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Focus on Faculty #58
Antonis Koromilas

As the Greek Poet George Seferis phrased it in his *Nobel Prize* award speech in 1963, " I come from a small country, a rocky promontory in the Mediterranean, with immense culture and tradition transcended through the centuries characterized by love of the human; justice is its norm". I was educated in Chemistry (BSc 1984) and Biochemistry (PhD 1988) at the Aristotelian University of Thessaloniki, the second most populous city after Athens, but perhaps the most beautiful city of Greece.

Motivated by my sincere interest in both science and culture, I pursued my first post-doctoral training (1988-90) in Molecular Immunology in Kyoto University, Japan, under the supervision of Tasuku Honjo, an awardee of the *Nobel Prize* in Medicine in 2018. My second post-doctoral training with Nahum Sonenberg was a serendipitous opportunity thanks to a journal club presentation of Nahum's seminal work during my sojourn in Honjo's lab. My training in the Sonenberg lab (1990-93) was both challenging and rewarding for my career and personal life. I was recruited to the newly formed Molecular Oncology Group at the *Lady Davis* Institute (LDI) in 1993 thanks to my productive training in Nahum's lab, strong recommendation from the Group Leader John Hiscott and approval by the LDI Director Sam Freedman. I belonged to the fortunate generation of young investigators to receive a tenure-track appointment with McGill, which allowed me to climb the academic ladder by being promoted to Associate (1999) and full Professor (2006) in the Department of Oncology.

For the past 27 years, I have been enjoying my employment with McGill by being a contributory member of the LDI and McGill communities as a tutor, researcher and mentor. My research interests focus on the molecular mechanisms employed by cells to adapt to different forms of environmental stress (e.g. DNA damage, virus infection, oncogene activation) through the regulation of protein synthesis. In recent years, I have been investigating the implications of adaptive stress response pathways in breast and lung cancer formation and treatments with protein synthesis inhibitors in pre-clinical models of both cancers.

My experience has taught me that good science and discovery often hides in ignorable but significant results. Also, research and innovation cannot be possible without the contribution of talented trainees and collaborators, which I have been fortunate to work with in the past 27 years. I have been a proud

mentor of dozens of trainees, many of whom have developed into successful policy makers, researchers, academics and biomedical entrepreneurs in Canada and elsewhere.

As time passes by and I get closer to my retirement, I consider myself fortunate to have been influenced by superb scientists and mentors, who assisted me in pursuing a fulfilling career in science. Copying the words of Alexander the Great, "I owe my life to my parents and good life to my teachers", I simply wish to pay tribute to my teachers and mentors, especially to T. Honjo, N. Sonenberg and S. Freedman. I hope I remain healthy to further provide my services to LDI and McGill communities until my retirement. When that moment arrives, I would like to be remembered for my contribution to science but equally important for what sort of person, colleague and mentor I have been in my career.

I am particularly proud of the following publications:

1. Koromilas, A. E., Roy, S., Barber, G. N., Katze, M. G. & Sonenberg, N. Malignant transformation by a mutant of the IFN-inducible dsRNA-dependent protein kinase. *Science* **257**, 1685-1689 (1992).
   This paper demonstrated, for the first time, the tumor suppressor properties of the eIF2 kinase PKR. It established the significance of translational control in cancer along with the role of eIF4E. It helped my recruitment to LDI and McGill and won significant funding to build up my lab.

2. Wong, A. H. *et al.* Physical association between STAT1 and the interferon-inducible protein kinase PKR and implications for interferon and double-stranded RNA signaling pathways. *EMBO J* **16**, 1291-1304 (1997).
   I am sentimentally attached to this paper because it was my first paper as an independent investigator. I often recall the decision letter from the Editor John Tooze thanking me and my students for submitting such an interesting paper to EMBO Journal.

3. Qu, L. *et al.* Endoplasmic reticulum stress induces p53 cytoplasmic localization and prevents p53-dependent apoptosis by a pathway involving glycogen synthase kinase-3beta. *Genes Dev* **18**, 261-277 (2004).
   The first paper in the field of environmetal stress and cancer to demonstrate that tumor adaptation to stress requires the inactivation of TP53. Highlinted by Genes Dev (journal cover and Perspective article) and Faculty of 1000.

4. Mounir, Z. *et al.* Akt Determines Cell Fate Through Inhibition of the PERK-eIF2 Phosphorylation Pathway. *Sci. Signal* **4**, ra62 (2011).
   The paper identified a novel connection between the integrated stress response and PKB/AKT. The functional interplay between the two pathways detremines tumor cell fate in response to stress and treatments with chemotherapeutic drugs. The first author was in the top 5% of students I have ever interacted with.

5. Darini, C. *et al.* An integrated stress response via PKR suppresses HER2+ cancers and improves trastuzumab therapy. *Nature Communications* **10**, 2139, doi:10.1038/s41467-019-10138-8 (2019).
   The paper demonstrates the anti-tumor function of PKR in HER2+ cancers and the therapeutic potential of the pharmacological stimulation of eIF2 phosphorylation in bypassing tumor resistance to Trastuzumab.