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Obituary

# Paolo Sassone-Corsi (1956–2020)

The untimely death of Paolo Sassone-Corsi at the age of 64 on July 22nd has left both science and humanity diminished. Best known in recent years for his work on circadian rhythms, "Stop all the clocks," the opening words of W.H. Auden's "Funeral Blues," have never seemed more appropriate.

Born in Naples, Italy on June 8th, 1956 to parents Mario and Anna, Paolo soon developed the three passions that would stay with him throughout his life: football, astronomy, and biology. While the desire to become a professional football player for SSC Napoli was to remain a dream, his first foray into the world of science came at the age of 12 when, together with his brother Emilio and other like-minded friends, he founded an amateur astronomers club (Gruppo Astrofili Napoletani). By the age of 16, Paolo and Emilio were regular users of the telescopes at the Astronomical Observatory of Capodimonte in Naples and the Swedish Observatory of Anacapri, located on the island of Capri. In 1978, Paolo and Emilio were hosted at the Paris-Meudon Observatory to study the seasonal variations of the bands of Saturn, findings that were published in the *Journal of the Association of Lunar and Planetary Observers* (ALPO). His passion for astronomy stayed with him throughout his life, as only a few days before he died, Paolo was discussing and sharing images taken from Italy of the NEOWISE comet.

In high school, Paolo became attracted to biology and in particular the central role of DNA in molecular biology. He went on to study at Federico II University in Naples before undertaking his thesis in 1976 at the Institute of Genetics and Biophysics. It was there that he became aware of the recent discovery that genes were spliced, an observation that led him to one of the central questions in biology: how are genes regulated? Few laboratories worldwide had the tools and insights to address that question. With the help of the Belgian biochemist Jean Brachet, Paolo successfully applied to join Pierre Chambon's group in Strasbourg, one of the most eminent laboratories that early on had embraced molecular genetics and had already purified eukaryotic RNA polymerases, pioneered work on chromatin, and discovered splicing in chicken genes.

Paolo Sassone-Corsi

Paolo moved to Strasbourg in December 1979 and immediately began contributing to the pioneering work on transcriptional regulation that was underway in the Chambon laboratory. Within a few months, using new site-directed mutagenesis technology, his drive and commitment led him to co-authoring an influential 1980 paper that identified a promoter sequence of the adenovirus major late gene that eventually became known as the TATA box, which was very quickly recognized as a hallmark regulatory element of most eukaryotic genes (Corden et al., 1980). This rapid and energetic engagement in research foreshadowed some of the defining characteristics of Paolo's career as a scientist—an enthusiasm for discovery, a huge capacity for work, and an incredible ability to take advantage of chance observations.

Paolo's tenure in Chambon's laboratory coincided with an exciting and crucial early period in the understanding of how eukaryotic genes are transcriptionally regulated. Using viral model systems, he drove the initial characterization of the transcriptional regulatory elements that became known as enhancers and published some of the earliest papers on the *trans*-acting protein factors that interacted with them (Sassone-Corsi et al., 1985). Soon after his arrival in Strasbourg, Paolo was joined by his wife Emiliana Borrelli, whom he had met as a teenager and married in April 1980. Although from different fields (Emiliana trained in neuroscience), Paolo and Emiliana began a scientific interaction in Chambon's laboratory that continued for four decades and spanned both of their areas of interest.

Despite their success in the Chambon lab, Paolo and Emiliana felt that to be truly innovative, they would need to see science from additional perspectives. With that in mind, and a long-term ambition to return to Strasbourg as independent researchers, they moved to the Salk Institute in San Diego, California, where Paolo joined the laboratory of Inder Verma and Emiliana followed her passion for physiology with Ron

Evans. Paolo's work in the field of transcriptional regulation was critical in defining the underlying biology of the *FOS* oncogene. From 1986 to 1989, Paolo and Inder Verma published a series of groundbreaking papers that ultimately launched his career trajectory. From the regulation of the *FOS* gene by cAMP, to the identification of the interaction of FOS with p39 or JUN and the elucidation of the leucine zipper as the association domain between FOS and JUN, these seminal papers were pivotal in the field of transcription (Sassone-Corsi et al., 1988).

Having made his mark in the field of nuclear oncogenes, Paolo and Emiliana returned to Strasbourg to establish their own laboratories. As a CNRS Directeur de Recherche, Paolo's independent scientific career was based on an ability to sense an opportunity to do something different. Rather than following the path of many in the field and continuing to work on the structural and biochemical aspects of nuclear oncogenes, Paolo chose a different path, influenced in no small part by Emiliana. Paolo began to explore links between gene regulation and the physiology of the neuroendocrine system, centered on the idea that adenyl cyclase plays a key role in hormone production in the pituitary. Paolo's lab screened a pituitary cDNA library synthesized by Emiliana for novel cAMP-regulated genes. Luck would give him CREM, a multi-isoform bZIP transcription factor related to CREB and FOS. Where luck ended, drive, energy, enthusiasm, and insight took over. Paolo's group rapidly established a role for CREM in the pituitary, but also found that it was highly expressed in testis, specifically in developing spermatids. Seeking to expand these observations, Paolo contacted Paul Pévet, whose work had shown that hamster spermatogenesis was regulated by day length. From the subsequent collaboration with the Pévet lab, Paolo's group demonstrated that CREM was instrumental in pituitary-derived follicle-stimulating hormone-driven spermatogenesis. Paolo's lab then examined CREM expression in the brain and in particular, the pineal gland. A subsequent pilot *in situ* hybridization experiment revealed weak pineal gland expression of a rat sacrificed during the day versus a spectacular signal when the rat was sacrificed at night. Through careful 24-hour time course experiments, they established that CREM was a circadian-regulated gene (Stehle et al., 1993) and went on to identify and characterize the transcriptional negative feedback mechanisms that mediated the cyclical pattern of its expression. These insights into how such cyclical gene expression could be established were a revelation and cemented Paolo's transition into the field of circadian biology.

In 2006, a new scientific opportunity arose that would prove irresistible. Paolo was recruited to the University of California, Irvine as Donald Bren Professor and Chair of the Department of Pharmacology, and he returned to Southern California with Emiliana, who moved her own laboratory to the School of Medicine at UCI. Beyond science, their move was also motivated by a desire for the sun and sea that had characterized their childhood in Naples and which they increasingly missed in Strasbourg. Establishing their home in Laguna Beach was therefore something of a homecoming; they had fallen in love with the area during their time at the Salk Institute and likened it as the closest they could find to the Italian Amalfi coast.

Paolo's ability to merge divergent scientific fields to create something truly innovative was his impetus for establishing the Center for Epigenetics and Metabolism at UCI. This new center was positioned at the major crossroads of his scientific interests and exemplified his vision of multidisciplinary research. As forged by Paolo, it provided a platform for deciphering how epigenetic control and metabolism influence cellular identity and plasticity. As the center director, Paolo organized the biennial "Epigenetic Control and Cellular Plasticity" symposium at UCI that attracted Nobel laureates and eminent scientists in the field. This symposium not only provided an exciting forum for new ideas, but was also infused with Paolo's energy and enthusiasm.

At UCI, Paolo's scientific career mainly focused on his pioneering work in the field of circadian rhythms. Paolo contributed broadly to the chronobiology field by defining light-induced chromatin modifications and enzymes that finetune circadian gene expression, such as Clock and MLL1. With Ueli Schibler, Paolo's lab characterized the role of the mammalian sirtuins, which led him down a branching path in the circadian field. Paolo became fascinated with how metabolite signaling impinges on chromatin modifications to control circadian gene expression. In parallel work with Joe Bass, Paolo's lab identified that $NAD^+$ levels were circadian, and this rhythmicity ultimately controlled the activity of the sirtuins and histone acetylation (Nakahata et al., 2009). Paolo extended these findings beyond isolated metabolites to define how dietary intervention is able to rewire the transcriptional and epigenetic landscape of the biological clock. Paolo's most recent scientific interests were focused on how clocks in different tissues were able to communicate—a fascination that led him to explore the realms of metabolite inter-tissue communication during homeostasis and disease state.

Paolo's extraordinary energy and innovative approach to biology is reflected in his scientific legacy. Paolo has authored more than 420 peer-reviewed scientific papers, with an h-index of 129. Paolo mentored over 200 trainees, mostly postdoctoral fellows, many of whom now run their own laboratories in the United States, Canada, Japan, Germany, England, France, Italy, Spain, Finland, and Mexico.

Paolo's scientific achievements are reflected in his many awards and prizes, including the EMBO Gold Medal in 1994, the Rosen Medical Research Prize in 1995, the Charles-Leopold Meyer Prize of the Academie des Sciences, the Edwin Astwood Award and the Roy O. Greep Award of the Endocrine Society, the CNRS Medal, and the Grand Prix Bettencourt for Medical Research. In 2018, Paolo was elected a fellow of the American Association for the Advancement of Science (AAAS).

For those who knew Paolo well, his legacy is not only his science, but the memory of the exemplary man that had deep compassion for others, followed personal convictions, and saw the beauty and magic in life every day. Paolo's love for astronomy, biology, and the pursuit of a deeper understanding of the complexities and intricacies of nature was his driving force, which was highlighted in the 2013 publication *Ti Sembra il Caso?*, a book of reflections on the nature of chance, circadian

clocks, and the rhythm of life, co-authored with the prize-winning Italian author Erri de Luca. His passion for film, music, great food, and exceptional wine was a testament to Paolo's ability to appreciate the smaller pleasures in life. Not surprisingly, the attention to detail and the warmth with which Paolo pursued science was no different than dinner gatherings at home with Emiliana. Being a guest at their table meant stimulating conversations that ranged widely in topic, progressed in seamless cycles between Italian, French, and English, and were interspersed with outstanding food and wine.

There are few that leave their mark so clearly visible on the world. These special individuals are visionaries in their craft and pave new paths for others to follow. Without that specific intention, and with an incredibly humble approach, Paolo paved not only paths, but roads, highways, and major interstates. While Paolo's vision, creativity, and multi-disciplinary approach within the fields of transcriptional regulation, epigenetic control, metabolism, and circadian rhythms are his lasting scientific legacy, it is his warmth and personality that have left the most indelible mark on those who knew him well.

Paolo is survived by Emiliana Borrelli, herself an eminent prize-winning neuroscientist, his brothers Lucio and Emilio Sassone-Corsi, and their extended families. For those of us fortunate enough to have been able to count Paolo as a close friend, the sadness we feel at his loss is a price we pay for the many years during which he enriched our lives. An irreplaceable loss, Paolo is deeply missed.

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## REFERENCES

Corden, J., Wasylyk, B., Buchwalder, A., Sassone-Corsi, P., Kedinger, C., and Chambon, P. (1980). Promoter sequences of eukaryotic protein-coding genes. Science *209*, 1406–1414.

Nakahata, Y., Sahar, S., Astarita, G., Kaluzova, M., and Sassone-Corsi, P. (2009). Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. Science *324*, 654–657.

Sassone-Corsi, P., Wildeman, A., and Chambon, P. (1985). A trans-acting factor is responsible for the simian virus 40 enhancer activity in vitro. Nature *313*, 458–463.

Sassone-Corsi, P., Lamph, W.W., Kamps, M., and Verma, I.M. (1988). fos-associated cellular p39 is related to nuclear transcription factor AP-1. Cell *54*, 553–560.

Stehle, J.H., Foulkes, N.S., Molina, C.A., Simonneaux, V., Pévet, P., and Sassone-Corsi, P. (1993). Adrenergic signals direct rhythmic expression of transcriptional repressor CREM in the pineal gland. Nature *365*, 314–320.

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