European School of Molecular Medicine

2026 spring call PhD selections

AVAILABLE POSITIONS

Principal Investigator	**GIOACCHINO NATOLI**
Institute of Affiliation	IEO

PROJECT INFO	
Title of the proposed project:	Setting up a photocatalytic proximity labeling platform for high-specificity detection of dynamic molecular interactions in the transcriptional machinery
Short description of the project	Protein-protein interactions are critical for biological processes. Many of these interactions are mediated by protein domains interacting with short sequence stretches (SLIMs, short linear motifs). Because the surface buried in SLIM-domain interfaces is limited to 3-5 aa, the resulting interactions are usually characterized by low-affinity and transience, which on the one hand allows for the dynamic nature of contacts among proteins engaged in signaling and transcription, but on the other poses challenges when attempting to detect them through traditional protein-protein interaction discovery techniques selecting for stable interactions, such as immunoprecipitation-mass spectrometry. For this reason, innovative approaches capable of capturing transient interactions are being actively developed, including methods in which proteins in close proximity to a bait (and therefore likely to include direct binders) are selectively tagged in living cells and subsequently identified by mass spectrometry. Among these "proximity labeling" strategies, photocatalytic proximity labeling offers particularly high spatial and temporal precision: upon light activation, a catalyst fused to or recruited near the bait generates short-lived reactive species that covalently tag only proteins within a very small labeling radius and during a tightly controlled time window (see Science 367, 1091–1097 (2020) and Science 385, eadl5763 (2024)). In this project, we will set up these techniques and apply them to the exploration of mechanisms involved in dynamic control of transcription in mammalian cells
Main research area for the project	Molecular Biology
Second research area for the project	Transcription control
3 key words for the project	Transcription; proximity labeling; mass spectrometry

LAB INFO	
Main topic/s of the lab	Transcriptional regulation
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) Sequence-specific RNA recognition drives Restrictor-mediated termination of extragenic transcription (Polizzese D. … Natoli G.) **Molecular Cell** 2026 Mar 19;86(6):1046-1060.e10. doi: 10.1016/j.molcel.2026.02.006, PMID: 41780532. 2) Control of myeloid lineage fidelity and response to stimuli by ISWI-enforced nucleosome phasing (Polletti S… Natoli G) **Immunity** 2025 Oct 14;58(10):2402-2418.e8. doi: 10.1016/j.immuni.2025.09.002. PMID: 41005292. 3) Mapping functional to morphological variation reveals the basis of regional extracellular matrix subversion and nerve invasion in pancreatic cancer (Di Chiaro P… 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 4) 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 5) 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)

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Lab website link	https://www.research.ieo.it/research-and-technology/principal-investigators/gioacchino-natoli/