**Presentation title:**

# "THE ENDS AT THE BEGINNINGS"

How Telomere Maintenance Mechanisms Influence Cancer Onset and Progression in Pediatric Neuroblastoma: does Age Make a Difference ?

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**Presentation type:** (**Oral presentation**/ ~~Poster presentation~~)

**Abstract (250-300 words):**

This presentation wants to address the question of the role of telomeres in the onset and progression of the pediatric tumor Neuroblastoma (NB), especially in its more aggressive form: High Risk Neuroblastoma (HR-NB). In Cancer, Telomeres are known to be activated and repaired by two mutually exclusive mechanisms: 1. TEL+ in approximately 85% of cancers, based upon the activation of the Telomerase enzymatic machinery and the Telomerase gene itself (hTERT) and 2. In the remaining 15% of cancers, an ALT+ mechanism is present, defined as Alternative Lengthening of Chromosomes (ALT+): it is based on homologous recombination and replication, but it is poorly understood. In a seminal paper by Cheung et al at MSKCC in 2012, it was initially found that mutations activating the ALT+ pathway seemed to be always present in HR-NBs from the AYA group (Adolescents and Young Adults, > 12 y.o), but totally absent in younger children (Infants 0 – 18 months). This interesting discovery is critically evaluated, because several corrections have been introduced in recent years thanks to more sophisticated NGS technologies, so that the initial values were corrected in a less dichotomized picture, presenting also many exceptions. Two interpretations are then critically evaluated: 1. in one, aging creates very different oncogene dependencies, which can lead to opposite clonal expansions; 2. in an alternative view, oncogenic pathways are differently expressed by the tumour background, because of differential responses to pathogenic/mutagenic insults. Although both explanations are presently possible, the second one better explains the phenomena associated with intra-tumour heterogeneity (ITH), which disrupt cancer clonality. Recent papers dealing with mutational signatures and clock-like mutations are utilized as exemplificatory tools. Special emphasis is placed on ATRX mutations of the ALT+ pathway, since very recent work from the Netherlands suggest that it may affect ribosomal biogenesis. Previous work from the author may be associated to such ALT+ pathways as well to mechanisms related to TEL+ and the reactivation of the Telomerase (hTERT gene).

**Biography (150-200 words):**

Dr. **Ugo Rovigatti** obtained his Ph.D. degree in Molecular Biology with Summa cum Laude in 1973 and in 1999 the Tenured Professorship. From 1979 to 1999 he worked with renown Scientists such as C. Basilico, R. Weiss, H. Varmus, S. Astrin, T. Papas, D. Watson, P. Duesberg, JJ Yunis, J. Bader, J. Trentin, B. Hirt at: ICRF in London, UK; the Rockefeller University in New York; the Fox Chase Institute in Philadelphia; St. Jude Children's Hospital in Memphis, TN; the NCI in Frederick, MD; the Ochsner Foundation-Clinic in New Orleans, LA; the Baylor College of Medicine in Houston, TX, with publications in Blood, Science, MCB etc. Between 1997 and 1999 he was a sabbatical professor in Switzerland (KISPI in Zurich and ISREC in Lausanne). His PI research work has been funded by grants from UICC, ICRETT, SCL, MIUR, MURST etc.

## Research Interests

His interests in cancer research progressed from work on oncogenic viruses –studies on SV-40 and on RSV- to oncogenes/TSGs –studies on cMYC, NMYC and ETS-, Immunoglobulin Rearrangements (childhood cALL, AML and T-ALL) and pediatric neuroblastoma. Starting from neuroblastoma studies, he has developed a model (based on Micro-Foci inducing Virus, MFV) for the origin of specific genetic aberrations, which is being tested by NGS technology. This model was eventually extended from paediatric neuroblastoma to paediatric lymphoma, from which similar viruses were isolated (MFRVs), and prostate carcinoma, where extensive genomic heterogeneity (chromoplexy) is present. In the past few years, he has elaborated a general analysis of cancer modeling, thus clarifying new upstream mechanisms (Genome-Snipers) and explicatory pathways. Very recently, he has provided a clearer explanation of the anti-GD2 therapeutic and curative effects in High-Risk Neuroblastoma (20% OS/PFS improvement especially when N-Myc is amplified), as this ganglioside appears to be a receptor (docking-point) for the virus MFV.