European School of Molecular Medicine

2025 summer call PhD selections

AVAILABLE POSITIONS

Principal Investigator	**Gioacchino Natoli**
Affiliation	European Institute of Oncology, Milan
Title of the proposed project:	Mechanisms and functional implications of control of extragenic transcription
Short description of the project	A fundamental issue in biology is to understand the principles and mechanisms governing the usage of the genomic information as well as the consequences of their deregulation. Mammalian genomes harbor a massive potential for transcription initiation that can pervasively occur at hundreds of thousands of cis-regulatory elements (i.e., enhancers and promoters) that provide modular platforms for the combinatorial binding of transcription factors and the subsequent recruitment of RNA Polymerase II. The ensuing promiscuity of transcription initiation may lead to the unscheduled occurrence of a vast amount of non-coding transcription, with possible harmful effects on maintenance of nuclear organization and genome integrity. Transcription termination pathways mitigate the detrimental consequences of such promiscuous initiation, thus representing cornerstones of genomic regulation in eukaryotes. We recently identified an insofar overlooked complex, Restrictor, conserved from worms to humans and representing a pivotal suppressor of long-range transcription at thousands of extragenic sites, with instead comparatively limited effects on gene transcription. This project now aims at: i) identifying mechanisms executing Restrictor-enforced transcription termination; ii) dissecting the mechanisms explaining the exquisite selectivity of Restrictor for extragenic transcription, and iii) understanding its functional role in the maintenance of genome integrity and nuclear organization. The results obtained will provide critical insights into the regulatory logic and the functional relevance of control of extragenic transcription in higher eukaryotes.
Main research area for the project	Molecular and Cellular Biology
Second research area for the project	
3 key words for project	Non-coding transcription; genomics
Main topic/s of the lab	Transcriptional mechanisms in cancer and inflammation
Short description of the lab activity	Research in the Natoli lab is focused on *molecular mechanisms of transcriptional and epigenetic regulation* in *three different areas*. ***a***) *How cell type-specific transcriptional responses to inflammatory stimuli are mounted* in immune cells and particularly macrophages, the key mediators of innate immunity. Among other findings, we showed that transcription factors driving and maintaining myeloid lineage differentiation specify the cell type-specific repertoire of genomic regions where transcription factors activated in response to environmental stimuli are recruited, thereby establishing the basis for tissue-specific, stimulus-induced gene expression. ***b***) *Mechanisms that control extragenic*

	Pol II activity Following the serendipitous discovery in 2010 of enhancer RNAs in activated macrophages, we became strongly interested in *mechanisms that control extragenic Pol II activity*, which led us to identify the Restrictor complex, today a central focus of our research. ***c***) The third and most recent research branch aims to understand the *regulatory basis of the massive loss of lineage identity observed in pancreatic cancer*, which underlies the extensive non-genetic heterogeneity characteristic of this tumor.
Recent bibliography	1. Activation of endogenous retroviruses and induction of viral mimicry by MEK1/2 inhibition in pancreatic cancer (Cortesi A, Gandolfi F, Arco F, Di Chiaro P, Valli E, Polletti S, Noberini R, Gualdrini F, Attanasio S, Citron F, Ho IL, Shah R, Yen EY, Spinella MC, Ronzoni S, Rodighiero S, Mitro N, Bonaldi T, Ghisletti S, Monticelli S, Viale A, Diaferia GR, Natoli G.) **Science Advances**. 2024 Mar 29;10(13):eadk5386. doi: 10.1126/sciadv.adk5386. Epub 2024 Mar 27. PMID: 38536927 2. Mapping functional to morphological variation reveals the basis of regional extracellular matrix subversion and nerve invasion in pancreatic cancer (Di Chiaro P, Nacci L, Arco F, Brandini S, Polletti S, Palamidessi A, Donati B, Soriani C, Gualdrini F, Frigè G, Mazzarella L, Ciarrocchi A, Zerbi A, Spaggiari P, Scita G, Rodighiero S, Barozzi I, Diaferia GR, Natoli G.) **Cancer Cell**. 2024 Apr 8;42(4):662-681.e10. doi: 10.1016/j.ccell.2024.02.017. Epub 2024 Mar 21. PMID: 38518775 3. Acetyl-CoA production by Mediator-bound 2-ketoacid dehydrogenases boosts de novo histone acetylation and is regulated by nitric oxide (Russo M., Gualdrini F., Prosperini E., Noberini R., Pedretti S., Vallelonga V., Di Chiaro P., Polletti S., Ghirardi C., Bedin F., Cuomo A., Rodighiero S., Bonaldi T., Mitro N., Ghisletti S., Natoli G.) **Molecular Cell** Mar 7; 84(5):967-980.e10. doi: 10.1016/j.molcel.2023.12.033. Epub 2024 Jan 18. PMID: 38242130 4. Restrictor synergizes with Symplekin and PNUTS to terminate extragenic transcription (Russo M., Piccolo V., Polizzese D., Prosperini E., Borriero C., Polletti S., Bedin F., Marenda M., Michieletto D., Mandana G.M., Rodighiero S., Cuomo A., Natoli G.) **Genes & Development** Dec 26, 37(21-24):1017-1040. doi: 10.1101/gad.351057.123 (Online ahead of print). PMID: 38092518 (2023) 5. H3K9 trimethylation in active chromatin restricts the usage of functional CTCF sites in SINE B2 repeats (Gualdrini F, Polletti S, Simonatto M, Prosperini E, Pileri F, Natoli G) **Genes & Development** Apr 1;36(7-8):414-432. doi: 10.1101/gad.349282.121. PMID: 35361678 (2022)
Group composition	4 Phd Students; 6 postdocs; 1 technician; 1 staff member
Institutional page link	https://www.research.ieo.it/research-and-technology/principal-investigators/gioacchino-natoli/