UNIVERSITA' DEGLI STUDI DI TORINO
DIPARTIMENTO DI BIOTECNOLOGIE MOLECOLARI E SCIENZE PER LA SALUTE
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The group headed by **Prof. Valeria Poli at the Department of Molecular Biotechnology and Health Sciences, University of Turin**, is looking for motivated candidates, committed to cancer research, to be enrolled as post-doctoral fellows and take part in the AIRC-funded project entitled ***"Exploiting network analysis to unravel breast cancer molecular features and identify novel targets"***.

The post-doctoral fellowship (Assegno di Ricerca), potentially funded for three years, will have a gross annual salary in the range between 25,000 and 30,000 Euros, depending on experience.
The candidate will have proven experience in cell culture (growth, characterization, transfection, infection, cloning), in the main molecular and cell biology techniques and in biochemical analyses. Previous experience in cancer research and bioinformatics skills will be considered a plus.

The project, the abstract of which is appended below, is based on an analysis of gene co-expression networks in mammary tumors (Savino et al., doi: http://dx.doi.org/10.1101/570051) that allowed us to identify potential central regulators of gene expression modules strongly correlated with poor prognosis in triple-negative / basal-like breast tumors. The goal is to functionally and transcriptionally validate the identified targets in a series of human breast cancer cell lines.

Interested candidates might feel free to contact Valeria Poli for further details at the following address: valeria.poli@unito.it, Department of Molecular Biotechnology and Health Sciences, University of Turin, Molecular Biotechnology Center, Via Nizza 52, 10126 Turin.

Applications, by email at the above address, must contain a detailed curriculum, a letter of intent and the contact of 3 potential referees. The selection will be based on curriculum and interview, online or in person depending on the possibilities. Deadline for applications is December 10, 2022.

Selected References of the laboratory

1. Savino et al., Network analysis allows to unravel breast cancer molecular features and to identify novel targets. 2019 BiorXive, doi: http://dx.doi.org/10.1101/570051.
2. Avalle L, Raggi L, Monteleone E, Savino A, et al, STAT3 induces breast cancer growth via ANGPTL4, MMP13 and STC1 secretion by Cancer Associated Fibroblasts, 2022 Oncogene, Online ahead of print, doi: 10.1038/s41388-021-02172-y.
3. Savino A, De Marzo N, Provero P, Poli V. Meta-Analysis of Microdissected Breast Tumors Reveals Genes Regulated in the Stroma but Hidden in Bulk Analysis. Cancers 2021, 13(13):3371. doi: 10.3390/cancers13133371.
4. Savino A, Provero P and Poli V. Differential Co-Expression Analyses Allow the Identification of Critical Signalling Pathways Altered during Tumour Transformation and Progression. *Int. J. Mol. Sci.* **2020**, *21*(24), 9461; https://doi.org/10.3390/ijms21249461.

5. Avalle L, Marino F, Camporeale A, et al. Liver-Specific siRNA-Mediated Stat3 or C3 Knockdown Improves the Outcome of Experimental Autoimmune Myocarditis. Mol Ther Methods Clin Dev 2020, 18:62-72. DOI 10.1016/j.omtm.2020.05.023.
6. Avalle L, Camporeale A, Morciano G, Caroccia N, Ghetti E, Orecchia V, Viavattene D, Giorgi C, Pinton P, Poli V. STAT3 localizes to the ER, acting as a gatekeeper for ER-mitochondrion Ca2+ fluxes and apoptotic responses. (2018) Cell Death Differ. 2019, 26(5):932-942. doi: 10.1038/s41418-018-0171-y.
7. Avalle L, Incarnato D, Savino A, Gai M, Marino F, Pensa S, Barbieri I, Stadler MB, Provero P, Oliviero S, Poli V. MicroRNAs-143 and -145 induce epithelial to mesenchymal transition and modulate the expression of junction proteins. (2017) Cell Death Differ., 24(10):1750-1760. doi:10.1038/cdd.2017.103. PMID: 28644441.
8. Avalle L, Camperi A, Camporeale A and Poli V. STAT3 in cancer: A double edged sword. (2017) Cytokine 98,: 42-50 doi: 10.1016/j.cyto.2017.03.018. PMID: 28579221.

ABSTRACT

Background

Gene co-expression networks have been used to define prognostic gene signatures and centrally connected genes as therapeutic targets in cancer. However, most of these studies are purely descriptive, not fully exploiting the wealth of information hidden in the constructed networks to investigate specific biological hypotheses. Moreover, networks have never been compared across breast cancer (BC) subtypes, despite the potential usefulness of such an approach to understand how specific molecular features are established and regulated.

Hypothesis

We posited that reconstructing BC transcriptional networks could allow us to address biological questions related both to BC in general and to specific BC sub-types. Allowing to formulate testable hypotheses about how biologically/clinically relevant gene expression patterns are established and maintained in specific BC sub-types, such an approach could be exploited to identify and validate potential key regulatory genes, developing them into therapeutic targets.

Aims

We have implemented a workflow based on the analysis of the METABRIC BC gene expression dataset, which we have validated both based on database analyses and on experimental approaches. We aim at confirming its validity as a tool to dissect molecular pathways linked to BC aggressiveness, particularly basal-like BC for which a targeted treatment is still lacking, identifying key regulatory genes amenable to therapeutic intervention.

AIM1) Discovering how clinically relevant BC gene expression patterns are established by identifying transcriptional regulatory hubs and validating them as therapeutic targets.

AIM2) Identifying drugs able to target relevant co-expression modules via a drug repositioning approach.

AIM3) Identifying central regulators of specific stromal signatures.

AIM4) demonstrating siRNA-mediated in vivo targetability of identified transcriptional regulators.

Experimental Design

The four experimental WPs aim at identifying and functionally testing the regulatory hubs of specific modules correlated with BC aggressive features (WP1), and with stroma-tumour cross-talk (WP3). Functional testing will be performed by gain and loss of function experiments in selected cell lines, followed by in vitro and in vivo assays and by RNA profiling to dissect their regulatory properties. We will identify drugs potentially hitting the relevant networks and test their efficacy in a high content screening, followed by in vivo validation in NSG mice (WP2). Finally, we will focus our efforts on demonstrating the feasibility of targeting regulatory hubs via in vivo siRNA delivery (WP4), and we will develop a web-based tool to interrogate our networks (WP5).

Expected Results

We expect to identify central regulators of BLBC and of stromal gene expression networks which inhibition can disrupt whole clinically relevant modules, and to develop them into therapeutic targets using both RNA- and drug-based approaches.

Impact On Cancer

Despite dramatic progress in the knowledge of BLBC gene expression patterns and biological features, translation into novel treatments has been difficult, due to the challenges of achieving effective in vivo inhibition and to the partial effects and resistance often observed by targeting single molecules. Our work will allow to discover therapeutic targets able to inhibit the expression of whole networks, potentially bypassing this problem. Moreover, the identification of already approved drugs and FDA-approved RNA-based treatments as network disruptors will provide reagents ready-to-test for the clinics.