# BANDO GIOVANI RICERCATORI 2009

**Ministero della Salute – Direzione Generale della Ricerca Scientifica e Tecnologica**

Application resume

**Title: Inhibition of phosphatidylcholine-specific phospholipase C as a new strategy to counteract tumor-promoting inflammation**

**Code** GR-2009-1596613
**Institution accepting the project:**
**Type of research:** Biomedical

Length (months) 36

**Total budget of the project** € 521.400,00

Funding required to Ministry of Health € 415.000,00

**Total amount of co-financings** € 0,00
**Institutional resources** € 106.400,00

## NIH primary classification

IRG: Oncology 1 -Basic Translational

**Study section:** Tumor Cell Biology -TCB
**Keyword:** OBT-TCB-1095 -The analysis of the composition and function of signaling complexes and their interactions among different signaling pathways in the context of tumor biology and tumor progression

## NIH secondary classification

**IRG (2):** Oncology 1 -Basic Translational
**Study section (2):** Tumor Microenvironment -TME
**Keyword (2):** OBT-TME-1100 -Dynamics of cell-cell communication for tumor cell survival, growth and invasion focusing on cell adhesion molecules, cell junctions, as well as intercellular signaling and production of paracrine factors, chemokines, and inflammatory cytokines
**IRG (3):** N/A
**Study section (3):** N/A
**Keyword (3):** N/A

## Principal Investigator

Name: Spadaro Francesca
**Role:** RICERCATORE
**Date and place of birth :** 09/07/1976 , Roma (RM)
**Address:** Senorbi, 176, 00148 Roma (RM)
**Phone number 1:** 0649902966
**Phone number 2:** 0649902552

# Profile of the principal investigator

## Selected publications 2001-2010


1.Ramoni C., F. Spadaro, M. Menegon, F. Podo. 2001. Cellular localization and functional role of phosphatidylcholine-specific phospholipase C in Natural Killer cells. **J. Immunol.**, 167: 2642-2650.

2.Piccolella E., F. Spadaro, C. Ramoni, B. Marinari, A. Costanzo, M. Levrero, L. Thompson, R. T. Abrahm and L. Tuosto. 2003. Vav-1 and the IKKalpha subunit of IkB kinase (IKK) functionally associate to induce nuclear factor-kB activation in response to CD28 engagement. **J. Immunol.**, 170: 2895-2903.

3.M.G. Quaranta, B. Mattioli, F. Spadaro, E. Straface, L. Giordani, C. Ramoni, W. Malorni and M. Viora. 2003. HIV-1 Nef triggers Vav-mediated signaling pathway leading to functional and morphological differentiation of dendritic cells. **Faseb J.**, 17:2025-2036.

4.L. Fantuzzi, F. Spadaro, G.Vallanti, I. Canini, C. Ramoni, E. Vicenzi, F. Belardelli and S. Gessani. 2003. Endogenous CCL2 (monocyte chemotactic protein-1) modulates human immunodeficiency virus type-1 replication and affects cytoskeleton organization in human monocyte-derived macrophages. **Blood**, 102:2334-2337.

5.C. Ramoni, F. Spadaro, B. Barletta, M.L. Dupuis and F. Podo. **2004**. Phosphatidylcholine-specific phospholipase C in mitogen-stimulated fibroblasts. **Exp. Cell Res.**, 299:370-382. (F. Spadaro and C. Ramoni contributed equally to this work).

6.E. Iorio, D. Mezzanzanica, P. Alberti, F. Spadaro, C. Ramoni, S. D'Ascenzo, D. Millimaggi, A. Pavan, V. Dolo, S. Canevari and F. Podo. 2005. Alterations of choline phospholipid metabolism in ovarian tumor progression. Cancer Research, 65:9369-9376.

7.F. Spadaro, S. Cecchetti, M. Sanchez, C.M. Ausiello, F. Podo and C. Ramoni. **2006**. Expression and role of phosphatidylcholine-specific phospholipase C in human NK and T lymphocyte subsets. **Eur. J. Immunol.**, 36:3277-3287.

8.L. Fantuzzi, F. Spadaro, C. Purificato, S. Cecchetti, F. Podo, F. Belardelli, S. Gessani and C. Ramoni. 2008. Phosphatidylcholine-specific phospholipase C activation is required for CCR5-dependent, NF-kB-driven CCL2 secretion elicited in response to HIV-1 gp120 in human primary macrophages. **Blood,** 111:3355-3363.

9.F. Spadaro, C. Ramoni, D. Mezzanzanica, S. Miotti, P. Alberti, S. Cecchetti, E. Iorio, V. Dolo, S. Canevari and F. Podo. **2008**. Phosphatidylcholine-specific phospholipase C activation in epithelial ovarian cancer cells. **Cancer Research**, 68:6541-6549.

10.S. Parlato, G. Romagnoli, F. Spadaro, I. Canini, P. Sirabella, P. Borghi, C. Ramoni, I. Filesi, S. Biocca, L. Gabriele, F. Belardelli. 2010. LOX-1 as natural IFN-alpha-mediated signal for apoptotic cell uptake and antigen presentation in dendritic cells. **Blood**, 115:1554-1563.


h-index (all publications): 9

## Rational purposes and specific impacts on the subject……

In the past ten years we learned a great deal about the different mechanisms by which cancer and inflammation intersect and it is now well accepted that inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression (Grivennikov SI et al, Cell 2010). What makes the same inflammatory response anti-tumorigenic in one cancer and pro-tumorigenic in another remains largely unknown and elucidation of the molecular pathways governing the dynamic cross-talk between immune and cancer cells could lead to the identification of new target molecules for cancer therapy, diagnosis and prevention.

An aberrant phosphatidylcholine (PC) metabolism is recognized as a hallmark of several cancers (Podo F et al, Curr Med Imaging Rev 2007). During malignant transformation the levels of phosphocholine (PCho) strikingly increase resulting in a remarkable PCho accumulation, as detected by magnetic resonance spectroscopy (MRS) in preclinical models and confirmed by in vivo examination of cancer patients.
Our research group, as first, showed that the elevated PCho pool detected in epithelial ovarian carcinoma cell lines not only resulted from upregulation/activation of choline kinase, well known for its implications in human carcinogenesis (Janardhan S et al, Curr Med Chem 2006), but also from protein overexpression and activation of a PC-specific phospholipase C (PC-PLC) (Iorio E et al, Cancer Res 2005, 2010). In particular, we reported that PC-PLC exhibited different cellular localization in relation to tumor progression, massively accumulating on the surface membrane of highly aggressive ovarian cancer cells, which underwent a significant G0/G1 cell cycle arrest due to PC-PLC inhibition (Spadaro F et al, Cancer Res 2008). Although the mammalian PC-PLC has not yet been cloned, many evidences have pointed to a critical role of this enzyme in cell signalling, such as mitogen- and oncogene-activated protein kinase pathways (Ramoni C et al, Exp cell Res 2004; Li et al, J Cell Biochem 2006), apoptosis (Cifone et al, EMBO J 1995), and activation of immune cells (Andrei C et al, PNAS 2004; Luft T et al, Blood 2006). In particular, we reported a pivotal role of PC-PLC in NK cell-mediated cytotoxicity, by regulating lytic granules exocytosis and CD16-triggered signal transduction (Ramoni C et al, J Immunol 2001; Spadaro F et al, Eur J Immunol 2006; Cecchetti S et al, Eur J Immunol 2007). PC-PLC was also indicated as an important factor affecting differentiation of stem cells (Wang N et al, Int J Biochem Cell Biol 2008), suggesting that this enzyme could be a good candidate target to selectively control aberrant cell signalling pathways regulating differentiation during tumorigenesis. Induction of terminal differentiation is one of the potent mechanisms by which some cancer therapeutic agents work. Our recent studies reported the first evidence that inhibition of PC-PLC induced differentiation in breast cancer cells and affected the epithelial-mesenchymal transition (EMT), critical to breast cancer progression and metastasis (Spadaro F et al, manuscript in preparation).
In particular, we showed that PC-PLC was strikingly up-regulated in the progression from non-tumor mammary epithelial to breast cancer cells, in which the enzyme control cell proliferation, HER2 intracellular trafficking (Paris L et al, Breast Cancer Res 2010), and also the acquisition of a well-differentiated phenotype, with up-regulation of E-cadherin, downmodulation of vimentin and progressive loss of MFG-E8, a protein which increases when tumor cells acquire invasion competence (Spadaro F et al, manuscript in preparation).

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Among the factors affecting EMT and cancer differentiation, inflammatory responses at the tumor site play a decisive role in controlling tumor cell survival, proliferation and growth, as well as invasiveness and motility (Mantovani et al, Nature 2008). In tumor microenvironment immune and cancer cells communicate each other by means of direct contact or production of Cytokines and chemokines, that act in autocrine and paracrine manners to control and shape tumor growth. Key endogenous factorshave been identified in cancer-related inflammation: transcription factors (mainly NF-kB and STAT3), major inflammatory cytokines (IL-1beta, IL-6, IL-23 and TNF-alpha), chemokines (CCL2, CCL20 and IL-8), chemokines receptor (e.g. CXCR4), and extracellular-matrix-degrading enzymes.

In the past years PC-PLC has been closely linked to inflammatory processes. PC-PLC is required for transcription factors activation (i.e. NF-kB) leading to inflammatory molecules release, such as IL-10, TNF-alpha, IL-8 (Wang Q et al, Infect Immun 2001), IL-1 and IL-6 (Procyk KJ, et al, Blood 2000), and it is also involved in IFN-gamma and IL-2 signalling (Tsai CC et al, J Immunol 2009). We pointed out the role of PC-PLC in the production of gp120-induced CCL2 in macrophages (Fantuzzi L et al, Blood 2008), where PC-PLC activity has been shown to control LPS signalling through CD14 receptor (Cuschieri J et al, J Leukoc Biol 2006) and COX-2 expression via NF-kB (Tzeng JI et al, Pharmacol Res 2009). Recently, PC-PLC has been indicated as an atherosclerosis-promoting factor by recruiting inflammatory monocytes/macrophages and by increasing metalloprotease activity (Zhang L, et al, Arterioscler Thromb Vasc Biol 2010). Based on this evidence, it is of interest to evaluate whether PC-PLC can support tumor-promoting inflammation and, if so, which cytokines/chemokines are controlled by PC-PLC during tumor progression.


Previous studies had shown that IFN-alpha can induce significant changes in PC metabolism, by altering primarily the intratumor concentrations of Cho and PCho in tumor-bearing mice (Proietti E et al, Cancer Res 1986). IFN-alpha is the cytokine exhibiting the longest record of use in clinical oncology, capable of both exerting direct antitumor effects and playing a key role in linking innate and adaptive immunity (Belardelli and Ferrantini, 2002). With regard to the biologic role of PC-PLC in cancer control, it is still unclear whether IFN-alpha can differentially affect the expression, cellular localization and enzymatic activity of PC-PLC in cells of the immune system, as well as in tumor cells, thus resulting in inhibition of proinflammatory factors endowed with tumor-promoting activity and in activation of some effector functions involved in the antitumor response. A major working hypothesis of the proposed study is that PC-PLC can support tumor growth by secreting factors such as cytokines/ chemokines and matrix metalloproteases that promote tumor cell proliferation, invasion and metastasis formation

from Letter of intent……

This three-year project will combine integrated multidisciplinary approaches to achieve the following main objectives:

1. Evaluation of the inflammatory pathways critically regulated by PC-PLC in the cross-talk between malignant (BC and EOC cells) and purified immune cells isolated from healthy donors (such as macrophages, DC and NK cells).

By co-cultured systems, we will evaluate: a) the up- or down-regulation, both in immune and tumor cells, of chemokines/chemokine receptors, cytokines/cytokine receptors, metastasis-associated, extracellular matrix remodelling genes, by low-density array, either in the presence or in the absence of a specific PC-PLC inhibitor. The levels of these inflammatory mediators in the supernatant of co-cultured cells will be also detected by ELISA and multiplex protein arrays to identify molecular targets for tipping the balance between tumor-promoting and tumor-inhibiting inflammatory responses; b) the role of PC-PLC in the cytolytic activity of immune towards tumor cells by cytotoxic assays; c) the PC-PLC-driven pathways eventually required by tumor cells for the positive feedback loop involving IL-6, NF-kB and STAT3 in the initiation of cell transformation, by biochemical and CLSM analyses.

2. Evaluation of the effecs of PC-PLC-inhibition on IFN-alpha-induced antitumor responses.

We will investigate: a) the effects of IFN-alpha on PC-PLC expression and/or activity in both tumor and immune cells by CLSM analyses and enzymatic assays; b) the possible role of PC-PLC in affecting the differentiation and activity of IFN-DC by flow cytometry and CLSM analyses, and by biochemical and functional assays.

3. Understanding the effects of the PC-PLC-driven inflammatory pathways on breast and ovarian tumor progression.

In particular, we will dissect, by confocal laser and electron scanning microscopy, the mechanisms affecting EMT (and MET), cell migration and invasion in a panel of tumor cell lines corresponding to different types and stages of BC and EOC cells. The expression of some typical differentiation markers will be evaluated in a time course of PC-PLC inhibition, by flow cytometry and biochemical analyses, in relation to changes in PCho and mobile lipid pools monitored by high resolution MRS examinations.

4. Assessment of PC-PLC as a potential target for new antitumor therapies.

The final part of our study will consist in assessing the strategy of downmodulating PC-PLC in breast and ovarian tumor xenografts as potential target for new antitumor therapies, either alone or in combination with IFN-alpha. In tissue samples of human ovarian and breast tumors recovered from SCID mice transplanted with the respective tumor type cell lines we will characterize the expression and activity of PC-PLC in different types and stages of tumor, in relation to: a) gene expression profiles, by means of microarrays for evaluating the modulation of genes related to the oncogenic potential of tumor cells; b) alterations of PC metabolism, with emphasis on the significance of MRS signals as fingerprints of tumor progression and indicators of altered cell signalling. Moreover, in a pilot study PC-PLC expression will be investigated in human breast tumor lesions recovered from either neoadjuvant-responder or non-responder patients or from patients who present metastatic spread at later stage. In the same surgical specimens we will identify the intratumor inflammatory mediators and characterize tumor infiltrating immune cells, correlating these data with alterations in the PCho pool and with gene expression profiles.

## Collaborations.

This 3-year project will be based on the complementary expertises of different Units at the ISS, in collaboration with the Department of Surgery (Policlinico Umberto I, Rome), to fulfil all the above mentioned tasks.

A major part of the work will be carried out at the Department of Cell Biology and Neurosciences of the ISS.
The scientific staff at Molecular and Cellular Imaging Section has wide experience in studying the biology of PC-PLC both in immune and cancer cells. They have appropriate background, knowledge and skill in the specific field of phospholipid metabolism in epithelial cancers and are participating in projects granted by Public or Private National and international Agencies. Dr F Spadaro (PI) will be responsible for the overall scientific coordination and direction of the project, in collaboration with Dr F Podo and Dr F Belardelli. She will also directly contribute to the planning and development of the research, maintaining close interactions with all the collaborators. In particular, she will participate, with Dr. S Cecchetti, Dr. L Paris and Dr. L Abalsamo, to the experimental studies on expression, sub-cellular localization and activity of PC-PLC in the dynamic cross-talk between cancer and immune cells, by investigating the inflammatory PC-PLC-driven pathways affecting cancer differentiation, EMT (and MET), cytotoxicity, trafficking and signalling of important receptors, such as HER2 and adhesion proteins. Dr E Iorio will be directly involved in MRS studies on breast and ovarian cancer cells, as well as on samples from tumor xenografts; Dr R Canese will be responsible for in vivo MRI/MRS studies on tumor-bearing SCID mice and in collaboration with the technical expertise of the animal facility will supervise the set-up of experimental designs.

The group of Experimental Immunotherapy Section has a long expertise in studying the immune mechanisms of action of type I IFNs and the biology of IFN-DC. Dr SM Santini, Dr C Lapenta and Dr S Donati will contribute to understand the effects of PC-PLC inhibition on IFN-DC functional differentiation. This Unit can also count on a microarray core facility, fully equipped and qualified for gene profiling studies, that are carried out on arrays printed and validated in house with 34,580 70mer oligos of the Operon collection (version 3.0). Dr I Canini and Dr L Gabriele will account for the microarray facility, will take care of all data management and will be responsible for performing systems biology statistical analysis. Dr L Fantuzzi (Section of Immunoregulation) will contribute to understand the effects of PC-PLC inhibition on macrophage-mediated immune responses. Dr P Sestili (Section of Clinical Applications of Biological Therapies) will be responsible for tissue section preparation from tumor xenografts or human tumor lesions and for the further immunohistochemistry and immunofluorescence analyses. Dr A Molinari (Department of Technology and Health, Ultrastructural Methods for Innovative Anticancer Therapies Section) will be responsible for all the studies on migration and invasive potential of cancer cells.
Dr B Salvati, Department of Surgery of Policlinico Umberto I (Rome), will provide human tissue samples from breast tumor lesions both in the neoadjuvant-responder and non-responder setting or from patients with metastatic disease and will be directly involved in the clinical evaluation of specimens. This study will be approved by the Comitato Etico dell'Azienda Policlinico Umberto I of Rome. Dr A Metere (ISS, Department of Cell Biology and Neurosciences, Biomarkers in Degenerative Diseases Section) will be responsible for maintaining appropriate records on anonymous correlation between clinical history of patients and experimental results obtained by this project on surgical specimens.

## Overall costs of the project

| Costs items and brief description | Total | Part covered by MoH funds [ a ] |
|---|---|---|
| **1. Permanent staff**<br><br>1 Research Director, 7 Researchers, 1 Physicist, 3 Technicians,1 Surgeon | €106.400,00 | None |
| **2. Project Staff (ad hoc contracts/consultants/fellowship)**<br><br>1 Researcher, 1 Fellow (for two years) | €150.000,00 | €150.000,00 |
| **3. Travel Costs and Subsistence Allowances**<br><br>Participation to National and International meetings | €15.000,00 | €15.000,00 |
| **4. Equipment**<br><br>Equipment for confocal laser scanning microscopy | €45.000,00 | €45.000,00 |
| **5. Consumables and Supplies directly linked to the Project**<br><br>Plastic material, reagents for molecular biology, mice, reagents for MRS examinations, cell cultures, antibodies, reagents and chips for microarray analyses | €140.000,00 | €140.000,00 |
| **6. Dissemination of results (publications, meetings/ workshops etc.)**<br><br>Submission fees, charges for pages and color figures | €13.500,00 | €13.500,00 |
| **7. Data handling and analysis (specify)**<br><br>Supplementary dedicated software (deconvolution, volume and surface rendering) | €10.000,00 | €10.000,00 |
| **8. Overheads for all Institutions involved (specify)**<br><br>flate rate of 10% for indirect cost | €41.500,00 | €41.500,00 |
| **Totale** | €521.400,00 | €415.000,00 |

| Final Score:31.0 | | |
|---|---|---|
| **2006301** | **1711137** | **1718727** |
| **Scientific quality and relevance of the research** | | |
| 4.5 | 4.0 | 6.0 |
| There is a high relevance for the inflammatory mediation of tumor growth, however this proposal is too broad in scope. | PI proposes to study the role of phosphatidylcholine -specific phospholipase C (PC-PLC) in epithelial-to-mesenchymal transition, tumor associated inflammatory pathways, and as a potential therapeutic target. PC-plc activity has been reported in ovarian cancer cells but the gene is not yet known. There is an inhibitor that blocks causes reduction of the phosphocholine in cells and presumably binds to this putative PC-PLC. understanding the mechanism of action of this enzyme without knowing what the gene and the protein are seems like a formidable task. | This proposal sets out to examine the role of phosphatidylcholine-specific phospholipase C (PC-PLC) in tumor promoting inflammation of breast and ovarian cancer. There have been a number of studies suggesting that PC PLC contributes to tumor inflammation; however, the importance, overall all effects (pro-tumor vs anti-tumor) and mechanisms remains poorly understood. This application has four stated aims: 1) Evaluate the inflammatory pathways critically regulated by PC-PLC in the cross-talk between malignant and immune cells, 2) Evaluate the effects of PC-PLC inhibition on IFN-alpha-induced antitumor responses, 3) Understand the effects of the PC-PLC driven pathways on breast and ovarian tumor progression, and 4) Assess PC-PLC as a potential new antitumor therapy. The main strength of the proposal is the relatively novel angle of investigation into how PC-PLC affects tumor inflammation. Unfortunately, the proposal suffers from a number of major weaknesses. First, it is a largely an unfocused and descriptive study on PC-PLC that is unlikely to generate substantial new insight. First example, the idea to study how PC-PLC affects a large panel of inflammatory mediators is a fishing expediation with no clear objective. |

| Methodology and development strategy of the project | | |
|---|---|---|
| 4.0 | 5.0 | 8.0 |
| The methods are diffuse and unfocused. There is such a wide array of factors involved in inflammation - the PI should try to focus on only a few to provide a better story. | In this proposal Dr. Spadaro proposes to elucidate inflammatory pathways and gene expression regulated by PC-PLC, evaluate contribution of PC-PLC driven inflammatory pathways to breast and ovarian tumor progression and explore it as a therapeutic target. It seems difficult to achieve these goals with a single inhibitor and without being able to specifically deplete or overexpress PC-PLC enzyme. | Most of the proposed experiments are superficial and descriptive. Hence, they are unlikely to lead to substantial new insight. |
| **Translational impact and clinical relevance** | | |
| 4.0 | 2.5 | 6.5 |
| It's difficult to understand how these findings will translate to the patient. | Breast and ovarian cancers reportedly accumulate PCho due in part to elevated activity or levels of PC-PLC. Results of this study will determine if combination of IFNa and PC-PLC inhibitor will have synergistic therapeutic effect. | The field of tumor inflammation is exciting and always certainly will be eventually targeted in patients with cancer. However, it is unlikely that this proposal would substantially quicken that process. |

| Profile of the investigator | | |
|---|---|---|
| 2.5 | 4.5 | 5.0 |
| the PI has a good background and publications thus far. | Dr. Spadaro has coauthored multiple publications in the field of proposed research demonstrating knowledge of the field of proposed study. On one of the publication she is a first author and on none none as a senior author. This raises the question of the PI independence. She has secured some important collaborators to help her complete proposed tasks. | Solid young researcher who is an author on a number of publications in subspecialty journals related to this topic. However, the applicant generally a middle author on most of these manuscripts and so one does not get the sense that she is driving this field. |

| Final assesment | | |
|---|---|---|
| The proposed study will investigate if PC-PLC can be required for tumor-promoting inflammation and if inhibition of this enzyme can represent a powerful target for a more effective therapy attacking both the malignant cells and the "other half" of the tumor mass, the tumor-associated inflammatory cells. While the proposal has potential, it is written diffusely and difficult to understand. | Dr. Spadaro proposes to determine inflammatory pathways regulated specifically by PC-PLC enzyme, determine how inflammatory pathways driven by PC-PLC impact on tumor progression and if there is correlation between gene expression, immune status, and PC-PLC expression. It seems that most tasks will be difficult to accomplish without being able to specifically deplete or overexpress PC-PLC. That somewhat diminishes enthusiasm about the output of the study. In addition, there is a question about PI independence due to few first/last author publications and thus her ability to complete all the proposed studies. | Overall, this is a fair/good proposal to examine the role PC-PLC in tumor inflammation by an up and coming investigator. While potentially interesting, the proposal is superficial and descriptive. As such, it is unlikely to yield sustantial insights into how PC-PLC functions in tumor inflammation. |

ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO

MFAG 2012

Codice Riferimento: 13226

**TITLE PAGE**

| | |
|---|---|
| Principal Investigator's full Name and Qualification<br>Doctor Spadaro Francesca - Researcher | |
| Proposal Title<br>Development of personalized therapeutic Follicular Lymphoma Vaccines | |
| Type of grant | MFAG |
| Area | Immunotherapy |
| Keywords | Lymphomas; Vaccine; Interferons; Dendritic cells; Immunization |
| Budget 2012 (euro): 99.000,00 € | Estimated budget 2012 - 2014 (euro): 297.220,00 € |

**Final score: 16,5**

**INVESTIGATOR (TRACK-RECORD AND INTERNATIONAL STANDING IN CANCER RESEARCH)**

Dr Spadaro's Blood paper is an excellent contribution to the field and overall her focus on a single thematic area is commendable.

**INVESTIGATOR (TRACK-RECORD AND INTERNATIONAL STANDING IN CANCER RESEARCH)**

The applicant Dr. Francesca Spadaro is a young investigator who has a background in dendritic cell function and tumor immunity. Her productivity (2 primary research articles in which she is first author and 0 senior author publications over the past 5 years) is only modest.

**INVESTIGATOR (TRACK-RECORD AND INTERNATIONAL STANDING IN CANCER RESEARCH)**

The project leader has published well in international journals