

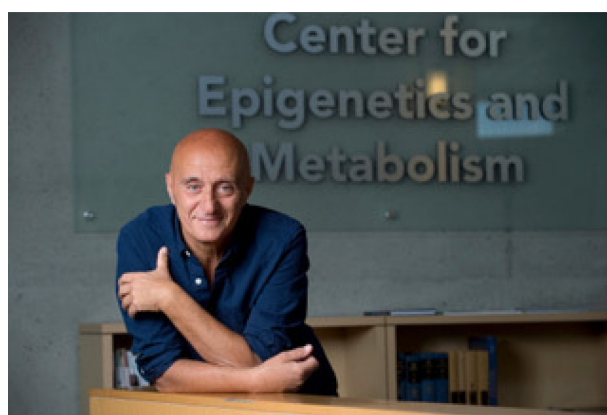
Paolo Sassone-Corsi (1956 - 2020)

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Paolo Sassone-Corsi, Pd.D. (Donald Bren Professor, Department of Biological Chemistry, and Director, Center for Epigenetics and Metabolism, University of California, Irvine), an eminent scientist who linked metabolism and epigenetics to the circadian clock, passed away on July 22nd, 2020 at the age of 64. His discoveries of metabolic and epigenetic control of the circadian clock activity, along with the discoveries of the circadian regulation of metabolism and gene expression, contributed to a better understanding of how the circadian clock governs a time-specific diversity of biological functions. Paolo's achievements were indispensable for the rapid development of the chronobiological research field.

Born in Naples, Italy in 1956, Paolo spent his early life dreaming about becoming a soccer player or an astronaut. Aside from biology, soccer and astronomy were his lifetime entertainments. Specifically, his childhood dream and interest in astronomy fostered his spirit of scientific inquiry, orienting himself toward becoming a biological scientist. He received his Ph.D. from the International Institute of Genetics and Biophysics, CNR, Naples, in 1979 with his thesis work on "Genetics of a plasmid-like DNA population in the petite-negative yeast *Schizosaccharomyces pombe*". After completing his Ph.D., Paolo traveled to Strasbourg, France, with his wife Emiliana Borrelli, Ph.D. (Chancellor's Professor in Microbiology & Molecular Genetics, UCI), to become a postdoctoral fellow in the Pierre Chambon laboratory at CNRS. Paolo immersed himself in the research of gene expression and transcription, which became an underlying and fundamental scientific interest of Paolo. He was committed to a large number of



discoveries, including the characterization of a trans-acting factor for the SV40 enhancer activity (Sassone-Corsi et al., *Nature* 1985). Paolo often referred to Pierre's sentiment, highlighting the importance of hard work and curiosity about science. Pierre as an active scientist at 89 years old continued to stimulate and fulfil Paolo's scientific enthusiasm.

Paolo and Emiliana moved to Southern California where Paolo served as a visiting researcher in the laboratory of Inder Verma, Ph.D., at the Salk Institute, La Jolla, CA. From 1986 to 1989, he applied his experience and knowledge of transcriptional regulation accumulated during his postdoc training in the Chambon lab to the nuclear oncogene *c-fos* (Sassone-Corsi and Verma, *Nature* 1987; Sassone-Corsi et al., *Cell* 1988; *Nature* 1988a; *Nature* 1988b). His works on the transcriptional control of nuclear oncogenes have had profound implications for gene regulation, signal transduction, and cancer.

After achieving success in CA, Paolo and Emiliana returned

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Paolo's memorial with lab members at Aliso Beach in Laguna Beach, CA on August 14th, 2020. We ate Paolo's favorite ice cream, wore black t-shirts that Paolo had worn most often during the stay-at-home period with a memorial pin of Paolo's logo, and recalled the good memories we shared with Paolo. We miss and love Paolo!

to France to launch their own independent laboratories at CNRS. Paolo led his group as Directeur de Recherche and tackled a key question of how extracellular signals elicited by hormones and growth factors modulate gene expression. Paolo discovered and characterized the CREM gene that leads to the inducible synthesis of a cAMP-inducible repressor engaged in the transcriptional suppression of cAMP-dependent immediate early response of many genes (Foulkes et al., Cell 1991; Molina et al., Cell 1993). Luck also favored Paolo – his early-bird research fellow sacrificed animals in the morning whereas his night-owl research fellow sacrificed animals at night, resulting in the discovery of cyclic gene regulation of CREM in the pineal gland (Stehle et al., Nature 1993). This fortune introduced him to the field of circadian biology and eventually brought the two of us together.

Numerous contributions to the circadian biology were made by Paolo's research, including the impact of light signals on the circadian clock in peripheral organs and cells (Whitmore et al., Nature 2000), key posttranslational modifications on clock proteins (Cardone et al., Science 2005), and a novel role for CLOCK as a chromatin remodeler (Doi et al., Cell 2006; Hirayama et al., Nature 2007). These findings challenged the common knowledge in the field that had been accepted for decades and paved a new avenue for further development of circadian biological studies. Around that time, his life had another turning point; In 2006, Paolo and Emiliana relocated to Southern

California. Paolo was recruited to UCI, as a Donald Bren Professor and Chair of the Department of Pharmacology. Regarding the relocation, Paolo advised me *"to be a successful researcher, you need to think about your best place to go at every single moment and you need to find out the place allowing you to be a special one"*. His advice was crucially valuable when I faced tough decisions regarding my personal career development. Paolo's word indicated that UCI was the best home for his science and inspired me to become a successful independent investigator. I now ask myself *"Which direction should I go in the absence of Paolo?"*.

Paolo's talent, experience, and worldwide fame enabled him to establish and lead the Center for Epigenetics and Metabolism at UCI. Paolo biennially organized landmark symposiums, entitled the Epigenetic Control of Cellular Plasticity to gather the latest evidence from leading researchers in the field. In the context of the circadian research linked to epigenetics and metabolism, his new team at UCI uncovered: 1) the implications of chromatin-modifying enzymes for the circadian clock mediating metabolic regulations and histone modifications (Katada and Sassone-Corsi Nat Struct Mol Biol 2010; Nakahata et al., Cell 2008; Science 2009), 2) circadian reprogramming of metabolic pathways under dietary challenges (Eckel-Mahan et al., Cell 2013; Murakami et al., EMBO Rep 2016; Kinouchi et al., Cell Rep 2018), aging (Sato et al., Cell 2017), and physical exercise (Sato et al., Cell Metab 2019),



From left, Marlene Cervantes (Paolo's last Grad Student), Paolo, and Shoko Sato (Paolo's last Lab Tech and my wife) in Paolo's office.

and 3) a tissue-communication of the clock and metabolism (Dyar et al., Cell 2018; Koronowski et al., Cell 2019).

Paolo's extraordinary intelligence and passion resulted in the publication of more than 420 peer-reviewed articles throughout his tenure with an H-index of 129. Paolo also received a number of brilliant honors and awards, including EMBO Gold Medal (1994), Grand Prix Liliane Bettencourt, France (1997), Grand Prix Charles-Léopold Mayer of the Académie des Sciences, Paris (2003), Edwin B. Astwood Award, Endocrine Society, USA (2004), Ispen Award in Endocrinology (2011), Transatlantic Medal of The Society of Endocrinology, UK (2012), and August and Marie Krogh Medal, Denmark (2015). Most recently, Paolo received the UCI Distinguished Faculty Award for Research in 2018, which is the highest faculty honor at UCI. He was also an elected Fellow of the American Association for the Advancement of Science (AAAS).

Notably, Paolo personally had a specific preference toward Japan – Japanese culture, identity, and loyalty-based and hard working-based characters. Out of the total 80 members in Paolo's lab at UCI, there are/were 15 Japanese members mentored by Paolo. He had many Japanese collaborators and friends, most of whom belong to the Japanese Society for Chronobiology. Paolo enjoyed traveling to *Okinawa* (*Ishigaki* island), *Nara* (the Great Buddha in *Todai* temple),

and *Kyoto* during his invited conferences and seminars. I am saddened that I did not have the opportunity to invite Paolo to my home town, Northern *Chiba* area (a famous area for eel (*Unagi*), one of his favorite foods).

Aside from Japanese fellows, Paolo's lab was internationally diverse at both the internal (lab members) and external (collaborators) levels. His open and frank personality invited active worldwide communication and collaborations. During my 5.5-years with Paolo, he provided me many meaningful and rewarding opportunities to collaborate with eminent scientists around the world. The intertwined network among researchers is one of the unconditional gifts from Paolo. What I respected and appreciated about him is that he offered autonomy. Paolo always valued my thinking and decisions, which I believe, could not be made possible without a relationship of mutual trust between Paolo and myself. When I went to an undesired direction, Paolo admonished me without saying “no”, and rather suggesting a secondary direction. This allowed me to learn the way of creative thinking outside the box and simultaneously foster my perspicacity for scientific observations and communication.

Paolo was the most honest person I have ever met. When we first met during my interview, he told me that he did not like people who are unwilling to dedicate time and effort to science. His honest and concrete implications, rather than suggestive implications, critically pointed to what he wanted me to do in his lab. I also have to underline that Paolo was friendly and lovely to everyone without any discrimination. There was a constant and endless flow of people visiting him. One day, Paolo suggested, “*You need to be an outgoing and social butterfly to bring yourself up to a global stage*”. Paolo's cheerful and extroverted personality at least partly made a success in epigenetic reprogramming of my intrinsic Japanese chromatin landscape into his Italian version.

It was my greatest honor and privilege to meet and work with Paolo. He was an irreplaceable mentor and father in the US. “*Domo-Arigato* (thank you so much)” is insufficient to express my gratefulness to Paolo. Paolo's lessons, passion, and attitude to science remain in the depth of my heart, marking the passage of my time. We miss and love you, Paolo, so much. RIP.

Acknowledgements

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