**Targeting the DNA damage response as a novel therapeutic strategy for high risk locally advanced prostate cancer**

**Proposer: Prof. Sabrina Arena**

The project aims to define novel therapeutic strategies for high-risk locally advanced prostate cancer (PC) by exploring the interplay between DNA damage response inhibitors (DDRi) and androgen receptor inhibitors (ARi). The primary goal is to contribute to a better understanding of the crosstalk between AR and DDR and establish a biobank of 2D and 3D patient-derived preclinical models.
The objectives and outcomes of the project are clearly described, adequate, and appropriate.
The proposed idea is moderately original and innovative, being the interplay between AR signaling and DDR in PC already extensively investigated. The procedures and methodologies of genomic analysis, functional testing, and validation in clinically relevant 2D-3D models are clearly described, adequate and well- integrated. However, the rate of success of these cultures is uncertain.
The project demonstrates a more than average standard of quality excellence.
The overall strategy, methodology, and analyses outlined in the project are well-reasoned and appropriate for accomplishing the specific aims. The project has a logical progression, starting with the establishment of a biobank of patient-derived 2D-3D cell cultures (with the uncertainty to achieve a good number of samples), followed by the study of DDR alterations in therapy response to AR inhibitors, the design of potential therapeutic strategies, and finally, the validation of results in clinically relevant models.

The timeline of 24 months seems underestimated for achieving these outcomes, especially considering the number and complexities of tasks and accomplishments.


Università degli Studi di Torino
Dipartimento di Oncologia
Regione Gonzole 10 - 10043 Orbassano (To)
Tel (011) 670 5403 | Mail direzione.onco@unito.it

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**Colorectal cancer metastatization: WNT pathway modulation and novel cellular signaling routes for Neuroligin 1**

**Proposer Prof. Marco Arese**

This project is aimed at investigating the functional crosstalk between NLGN1 and WNT in CRC pathogenesis with particular interest in the process of metastatization. The proposal will elucidate the molecular circuits involved in NLGN1 and WNT crosstalk, evaluating also the role of NLGN1 in the modulation of TAM biology. Finally, the impact of exosomes in NLGN-mediated TAM biology will be investigated as well. The methodologies are suitable to reach the proposed outcomes. Tasks integration will render the project more robust. The experimental plan regarding the study of TAM is not clearly described, although potentially innovative. The research strategy is clear, although extremely articulated and complex. The high number of tasks negatively impact in terms of feasibility as the complexity of the global experimental plan is high. It is unlikely that the proposed outcomes and objectives can be fully accomplished in two years. Less Aims and Tasks could render this project more suitable for a RiLo Grant. The requested budget exceeds that allocated for the RiLo. The infrastructures and the research team are competitive. The applicant has a strong commitment in the study of NEUROLIGIN 1 in colorectal cancer. Overall, this is a good project that can benefit of a revision, reducing the complexity of the research proposal.

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**Unraveling the transcriptional and functional program triggered by TFEB in lymphatic endothelial cells**

**Proposer: Dr Elena Astanina**

**Significance**

**Are the objectives and outcomes of the project clearly described, adequate, and appropriate?**

The general objectives should be more precise; however, since this is a seed project, this is somehow acceptable. Main criticism: the potential outcomes are totally ascribed to the key role of TFEB on vascular endothelial cells, as no potential impact on LEC biology is provided.

**Are proposed idea, procedures, or methodologies innovative, original, clearly described, suitable and properly integrated?**

The proposed idea is not original; the procedures and methodologies are not innovative. Main criticisms: only in vitro assay with one Human dermal lymphatic microvascular endothelial cells and commercially available cell lines isolated from lymph node metastases. The project is mainly based on the potential phenotype observed in HDEC cell upon a loss of function approach. This kind of approach is weak. Since the biochemistry and the biology of TFEB are well established, additional methodologies should be included to clarify its potential role in lymphatic metastatization (i.e. Mass Spect analysis of TFEB interactors in LEC cells). It is not clear why the gain of function approach is used only in Task3 to identify TFEB-target genes,

**Does the project exhibit standards of high quality excellence?**

Overall, the project is of potential interest as TFEB plays a pivotal role in metabolism and tumor biology. However, the proposal lacks a robust architecture and requires several methodological improvements.

**Feasibility**

**Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?**

The information collected from in vitro experiments will serve as the basis for the generation of LEC-specific Tfeb deletion and Tfeb overexpression mouse tumor models. Main criticisms: the proposed strategy is based only on the key role of TFEB abundancy in LEC. TFEB is directly modulated by mTOR via phosphorylation. Thus, additional aspects of TFEB biology need to be investigated to clarify its potential role in lymphatic metastatization.

**Are expected results or outcomes clearly stated, and achievable within the allotted time frame (24 months)?**

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Yes, but as this is a very preliminary project there are some important pitfalls related to the discovery phase (e.g. in the case TFEB would not have a clear role in LEC, most of the tasks would not be pursued). The outcomes and the expected results can be reached in the timeframe of the RILO projects, but possibly without robust results in 24 Months .

Not all the reviewers judged the project worth of funding

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**Radiomics in-vivo study of pulmonary lesions diagnosed with ct-guided percutaneous bioptical approach: impact of radiation dose levels and reconstruction parameters**

**Proposer: Dr Maurizio Balbi**

The project has the ambitious purpose of investigating the robustness of a panel of predictive radiomic features in the diagnosis of lung lesions, including those identified with screening programs, and suitable to percutaneous biopsy procedures.

The topic itself is highly original and innovative and the research team clearly describes the project methodology, purposes and outcomes.

The project meets the requirements for a standard quality of excellence.

The overall strategy, methodology and analyses are well-reasoned and appropriate to accomplish the specific project aims. The research teams properly highlights the main pitfalls of the project, in particular the possible uncertainties in stability and reproducibility of the radiomic features detected in this analysis.

The timeline of 24 months seems appropriate to reach the goals of the project. Anyway, the timepoints of project progress in the allotted time frame are not clearly stated and this represents a potential weak spot.

Overall, the project is unanimously positively evaluated for its high quality of excellence and for its focus on a cutting edge technology in oncologic research and finally deemed worthy of funding.

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**Characterization of the role of peroxisomes and actin cytoskeleton dynamics in oxygen-mediated directed cell migration (aerotaxis)**

**Proposer: Prof. Enrico Bracco**

The seed project is aimed at characterizing the role of peroxisomes and cytoskeleton dynamics in aerotaxis, which is involved in tumor metastatization. The proposal will investigate and translate recent discoveries on aerotaxis (obtained on the social amoeba Dictyostelium discoideum) into mammalian cells, focusing on subcellular dynamics, peroxisomes and actin cytoskeleton. The PI has a consolidated background in the field of aerotaxis. The proposal is adequate but seems ambitious with many tasks, that might limit the chance of success. The methodologies and the analyses are appropriate to reach only in part the proposed objectives and outcomes. Some criticisms emerge on the study of aerotaxis in tridimensional models. The research strategy is in general quite clear, although the project is very articulated and complex. In terms of feasibility some concerns emerge regarding the possibility to accomplish all the proposed 8 Tasks in two years. This is an interesting seed project with potential innovative elements but requires a systematic revision of the research strategy.

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**Metabolic analysis of NSCLC to improve patient stratification and identify new biomarkers of cancer progression and metastasis.**

**Proposer: DR Gabriella Doronzo**

Dot. Doronzo via a preclinical platform will develop a predictive metabolic signature to better profiling stage I-IIIA adenocarcinoma NSCLC and to identify new therapeutic targets involved in tumour progression, metastasis and drug resistance. The study intends to explore in greater detail (prospectively) the role of metabolomics in early stage lung tumours based on an exploratory cohort whose data are already available to the investigator. The possibility of accessing other samples from another DB makes the study feasible in the time foreseen by the financing. The applicant already has research experience in the specific sector. The project will be organized in three phases: "screening phase" based on analysis of transcriptome data of adenocarcinoma NSCLC(stage IB-IIIA) tissues collected from patients enrolled in the prospective observational clinical trial PROMOLE; "validation phase" will support and be able to confirm the screening analysis on a portion of the PROMOLE patients; "application phase" that will be performed on a new unselected cohort of adenocarcinoma NSCLC patients enrolled in the prospective observational clinical trial PROFILING. The preliminary data clear and well analysed, the only perplexity is about 3 task 4. Most of signatures are prognostic rather than predictive. The study design is appropriate and the analyses well-reasoned to accomplish the specific aims of the project and the "screening phase" will be support by the "Validation phase". It is not clear in "screening phase" which prognostic clinical variables, if any, will be plotted along with metabolic groups in order to clarify the exact role of the metabolic classification in terms of prognostic stratification. The project lacks a GANTT diagram to properly assess this point. The objectives of the project are well and clearly described, the outcomes adequate and appropriate. The proposed idea is appropriate; the procedures are clearly described; the methodologies are suitable.

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**Rewiring cancer stem cell metabolism as a strategy to overcome cancer drug resistance**

**Proposer: DR Joanna Kopecka**

**Significance**

**Are the objectives and outcomes of the project clearly described, adequate, and appropriate?**

The objectives are a bit fragmented, too many models not exactly comparable to each other (cell lines, PDO, PSC-derived organoids); the outcomes are not so adequate and appropriate.

**Are proposed idea, procedures, or methodologies innovative, original, clearly described, suitable and properly integrated?**

The proposed idea is not original, considering that it is a seed project; the proposed methodological approaches are clearly described and the methodologies are standard.

**Does the project exhibit standards of high quality excellence?** Some reviewers commented on the low quality of the project.

**Feasibility**

**Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?**

The project lacks theorical preliminary data available in public datasets e tools. The strategy is not always adequate as it does not take into account the heterogeneity between tumors and the variability in the dedifferentiation result, thus the general value of results is difficult to assess. As discussed by the proponent, some pitfalls may be encountered especially when dedifferentiating multiple cell lines and when trying to establish organoids from these lines. Another issue might be that dedifferentiation with chemotherapy only approach may not encompass the real world scenario (e.g. prostate cancer is usually treated with uprfront castratation with/without chemotherapy and/or ARSI; breast cancer is treated according to the subtype sometimes with hormone therapy with or without CDK4/6 inhibitors, HER2 pos tumors with targeted agents; NSCLC is treated depending on the presence or absence of driver; colorectcal cancer depending on the molecular profile). Indeed, creating CSCs with chemo alone may not be a strong surrogate of what happens in the clinical scenario.

**Are expected results or outcomes clearly stated, and achievable within the allotted time frame (24 months)?**

Too many objectives make the proposed analyses excessively long for the duration of the project

Not all the reviewers judged the project worth of funding

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**Multi-omics and hypothesis-driven investigation of lipid metabolism in breast cancer**

**Proposer: Prof. Letizia Lanzetti**

Increased lipid metabolism appears to be a key feature of the most aggressive breast tumors. Dysregulation of lipid metabolism occurs through both cell-autonomous events and stromal interactions, mostly between adipocytes and breast cancer cells.

Prof. Lanzetti in its project aims at 1) identifying "lipid signatures" that correlate with aggressiveness within the Luminal breast cancer subtype by spatial lipidomic coupled to transcriptomic and 2) reveal signaling pathways that regulate lipid storage and catabolism in breast cancer cells by studying TBC1D7, a gene whose upregulation correlates with worse prognosis in breast cancer patients, and that controls both lipid synthesis and consumption.

The proposed idea, the procedures and methodologies are innovative, original, quite clearly described, suitable and properly integrated.

However the following concerns are highlighted:

1) It is not completely clear whether the study of TBC1D7 is only on luminal breast cancer or also in TNBC.

2) The large amounts of data that will be generated, raise the worry that PI might not have the ability to accomplish all that has been proposed in 24 months

3) Budget might not be sufficient to cover the cost of the entire project.

4) External collaborations should not be integrated in current application

Overall, the research proposed shows high quality of excellence, it is significant, mostly feasible and is therefore worthy of funding.

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**Role and function of adult thymic stem cells in Thoracic Oncology.**

**The Adult Thymus Project (ATP)**

**Proposer: Prof. Francesco Leo**

The projects aims at investigating the role and function of adult thymic stem cells. Upon the confirmation of their presence in healthy adults as well as in patients with thoracic tumors, the project aims at isolating and expanding them as well as studying their interactions with T lymphocytes. Finally, the proponent aims at reconstruct decellularized thymic 3D scaffold to be recolonized by thymic stem cells. While the project is undoubtedly ambitious, and the proposed collaboration with a foreign partner is appreciable, some major points are not addressed:

- The PI role seems to be at least marginal;
- The experimental design (including procedures and analyses) is not precisely detailed;
- While the objectives are 4, only two of them are analyzed by the proponent;
- The project lacks any timeline/GANTT that could be used to assess if the allotted time frame will be enough to reach any of the proposed goals.

Considering the aforementioned limitations, even if the scientific potential of the whole aim is notable, the project does not reach the necessary score to be financed.

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**Unhide genetic and metabolic vulnerabilities of PTEN null colorectal cancer that could overcome cancer therapies resistance**

**Proposer: DR Annalisa Lorenzato**

This project will define PTEN-related vulnerabilities in CRC, identifying predictive biomarkers critical to improve CRC patient survival. Since the role of PTEN as biomarker at both the predictive and prognostic levels remains controversial, this topic requires further investigation. Specifically, a Crispr/Cas9 screening will be applied in a panel of CRC cells to identify genetic vulnerabilities, the key candidates will be tested in terms of DDR and metabolomics. The research plan is logic and well-articulated. The expertise of the proponent in the field is solid and competitive. The objectives and the outcomes are clear and well-described. The expected results are, however, ambitious. The overall strategy and the methodologies are innovative but not totally original. Overall, this is a high-quality project with elements of excellence. The proposed strategies (i.e. Crispr/Cas9 screening, metabolomics and pharmacogenomic) are state of the art, appropriate and accurately described. Some concerns arise in terms of feasibility for the complexity of the proposed methodologies, high number of cell lines and preclinical models included in the project. The budget is not accurately described and could likely cover only in part the proposed project. The proposal is very competitive but in terms of feasibility there are concerns related to its full accomplishment in the timeframe of the RiLo.

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**Between endothelial and sarcomatous identity: Angiosarcoma Preclinical Platform EStablishment (APPLES).**

**Proposer: DR Alessandra Merlini**

The project proposal aims at integrating data from both genomic, transcriptional and immunophenotypic analyses and functional characteristics of response/resistance to treatment in the model of angiosarcoma (AS). The project meets the strong needs of improving knowledge on the pathogenesis and of identifying optimal therapeutic strategies in this highly aggressive type of neoplasm.

Main innovations of the study are:

- the high translational relevance of the project, with a strong integration between basic and clinical researchers;

- a clearly defined timeline and a well-constructed overall workflow;

- strong preliminary data already providing reliability of the pre-clinical models;

- an active and efficient protocol of sarcoma sample accrual (Leopard);

- the establishment of optimal experimental conditions for in vitro and in vivo AS models;

- the establishment of research models that may be source of material/investigation for future studies by the group or external collaborators.

Feasibility is sustained by the expertise of the PI, the network of collaborators (including centers participating to sample collection and researchers active in the PI's group) and all the equipment available at the Gilardi's laboratory of the Department of Oncology, with an easy access "in house" to all technological platforms needed for the project.

A robust regulatory/ethics framework and data collection system is also already established.

Main weaknesses of the project proposal are:

- a possible limited access to drugs for experimental testing;

- the rarity of the disease; however, for this latter aspect, the PI's group has already demonstrated a high rate of sarcoma sample collection (90 samples in the first year of accrual, including angiosarcomas) since the activation of the Leopard protocol.

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**A personalized translational platform to improve clinical management of young (under-50) lung cancer patients**

**Proposer: Prof. Luisella Righi**

The project aims to setting up a platform that will refine the diagnostic and molecular classification of non-small cell lung cancer in young patients by analyzing molecular alterations in tumor tissue and the molecular mechanisms responsible of molecular targeted therapy response in primary cells and to enroll patients in clinical trials using EPROPA platform promoted by WALCE.

Strengths:

- the topic is interesting and clinically relevant
- methodologies are suitable and properly integrated
- the proposed strategy is appropriate
- the PI has a valuable expertise and scientific curriculum

Weaknesses:

- the project lacks in terms of innovation (the study of genomic profile in young patients has been extensively investigated as correctly described in the background section)
- more sophisticated analyses should be taken in consideration to better characterized poor responsive patients
- some preliminary data are lacking (e.g. the rate of success of 2D-3D cultures), the time to obtain cases of explorative cohort)
- the project seems overambitious considering the timeframe (24 months)

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**Cutaneous squamous cell carcinoma: a study on the risk of progression and the immune profile across the different stages**

**Proposer: Prof. Rebecca Senetta**

This proposal is aimed at identifying prognostic and predictive biomarkers of response to CPI (i.e. cemiplimab) in poorly differentiated (G3)-Cutaneous squamous cell carcinomas (cSCC, exhibiting poor prognosis), including also locally advanced or progressed cSCC treated with immunotherapy. The objectives and the research strategy are clearly described. The methodology is in part adequate to reach the proposed outcomes, additional analyses should be included in the proposal. The research plan is adequate with elements of innovation. The large cohort of retrospective samples is a strength of the project while the total absence of functional validation analyses is a limitation. The possibility to collect biopsies during immunotherapy treatments is relevant to identify key biomarkers and improve patient stratification. This is a good project, not totally original in the highly competitive landscape of biomarkers of ICI response. The research team is robust and competitive in the field. In terms of feasibility, the PI has the expertise and the technological infrastructure to accomplish the proposal. The time-frame of 24M appears reasonable for the proposed studies.

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**Defining the role of the transmembrane protein tyrosine phosphatase PTPRF in autophagy to target BRAF-mutated melanomas and normalize cancer blood vessels**

**Proposer: DR Donatella Valdembri**

The Valdembri's project aims at evaluating the correlation between PTPRF and autophagy markers expression in human melanoma cells and tumour endothelial cells, on specimens derived from cancer patients, characterizing the molecular pathway(s) by which PTPRF and its regulator PPFIA1 control autophagy in endothelial cells and assessing the effect of PTPRF inhibitors on autophagy induction, tumour growth and vessel normalization in murine melanoma models in combination or not with targeted therapy. The aims are the same as the dot. Valdembri described in the RILO 2022.

In endothelial cells dot. Valdembri in 2016 found that: PTPRF and PPFIA1 reside at focal adhesions, where these proteins drive the basolateral exocytosis of fibronectin containing post-Golgi carriers and contribute to establishing the functional apicobasal organization; while the silencing of PTPRF strongly increases AKT signaling, the lack of PPFIA1 impairs AKT phosphorylation; AKT phosphorylation and the ensuing mechanistic target of rapamycin (mTOR) activation inversely correlated with autophagic flux induction.

The preliminary data are the same as the Valdembri's RILO 2022 and show that PPFIA1 and PTPRF oppositely control autophagy induction, and PTPRF promote autophagy through AKT-mTOR-TFEB axis. While preliminary data on PTPRF in endothelial cells metabolism are convincing, the potential impact of PTPRF in melanoma pathogenesis is weak. It is not clear how IHC analysis (which is not quantitative by definition) on primary melanoma specimens can dissect in a very fine/subtle manner the role of autophagic markers. There are no evidences that autophagic markers, especially their subcellular localization, can be defined and quantified using standard IHC analysis. The proposal lacks some numbers: how many normal skin/nevi specimen will be used to make a comparison with melanoma cases? Although maybe implied, is the project on BRAF mut (V600?) only cases?

The methological part is clearly described but not innovative. The tasks are correctly integrated but sevaral methodological limitations.

The project benefit of the robust background of the PI. However, it is too descriptive and vast. It is unclear the real impact in terms of outcomes.

In terms of feasibility the project is very ambitious. Several in vitro tasks, including also in vivo experiments.