# EURYI Awards 2004

*Press Information*

## Dr. Miguel Angel DEL POZO

*– Biomedicine –*

## Project:

**Role of Calveolin-1 in the Regulation of Membrane Micro domain Trafficking, Integrin Signalling and Tumour Suppression**

Integrins are crucial regulators of essential cellular processes such as gene expression, cell proliferation and migration. Alteration of these processes is central to tumorigenesis. Integrin signals mediate anchorage-dependence of cell growth, while growth of cancer cells is anchorage-independent. Integrins regulate membrane targeting of Rac, a Rho family GTPase also involved in cell cycle progression and oncogenesis. Recent findings show that integrin-regulated Rac binding sites are in CEM (cholesterol and glycosphingolipids-enriched membrane domains, also referred to as "lipid rafts"). Internalization of Rac binding sites is mediated by caveolin-1, a structural component of a subtype of rafts termed caveolae. Caveolin-1 regulates anchorage-dependent growth and is a candidate tumour suppressor. Integrin-mediated retention of phosphorylated caveolin in focal adhesions inhibits raft internalization, which occurs upon its recruitment to caveolae after cell detachment. These results may
provide a molecular explanation for the role of caveolin-1 as tumor suppressor and provide insight into the mechanism of anchorage-independent growth, one of the hallmarks of cancer. The main goal of this research proposal is to study the relevance of this novel mechanism to cancer. The **first aim** is to identify molecular mechanisms by which caveolin regulates anchorage-dependent signaling pathways and cell cycle progression. Whether integrin-dependent Rac effects on cell cycle progression are dependent on caveolin and whether caveolin is involved in suppression of signaling pathways other than Rac (Ras/Erk, JNK, FAK and PI3-kinase/Akt) in non-adherent cells will be investigated. The **second aim** is to identify sequences within caveolin involved in regulation of raft internalization, cell cycle progression and anchorage-dependent cell growth.
Caveolin sporadic mutations occurring in human cancers will be tested for these effects. The **third aim** is to identify oncogenes that in normal cells lie in an integrin pathway and that when abnormally activated will induce constitutive surface localization of rafts (and hence Rac), and/or changes in phosphocaveolin localization. Combination of candidate and genetic screening approaches will be employed to identify genes involved. These studies will contribute to a better understanding of adhesion-dependent signalling and anchorage-dependence of cell growth, and therefore to the pathogenesis of the malignant disease. They will also help in identifying genes and molecular mechanisms that could be used as selective targets for cancer therapy.

## Comments:

This is a timely proposal exploring recently developed tools that are likely to unravel new therapeutic targets to prevent cancer progression.
The candidate has an excellent track record both as Ph. D and post-doctoral fellow; he has recently established his own group, from which much is expected. He is exceptionally well trained with a very strong publication record. He is a serious and mature scientist well prepared to lead a strong research team.
The proposed project will apply and further extend a very recent ground-breaking discovery of the candidate. It has the potential of uncovering novel cellular mechanisms relevant to the understanding of cancer invasion.
The candidate has recently moved to an exciting new cluster of well-resourced institutes with very strong scientific leadership

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**New institution:** Fundacion Centro Nacional de Investigaciones Cardiovasculares Carlos III

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