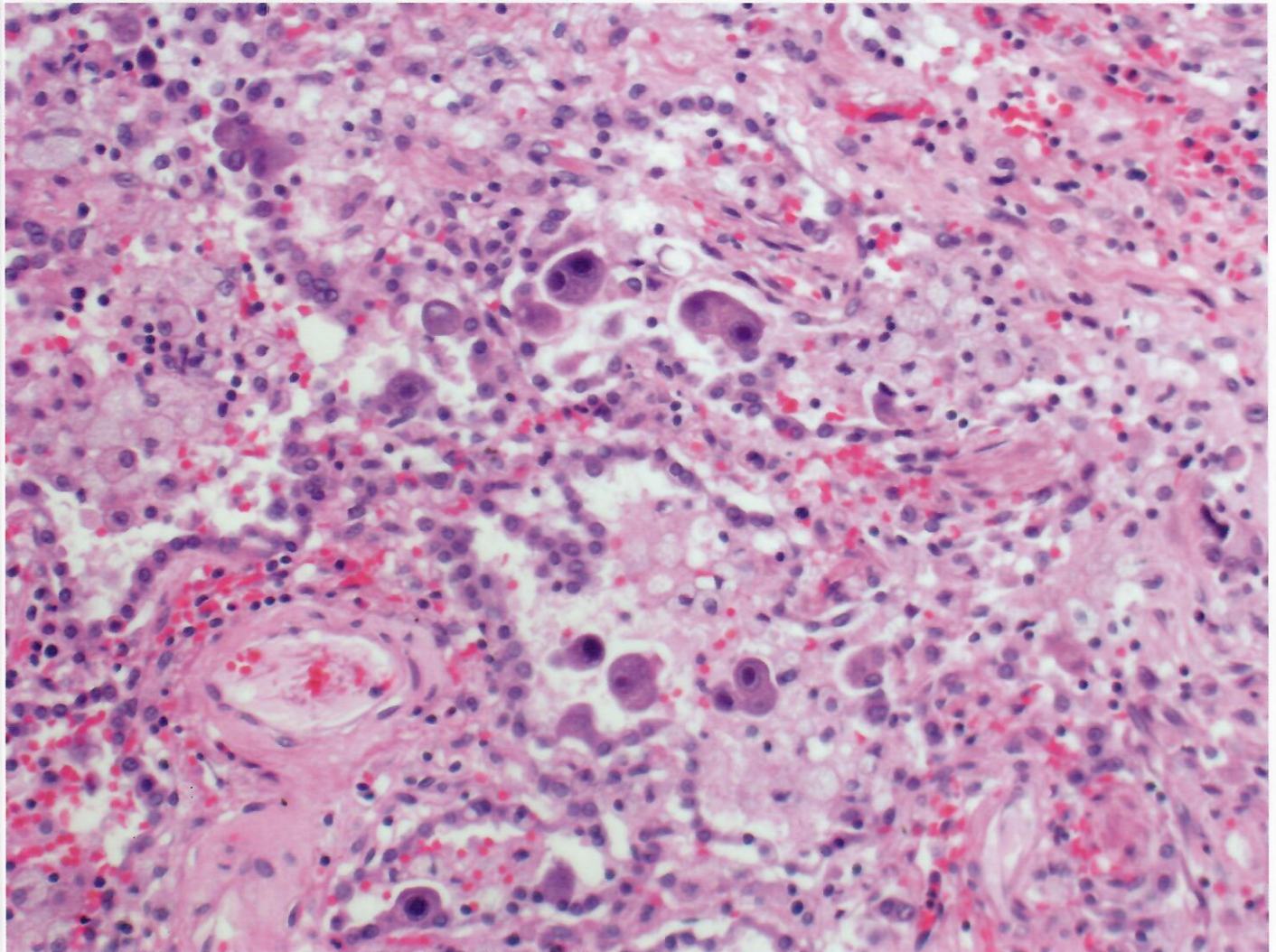




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ameliorated hepatic IRI and inflammatory responses, demonstrating the potential pathogenic role of ALOX12-12-HETE signaling in IRI.

Zhang and coworkers also showed that ALOX12-12-HETE-mediated liver inflammation through cell signaling metabolite GPR31 expressed on inflammatory cells leading to the synthesis and secretion of inflammatory cytokines and chemokines.<sup>8</sup> Although many G protein-coupled receptors can serve as receptors for lipid metabolites, Zhang et al identified GPR31 as a key receptor for 12-HETE triggering liver IRI.

Hypoxia can directly activate Kupffer cells that are a major source of ROS produced during the early postischemic period. Moreover, ROS generated by neutrophils contribute additionally to oxidative stress. Indeed, macrophages and neutrophils have been identified as key-players in hepatic IRI. Myeloid specific ALOX12-deficient mice may thus be useful for dissecting the mechanistic crosstalk between ALOX12 and ROS signaling pathways. The authors also demonstrated that treatment of primary hepatocytes with 12-HETE activated NF- $\kappa$ B and mitogen-activated protein kinase (MAPK) signaling, whereas inhibition of 12-HETE diminished NF- $\kappa$ B/MAPK activation and inflammatory programs initiated by IRI. However, potentially protective antiapoptotic survival factors produced by hepatocyte NF- $\kappa$ B and JNK need to be considered as well.<sup>9</sup> As both NF- $\kappa$ B and JNK not only prevent apoptosis but also promote inflammatory response,<sup>10</sup> the cellular location of NF- $\kappa$ B/JNK activity appears critical.

Of note, the interesting preclinical data by Zhang may not have direct clinical application. The leukocyte-type LOX12,

found in mice, rats, cows, and pigs but not humans, shares 73% to 86% amino acid with human ALOX15, but only 57% to 66% with human platelet-type ALOX12.<sup>3</sup> Nevertheless, the data by Zhang provide novel and fascinating links between metabolism, inflammation, and hepatic IRI that will hopefully translate into much needed novel clinical applications.

## REFERENCES

1. Zhai Y, Busuttill RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant.* 2011;11:1563–1569.
2. Zhang XJ, Cheng X, Yan ZZ, et al. An ALOX12-12-HETE-GPR31 signaling axis is a key mediator of hepatic ischemia-reperfusion injury. *Nat Med.* 2018;24:73–83.
3. Yamamoto S, Suzuki H, Ueda N. Arachidonate 12-lipoxygenases. *Prog Lipid Res.* 1997;36:23–41.
4. Lambeau G, Gelb MH. Biochemistry and physiology of mammalian secreted phospholipases A2. *Annu Rev Biochem.* 2008;77:495–520.
5. Morgan AH, Dioszeghy V, Maskrey BH, et al. Phosphatidylethanolamine-esterified eicosanoids in the mouse: tissue localization and inflammation-dependent formation in Th-2 disease. *J Biol Chem.* 2009;284:21185–21191.
6. Dioszeghy V, Rosas M, Maskrey BH, et al. 12/15-Lipoxygenase regulates the inflammatory response to bacterial products in vivo. *J Immunol.* 2008;181:6514–6524.
7. Dobrian AD, Lieb DC, Cole BK, et al. Functional and pathological roles of the 12- and 15-lipoxygenases. *Prog Lipid Res.* 2011;50:115–131.
8. Sun L, Ye RD. Role of G protein-coupled receptors in inflammation. *Acta Pharmacol Sin.* 2012;33:342–350.
9. Papa S, Bubici C, Zazzeroni F, et al. Mechanisms of liver disease: cross-talk between the NF- $\kappa$ B and JNK pathways. *Biol Chem.* 2009;390:965–976.
10. Han MS, Barrett T, Brehm MA, et al. Inflammation mediated by JNK in myeloid cells promotes the development of hepatitis and hepatocellular carcinoma. *Cell Rep.* 2016;15:19–26.

## People in Transplantation



# Mehmet Haberal, MD: Transplant Pioneer, Entrepreneur, President-elect, The Transplantation Society

**You were born in Pazar, a small town on the coast of the black sea in the east of Turkey. What shaped you during your early years and what motivated you to start a career in Medicine?**

**MH:** I spent most of my elementary school years in a small school in the village. In my final year of elementary school, my family moved to Zonguldak—a city in the Black

Sea area, known for its coal mines. I finished middle and high school there, and it was in my second year of high school that I finalized my decision for a future profession. Until that time, I had always imagined becoming an engineer. However, when I made a list of all possible career paths, I realized that medicine would be ideal: not only would I be able to help people, but I would probably still be able to integrate many other areas that interested me into Medicine!

**You have been a pioneer of organ transplantation in Turkey with many 'firsts' in living and deceased donor kidney and liver transplantation. What is your most memorable surgery? What is your most memorable patient?**

**MH:** I think my most memorable surgeries will always be those "firsts"—especially the first successful kidney transplant

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<sup>1</sup> Dumont-UCLA Transplant Center, Los Angeles, CA.

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performed in Turkey on November 3, 1975, at which time I was still only an Assistant Professor at Hacettepe University Department of General Surgery, just returning from Denver where I trained with Thomas Starzl. The President of Hacettepe University, Prof. İhsan Dođramacı, had appointed me as a consultant to the department of Pediatric Nephrology. It was a turning point for our country in terms of medicine and education. Of note, we did not even have a law regarding transplantation in my country at the time.

Many other “firsts” have been memorable and important: I recall the first deceased-donor liver transplantation (1988) in the Middle East, the first pediatric segmental living-related liver transplantation in Europe (1990) and only shortly thereafter, the worldwide first adult segmental living-related liver transplantation and, in 1992, first combined liver-kidney transplantation.

**You have an outstanding publication record with more than 880 PubMed listed articles. What do you consider your single most important scientific publication?**

**MH:** I have to admit that it is a challenge to select a single “most important” publication from a broad body of academic contributions that covered both clinical and experimental interests. However, I think the publication that I took the most pride in was “Failure of angiotensin II inhibitor to modify hyperacute rejection (Surgery, 1975). This study delineated the role of vasoconstriction in a large animal xenotransplantation model. Having had a “negative result” published spoke for the genuine interest this created, in addition to the relevance and the significant contribution of this study. Moreover, the publication of this article, designed and implemented by myself in such a prestigious journal provided a great source of motivation for me in my young academic career.

**Many of us are fully occupied with our busy life as clinicians/researchers. In addition to your clinical achievements, you are a uniquely successful entrepreneur. Among many enterprises, you founded Baskent University in Ankara as a private, nonprofit institution. What makes this university so special?**

**MH:** Often, circumstances that people find themselves in make it necessary to act in ways you may not have thought possible. When I started transplantation in Turkey there were very few dialysis centers in the country and often patients with kidney failure would need to wait 6 months for an appointment. Even after dialysis became available, most patients could not afford the treatment. In short, there were many patients but only few treatment options. Of course, this was only 1 problem among many in Turkey at the time, and I realized that if something was to be done in this area, I would need to do it myself.

At the time, there was no law governing transplantation and deceased donation was not an option. To have a law passed, I needed to show that deceased donor organs could be used successfully, and as such I contacted Eurotransplant and the Southeastern Organ Procurement Foundation requesting that they send us organs that they would not use. The maximum cold ischemia time possible for organs at the time was

12 hours. The first kidney that we received from Eurotransplant in 1978 had an ischemic time of more than 24 hours. Even more, we showed subsequently that we could successfully transplant kidneys that had ischemic times exceeding 110 hours. Our success opened the door to get a Transplant Law passed in 1979. This law provided the legal background not only for living and deceased organ donation but also banned all financial transactions related to organ transplantation. A legal addendum in 1982 supported an opt-out approach.

In the meantime, in 1980, I had established the Turkish Organ Transplantation and Burn Foundation, a nonprofit organization aiming to support patients financially as well as medically. In 1982, we established our first hemodialysis center and in 1985 our first Hospital, both in Ankara. Following requests from patients, we continue to establish dialysis centers around Turkey. Education and medical training became a necessity which led me to found the Haberal Education Foundation in 1986.

In 1993, under the umbrella of these 2 foundations, I established Baskent University. Today, the university includes 12 faculties, 7 institutes, 3 vocational schools, 2 private schools (preschool to high school), 10 hospitals and 20 dialysis centers. Our educational institutions host currently approximately 20 000 students of which 32% receive a scholarship; our institutions are supported by a staff of approximately 11 000 employees. The goals of those institutions *have always been to educate, train and ultimately treat more patients. We continue to work towards these goals every day.*

**Overseeing all your enterprises requires great skills. How would you describe your leadership style?**

**MH:** I am a great believer that every success carries the signature of an entire team. None of our endeavors would have been possible if I was working alone. Thus, I have always taken great care to handpick my team and the people I work with to ensure that I always work with those who are best at their jobs and who are willing to work 24/7 by my side.

**Turkey has one of the largest volume of living donor kidney and liver transplants worldwide, a wonderful success. How many surgeons have you trained yourself and how have you contributed to establish those complex surgical procedures in Turkey? What makes you special as a mentor?**

**MH:** I have worked my whole life to establish transplantation in Turkey as a feasible and desirable treatment method for end stage organ failure and I take great pride in mentoring: I have trained doctors at Hacettepe University, the Transplantation and Burn Treatment Foundation Hospital, and then later at Baskent University in general, burn and transplantation surgery; the passing of our transplant laws opened the doors to further progress within ethical boundaries; the establishment of the foundations and the founding of the Turkish Transplantation Society in 1990 have all been avenues to educate both medical professionals and the public at large.

I do not know if anything makes me particularly special. I work to fulfill my desire to offering the best care to my patients: more options, better results, healthier lives.

**Deceased donor rates are currently not keeping up with the high living donor rates in Turkey. What do you envision as steps to advance deceased donation in Turkey?**

**MH:** The laws passed in 1979 and 1982 are designed to optimize the use of organs from deceased donors. In fact, we performed our first local deceased donor kidney transplant in 1979, just 1 month after passing of the law. Since the very beginning, we have had the support of the religious leaders, the parliament, and the media. Yet only 30% of our organ transplants are from deceased donors. However, in 2001, the Ministry of Health established a national organ sharing network, dividing Turkey into 9 regions within which deceased donor organs are equally distributed. This has helped to increase deceased donation, and hopefully will continue to increase numbers, although it is of course a slow process.

**You have established a wonderful network of support in transplantation around the world with a focus on the Middle East. How do you envision promoting transplantation in this area?**

**MH:** Turkey and many countries in the Middle East show commonalities on many levels: culturally, socially, and economically. I came to see that many of the problems in Turkey were equally true for the remainder of the region, and that there were very high rates of chronic kidney and liver diseases which required activities taking place in Turkey to be established beyond our own borders. As such, in 1984, I established the Middle East Dialysis and Organ

Transplantation Foundation, followed in 1987 by the Middle East Society for Organ Transplantation. We focus very much on equal and democratic representation (every 2 years, we elect a President and organize a congress in a different geographic area of the Middle East. Our meetings are of paramount importance, as these are ideal opportunities to share knowledge and experience while promoting ethical organ transplantation through the mass media, which will ultimately be a medium to educate the public. Our Fellowship Program and MESOT Transplant games have also been tremendously effective in promoting organ transplantation throughout the region. Moreover, to encourage communication and collaboration in the field of organ transplantation among the Turkic States of the world (Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkey, Turkmenistan, and Uzbekistan), I have also founded the Turkic World Transplantation Society in 2014.

What makes Baskent unique is its ability to be almost entirely self supporting, in provides all its own services outside of banking and logistics. In short, medical facilities, education institutions for all age levels, a dairy farm, a construction company, textile factory, 2 hotels and a television channel.

**We have heard about the clinician/Scientist and entrepreneur. Is there any time left for interests outside of your busy professional life?**

**MH:** I must admit that I dedicate most of my time to my patients, my university and my other professional interests. That does unfortunately leave very little time for anything else. However, when the opportunity arises, I enjoy football, swimming, dancing (both traditional Turkish folk dancing as well as ballroom dancing), and photography.

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