was successfully treated via 3 cycles of BFM-90 B-cell NHL protocol, triple intrathecal therapy (Mtx, Ara-C, HydroCortisone) and subsequent autologous stem cell transplantation with BEAM preparation (Anak et al., 1998). Such cases pioneered and forced the treatment of pediatric cancers with dismal prognosis in Turkey.

**OCLF is the first institution gaining EBMT accreditation for allogeneic marrow transplantation in Turkey and its successes were awarded with the distinguished service award of the Turkish state.**

### **Microbiologic investigations performed in OCLF lead to significant scientific data**

OCLF provided detailed microbiologic analysis and screening for all its patients and careful examination and monitoring of patient specimens revealed many firsts for Turkey. Cyclospora infection, which was reported to cause human disease first in 1979 in USA, was first reported in

Turkey in a patient of OCLF (Buget et al., 2000). As a clinical microbiological research, fungal etiological agents were investigated retrospectively in stool samples of 80 patients followed in OCLF to compare fungal flora of pediatric healthy volunteers and immunosuppressed patients. As a significant finding, non-*albicans* *Candida* species were found to be significantly higher and *C. glabrata* more prevalent in patients than in controls, which could guide for anti-fungal treatment selections in immune compromised children (Agirbasli et al., 2005). The first human case of *Trichosporon japonicum* is also proven in one marrow transplant patient in the OCLF and published very recently (Agirbasli et al., 2008).

### Hemoglobinopathy/Anemia screening center

Dr. Gedikoglu also founded a thalassemia/hemoglobinopathy screening center in the place of OCLF with the extension of the scope to fight another frequent hematologic disease in Turkey causing profound morbidity and mortality. For the analysis of the routine erythrocyte indices, a conventional cell counter (Counter Gen-S) was applied, whereas levels of HbA2 and HbF were screened via fully automated cation exchange HPLC system. By performing mass analyses in the Marmara district of Turkey, the prevalence of beta-thalassemia trait was found to be as high as 9.8% (Gedikoglu et al., 1999) in comparison to the previously reports of 2% based on much fewer patient numbers. In this center, OCLF team also performed dermatoglyphics-based genetic characterization of other frequent anemias such as the Fanconi disease and results of these studies were published in an international congress (Polat et al., 1999).

### OCLF contribution to the education

Doctors working in the OCLF have achieved residency training in Bakirkoy Maternity Hospital, Okmeydani State Hospital, Goztepe Education Hospital, Taksim first aid hospital, Dicle Medical Faculty, Zeynep Kamil Hospital and Kartal State Hospital. During its clinically active years, OCLF has also given grants to 120 medical students throughout their education. Laboratories of biochemistry, microbiology, bone marrow freezing and transfer, apheresis and thrombopheresis, blood and blood products-irradiation, color doppler ultrasonography and of X-ray were serving at the same complex for OCLF patients. Besides, child psychology services and continuing primary school education were provided in the OCLF.

### Hospital project of the OCLF

With the experience, know-how and experienced staff serving more than 25 years, OCLF defined its biggest project as the realization of a hospital construction, which would serve for all pediatric diseases and provide enough



**Figure 2.** Main Entrance of the Hospital for the OCLF and the Medical Faculty Building of Halic University

space for all patients (Figure 2).

### Recent scientific projects of the OCLF

OCLF always provided support for the young investigators in the clinical and molecular medicine area. DNA polymorphism-based chimerism analysis in marrow transplantation (Ozbek et al., 1997), oxidative DNA damage (Senturker et al., 1997)-, wt1 (Ozgen et al., 2000), AML1/ETO (Arper et al., 2000), and TEL AML- 1 (Ozbek et al., 2003) oncogene expression analyses in leukemia were published as the products of the Turkish medicine via the support of the OCLF. OCLF experiences provided an important clinical publication in 2005, which was comparing autologous and allogeneic transplantation results in all at the first complete remission (Anak et al., 2005). OCLF experience on the reactivation problem in familial hemophagocytic lymphohistiocytosis was revealed (Devecioglu et al., 2002). Very recently, OCLF increased its experience reports on chimerism analysis to FISH-based analysis (Aydin et al., 2007) in extension to previous DNA polymorphism analysis (Ozbek et al., 1997) mentioned above. OCLF also pioneered comparative cost-effectivity analysis of different antibiotic regimes in febrile neutropenia treatment in Turkey (Agaoglu et al., 2001).

### Melvin Jones fellowship

Dr. Gedikoglu was awarded with the prize of the Melvin Jones fellowship of the International Rotary Club. Melvin Jones fellowship is one of the important prizes given to

the persons, who achieved extraordinary service for the society. For instance, Lynda Mc Cartney, wife of Paul Mc Cartney from Beatles won this prize with her campaign for cleaning the land mines. From the scientific community, Donald Roy Bergsma working on the retinitis pigmentosa and the refractive ophthalmologic surgery, Lloyd McCaerney working on the cornea epithelium, Guiseppe Grimaldi working on the neuro-psychiatric research and the mathematician Frank B Allen are also among the award winning persons from different countries.

### Establishment of the Halic University

With the aim of giving a wider educational and medical service and also according to the existing aims and principals written on the trust indenture, Our Children Leukemia Foundation has founded the Halic University with special emphasis to the health sciences institute and to the medical faculty. T.C. [Turkish Republic]- Halic University establishment was heralded in the official gazette at the January of 1998 and it has began its academical life at the November of 1998. Today, Halic University is successfully continuing education with over 4500 students and with an instructor/ professor framework of 700 employees. At the establishment act of the Halic university, the following faculties or institutions were mentioned: Medical faculty, faculty of arts and sciences, faculty of engineering, business faculty, nursing high-school, conservatoire, physical education and sports high-school, health sciences institute, social sciences institute and natural sciences institute. Currently, the hospital project is about to finish realizing its medical faculty in 2009; all the other faculties and institutions are realized with a growing success every year.

### Establishment of the brain Power Research Group at the Halic university

Dr. Gedikoglu believed that the developing countries can not find equal financial resources to apply medical research as much as in the highly developed western countries, yet he believed that translational medical investigations can be applied if institutions focus specifically on special areas and if theoretical medicine studies are supported to establish framework and direction for molecular research groups. To achieve this aim, he founded "The Brain Power Research Group" at the university centrum. At first, he highered Dr. Meric Altinoz with expertise in cancer cell culture / basic studies, with research experience in Harvard Medical School and post-doctoral fellowship from Montreal Neurological Institute in McGill University. Under the supervision and guidance of Dr. Gedikoglu, this research group constituted an advance courier section of the Halic university with fastest growing numbers of research articles in a short period (Ozcan et al., 2006; Caner et al., 2007; Gedikoglu et al., 2007; Bilir et al., 2007; Altinoz et al., 2007; Gedikoglu and Altinoz,

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