2025 summer call PhD selections

AVAILABLE POSITIONS

| Principal Investigator | Gioacchino Natoli |
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| **Affiliation** | European Institute of Oncology, Milan |
| **Title of the proposed project:** | Molecular bases and functional implications of cellular heterogeneity in pancreatic cancer |
| **Short description of the project** | Because of its progressively increasing incidence, lack of feasible population screenings and limited therapeutic efficacy, PDAC will become the second cause of cancer deaths by 2040. Due to advanced disease at diagnosis, 80-85% of PDAC patients cannot undergo surgery and have a median life expectancy lower than 6 months. A large share of treatment failures is rooted in the peculiar biological properties of this cancer and specifically in its extensive cellular heterogeneity. Current data indicate that the contribution of genetic diversity to transcriptional heterogeneity in PDAC, albeit detectable, is lower than that of instructive signals generated by the tumor microenvironment (TME). Therefore, different PDAC "cell states" appear to be mainly driven by local tissue signals rather than being hardwired in cancer cell genomes. The overall objective of this project is to apply a combination of computational approaches to identify the local signals and the downstream gene regulatory networks controlling the generation and maintenance of different PDAC states and to determine their distinctive functional properties |
| **Main research area for the project** | Computational biology |
| **Second research area for the project** | Cancer Biology |
| **3 key words for project** | Pancreatic cancer; genomics; heterogeneity |
| **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 |

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| | underlies the extensive non-genetic heterogeneity characteristic of this tumor. |
| **Recent bibliography** | 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.)<br>**Science Advances**. 2024 Mar 29;10(13):eadk5386. doi: 10.1126/sciadv.adk5386. Epub 2024 Mar 27.<br>PMID: 38536927<br><br>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.)<br>**Cancer Cell**. 2024 Apr 8;42(4):662-681.e10. doi: 10.1016/j.ccell.2024.02.017. Epub 2024 Mar 21.<br>PMID: 38518775<br><br>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.)<br>**Molecular Cell** Mar 7;84(5):967-980.e10. doi: 10.1016/j.molcel.2023.12.033. Epub 2024 Jan 18.<br>PMID: 38242130<br><br>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.)<br>**Genes & Development** Dec 26, 37(21-24):1017-1040. doi: 10.1101/gad.351057.123 (Online ahead of print). PMID: 38092518 (2023)<br><br>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)<br>**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/ |