PASPCR COMMENTARY
June 1, 2008

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When I was asked to write this commentary I hesitated, especially due to the list of people that had done it before me and their significant accomplishments as researchers. John Pawelek kindly eased my concerns and I accepted, despite my feeling that "I am not there yet". Considering that this series is about our personal journey, here is mine.

I was born in a small town in the state of Sao Paulo, Brazil. I am one of four siblings of a second generation Japanese family. My grand parents immigrated from Okinawa to Brazil in the early 1920's, following an agreement between the Japanese and Brazilian governments that would benefit both countries. Japan needed relief from overpopulation and Brazil needed laborers to work in agriculture. The immigrants were indoctrinated to believe that Brazil was a wonderland, a place were they could prosper. The reality showed, however, that life was very difficult in a country with a totally different culture and customs, and a strange language. From there, my family history is not very different from all of the other immigrant families who worked their way out from adverse situations with hard work and personal sacrifices. I had the good fortune to grow up in a much healthier environment where people from Italy, Germany, Africa, Portugal, China, Korea, and Greece (just to mention some) contributed to the diversity of the Brazilian population. Very similar to the United States in this regard, Brazil is a multicultural melting pot. I like to tease people telling them that I represent the typical Brazilian woman.

My passion for Bilological Sciences was manifested early during my High School years, when I decided that I would choose a career in sciences. I did my undergraduate studies and received my B.S. degree from the Biosciences Institute, University of Sao Paulo (USP), one of the most prestigious universities in Brazil. USP is a state funded university with about 75,000 students distributed over eleven campuses. It is one of the largest institutions of higher education in Latin America and extremely competitive. The Biosciences Institute is located on the main campus called Armando Salles de Oliveira, with an area of 7,443,770 m^2. The Biosciences Institute, originally created in 1969, comprises the Departments of Genetics and Developmental Biology, Botany, Physiology, Zoology and Ecology.

I received my Master and Ph.D. degrees from the Department of Physiology. This Department was one of the rare places in Brazil that offered a graduate degree in Comparative Animal Physiology. The Department's mission was to contribute to the understanding of physiology focusing primarily on questions of how animals function in diverse environments or under environmental changes. We studied physiology within the conceptual frame work of the "Krogh Principle" which postulates that for each

physiological question there is a suitable animal-model to be studied. We learned that different environments constitute natural laboratory conditions where animals are selected by their uniqueness, sometimes exaggerated characteristics, that allow for their survival. As a consequence, we looked for answers comparing different species in the context of their environment, with the intent to uncover the basic physiological principles of adaptation.

My experience in the pigment cell field started in 1989 in the laboratory of Dr. Ana Maria de Lauro Castrucci, the director of the Laboratory of Comparative Physiology of Pigmentation. The main topic of investigation in her laboratory was the hormonal control of vertebrate pigment cell. During that time, I was introduced to different animal models, from crustaceans, fishes, amphibians, and avians to mammals. To my benefit, the variety of animal models allowed me to investigate mechanistic problems in a broader view, taking into consideration that it is the individual/organism as a whole that is exposed to the environment and not only its parts (Castrucci *et al*., 1997).

Although I always valued my background in comparative physiology, the reality of the Brazilian economic recession and consequent shortage of funding opportunities generated pressure on scientists to focus research targeting specific diseases. Although I did not agree with the imposition of research subject by the financial agencies, the outcome of my research proved to be beneficial to the investigation of mechanisms of melanoma growth inhibition. It turned out that melatonin; the hormonal transducer of the environmental day and night cycles in vertebrates, has a significant influence on melanoma growth, both *in vivo* and *in vitro* conditions (Kadekaro *et al*., 2004). Half-way through my studies for my Ph.D., I had the opportunity to apply for a fellowship that provided funds for students to develop part of their research projects abroad.

In 1998, I came to the United States to work in Dr. Mark Rollag's laboratory, at the Uniformed Services University of Health Sciences (USUHS) in Bethesda, Maryland. Dr. Rollag dedicated his career studying melatonin, its role in circadian rhythms and its impact on the physiology of different animals. In 1998, he and his post doctoral fellow Dr. Ignacio Provencio, gained notoriety for their discovery of melanopsin, a G-coupled receptor found in specialized light-sensitive cells in the skin of *Xenopus laevis*. The importance of their discovery became clear the following year when Dr. Russell Foster showed that a third class of photoreceptor existed in mammalian eyes, which happened to be very similar to the melanopsin found in the frog. Soon after, Dr. Provencio showed that humans also express melanopsin in a rare subtype of retinal ganglion cells, the output cells of the retina. It turns out that when light activates the melanopsin-containing ganglion cells, a discharge of nerve impulses are conducted to specific brain targets. Among the targets in the central nervous system is the suprachiasmatic nucleus of the hypothalamus, the master pacemaker of circadian rhythms.

It is needless to mention the implications of their discovery for light entrainment and synchronization of light-dark cycles in behavioral activity (or inactivity) in all

animals, including humans. This reassured me the value of Krogh's Principle and reminded me that nature does not draw lines dividing applied and basic science research.

In Dr Rollag's laboratory, my overall goal was to learn more about circadian rhythms in mammals. I wanted to express the MT-1, human melatonin receptor, in the S-91 mouse melanoma cell. This was the appropriate model for my studies since S-91 melanoma cells are known to be derived from spontaneous tumor growth in DBA/2J mouse. Therefore, I could easily perform the *in vivo* studies by inoculating the cells into the mice subcutaneously, obtaining close to 100% tumor development. As soon as I started working in the lab, Dr. Rollag advised me to take advantage of being just across the street from NIH and encouraged me to contact Dr. Vince Hearing. Dr. Rollag arranged a joint lab meeting between us in a few days and, to my surprise, Dr. Hearing gave me the opportunity to learn and run some experiments in his already crowded laboratory. In the following months I divided my time between the USUHS and NIH. I learned a lot by shadowing Victoria Virador, Nobuhiko Kobayashi, Jun and Naoko Matsunaga, Minao Furumura and of course, the dearest Wilfred Vieira.

After 9 months in the United States I returned to Brazil. The results from my studies demonstrated that melatonin significantly inhibited *in vitro* S-91cell proliferation and *in vivo* tumor growth. The effect of melatonin partially happened through its direct effect, possibly by binding to tubulin and disrupting its polymerization. We have learned that heterologous expression of human MT-1 receptor resulted in dramatic reduction of *in vitro* cell proliferation. We concluded that melatonin, besides its effect in activating catalase and glutathione peroxidase activities, could provide a new alternative approach in reducing melanoma growth. During the process of writing my Ph.D. dissertation, it became crystal clear to me what direction I wanted my research to follow after obtaining my degree. I argued that if pigmentation was important for the survival of so many phylogenetically distant animals, this should also hold true for survival of humans. I recognized the significance of exploring the role of pigmentation in the well being of humans. In the fall of 1999, I planned to attend the 17th International Pigment Cell Conference (IPCC) to be held in Nagoya. Without any financial means, I wrote to Dr. Wakamatsu and Dr. Nordlund asking for financial support. This meeting was very important to me because I could finally exchange ideas with some of the most renowned researchers in the field. It was during this meeting that I met Dr Zalfa Abdel-Malek and expressed my interest in working with normal human melanocytes and their responses to ultraviolet radiation. A few months later, I successfully applied and obtained a post-doctoral fellowship sponsored by the Brazilian government to spend one year in Zalfa's laboratory.

I came to Cincinnati in the fall of 2000, where I started my research in the Department of Dermatology of the University of Cincinnati. Dr. Abdel-Malek is a very passionate scientist, but above all, she is a wonderful person. During my post doctoral training, she gave me not only guidance, but also the necessary freedom to develop and express the ideas, which contributed to the ongoing projects in her lab (Scott et al., 2002; Kadekaro *et al*., 2003). Together, we found evidence supporting her long-term

hypothesis that melanocortins prevent melanoma formation by reducing UV-induced DNA damage. We found that this is accomplished in two ways, the first by increasing the rate of repair of DNA damage and reducing the generation of reactive oxygen species and second by the subsequent increase in melanin synthesis (Kadekaro *et al.*, 2005). These findings have several important implications, especially in the context of the variety of MC1R alleles present in the human population. We provided experimental support for the epidemiological and clinical data showing that melanoma risk correlates inversely with skin pigmentation (Kadekaro *et al*., 2006; Hauser *et al*., 2006; Abdel-Malek *et al*., 2006). In collaboration with Dr. Ito and Wakamatsu, our studies revealed that MC1R loss-of-function mutations do not necessarily alter the phenotype of cultured melanocytes, but rather relate to increased sensitivity to UV-induced DNA damage (Wakamatsu *et al*., 2006).

In 2005, I was offered the position of Research Instructor in the Department of Dermatology and more recently, with my promotion to Research Assistant Professor on April 2008, our association was brought to a new level, now as colleagues. As a continuation of my work that I developed previously under Dr. Abdel-Malek's mentorship, my goal is to uncover the mechanisms by which melanocortins provide protection against oxidative stress, particularly that induced by UV. What we do know at this moment is that melanocortins, acting via the MC1R, modulate different pathways not only at the level of prevention of oxidative stress, but also at the level of damage management, increasing the efficiency of DNA repair in sites of oxidative stress. Our data suggest that at least part of these effects involve the activation of p53 and its gene targets. The importance of oxidative stress in cell biology in general, and its involvement in diseases, especially cancer formation, opens numerous opportunities to be explored. It would be interesting to determine if the presence of melanocortins modifies the fate of melanocytes derived from patients with vitiligo; or to determine if melanocortins could protect against oxidative stress induced by other agents; equally exciting would be to determine if melanocortins could provide similar protective effects in cells expressing melanocortin receptors in other systems. This is a very exciting road, not traveled before, that is just in front of me.

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