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## Research interests

The Laboratory is focusing on tissue repair during development and ageing with an emphasis on the role of growth factors, and especially that of TGF-β. The action of growth factors on cell proliferation and extracellular matrix production, as well as the responsible signaling pathways are investigated. Alternative mechanisms of cell proliferation and differentiation, such as autocrine regulation, cell-matrix interactions, exogenous stresses and the effect of mechanical forces are also studied.

Main goal of the Laboratory is the investigation of the mechanisms of ageing and longevity. The structural and functional characteristics of the senescent cell - as a result of successive duplications or of exogenous stresses - in comparison to that of the young or the cancer cell are investigated. Especially, we are interested on the role of the senescent – somatic and stem - cell in the process of ageing and the development of age-related diseases, including cancer. In this direction, we study the interaction between the senescent stromal fibroblasts and adjacent cancer cells. Emphasis is given in tissues, such as the intervertebral disc, the degeneration of which provokes severe dysfunctions during ageing.

Aim of our studies is the elucidation of the mechanisms underlying the regulation of tissue homeostasis, especially during ageing, and furthermore the contribution, through research networks, in the development of cell replacement therapies. Finally, we study natural products and new synthetic compounds with putative anti-cancer, anti-ageing/anti-oxidant and wound healing action, as well as their mode of action.

## Current Research Projects

## The role of growth factors in tissue homeostasis and repair

TGF-β is a multifunctional growth factor. Especially concerning the regulation of cell proliferation it is well known that it can inhibit epithelial and endothelial cells, while it can stimulate cells of mesenchymal origin. Having in mind the crucial role of TGF- β in wound healing and the different strategies in skin repair followed between fetuses and adults, we studied the effect of this growth factor on the proliferation of fibroblasts from these two developmental stages. We found that TGF- β exerts a differential effect on the proliferation of these cell types: while it inhibits the proliferation of fetal fibroblasts (via the activation of PKA and subsequently of the up-regulation of cell cycle inhibitors
p21 and p15), it stimulates cells from adult individuals (mediated by the release of FGF-2 and the consequent activation of the MEK-ERK pathway) (Figure 1). Currently, we are investigating the role of the extracellular environment in this phenomenon, and especially of the presence of components of the extracellular matrix, such as collagen and hyaluronate.
In parallel, other growth factors, such as PDGF, bFGF, IGF-I (exogenously administered or produced in an autocrine/paracrine manner) are being studied in the Laboratory, along with the signaling pathways they activate, for the control of cell proliferation or other cellular functions in normal and pathologic conditions.

Relevant publications:

Pratsinis et al. (2004) Wound Repair Regen. 12: 374

Giannouli and Kletsas (2006) Cell. Signal. 18: 1417

Liontos et al. (2007) Cancer Res. 67: 10899

Pratsinis and Kletsas (2007) Eur. Spine J. 16: 1858

Gioni et al. (2008) Mol. Cancer Res. 6: 706

Chrissouli et al. (2010) Wound Rep. Regen. 18: 643

Mavrogonatou and Kletsas (2010) J. Orthop. Res. 28: 1276

Pratsinis et al. (2012) J. Orthop. Res. 30: 958

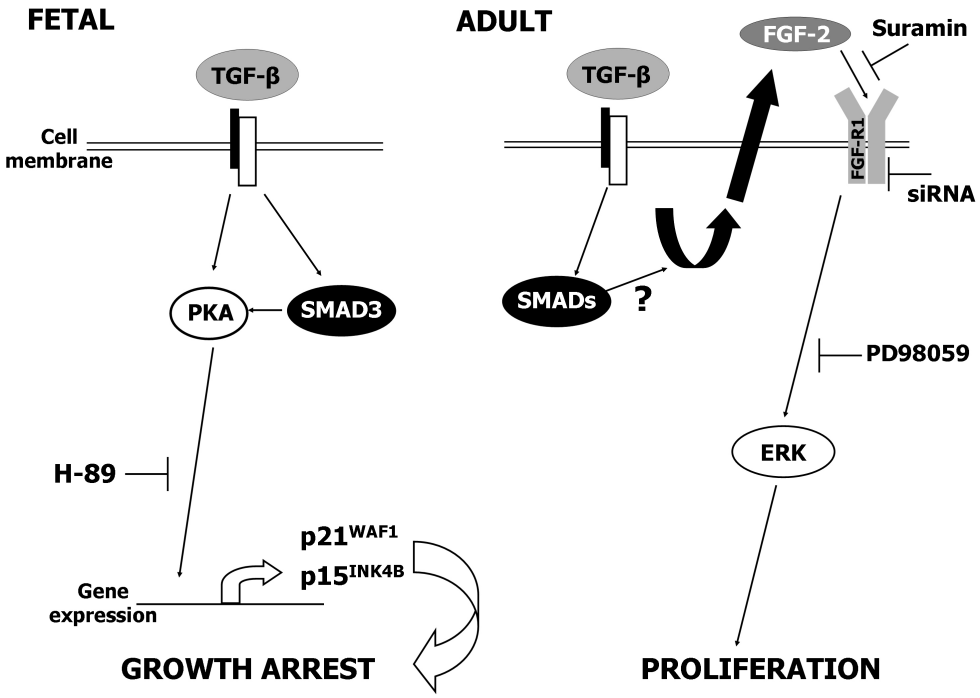



Figure 1.Molecular mechanisms of the differential response of fetal and β adult skin fibroblasts to TGF

**Cellular senescence: Molecular mechanisms and role in tissue homeostasis**

Cellular senescence is considered nowadays a major parameter of tissue homeostasis. It represents a potent anticancer mechanism and is involved in several age-related pathologies.

1.

***A novel  biomarker of cellular senescence***

The identification of senescent cells in vitro and in vivo is a major task for understanding their role in tissue homeostasis. Recently, a novel such biomarker has been developed, based on a specific lipofuscin staining, with two major advantages over existing markers: the recognition of senescent cells is independent of culture conditions and it can be used in cryo-preserved archival materials (Figure 2).

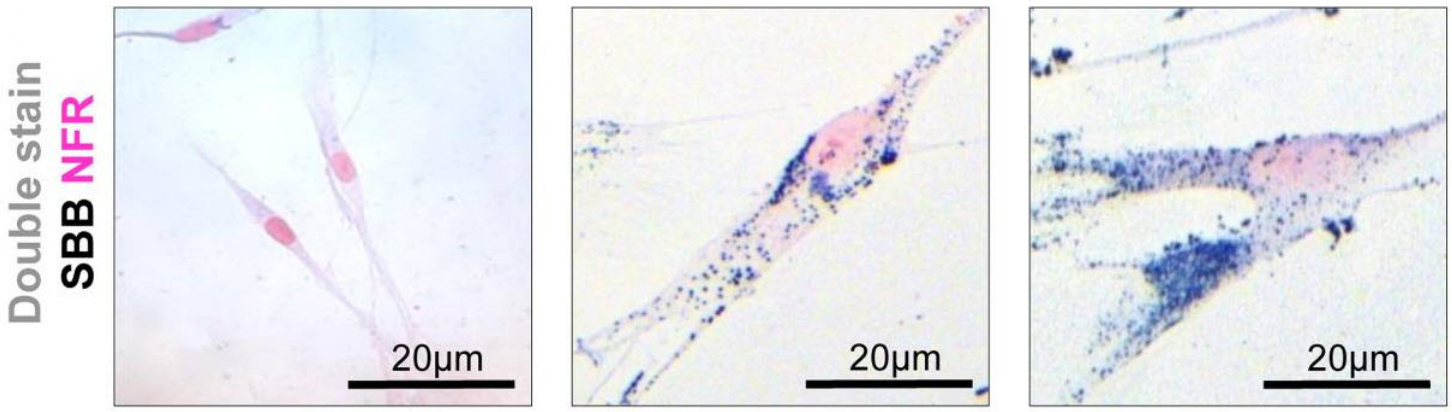



Figure 2. Identification of  senescent cells by the Sudan Black B staining

1.

***Molecular  mechanisms of cellular senescence***

Various types of stress can lead to a senescent phenotype. Oncogene-induced senescence (a major anticancer mechanism) is linked with an activation of a DNA Damage Response (DDR) pathway [Bartkova et al. (2006) Nature 444: 633] (Figure 3). On the other hand, anticancer treatments, such as ionizing radiation or genotoxic anti-cancer drugs also provoke premature senescence and activate a DDR.

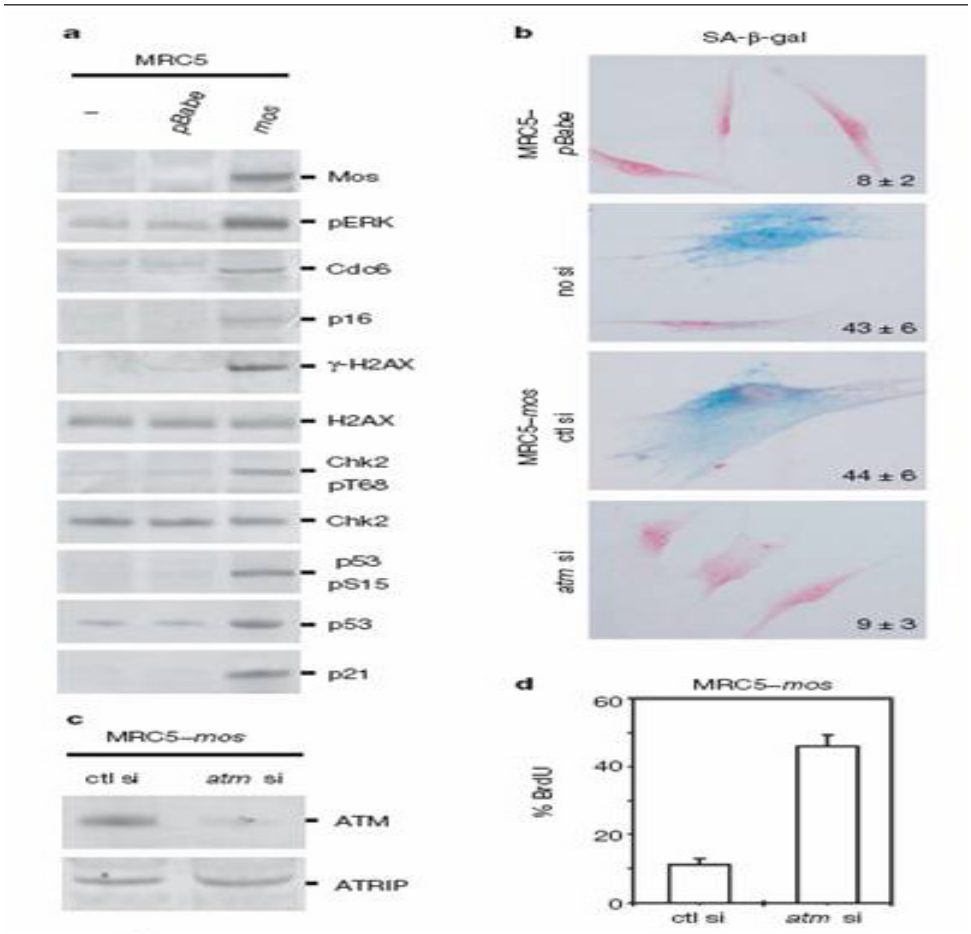


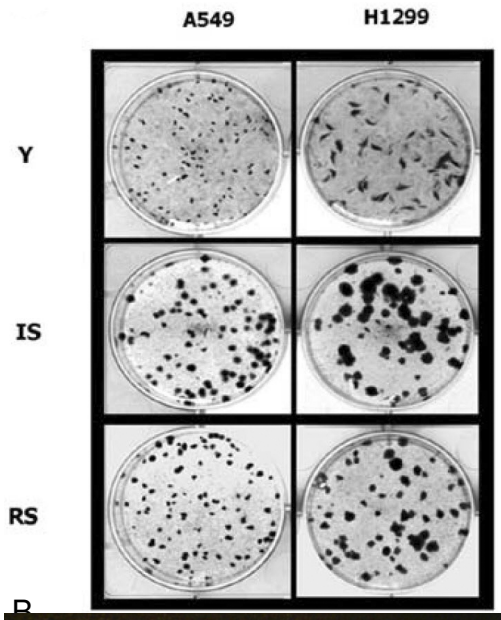
Figure 3. Oncogene overexpression provokes premature senescence in normal fibroblasts by activatin

1.

***Effect of cellular senescence on tumor development***

Although cellular senescence is a potent anticancer mechanism, after becoming senescent, stromal cells can enhance tumor development, a mechanism that involves increased expression of matrix metalloproteases (Figure 4).

A




B

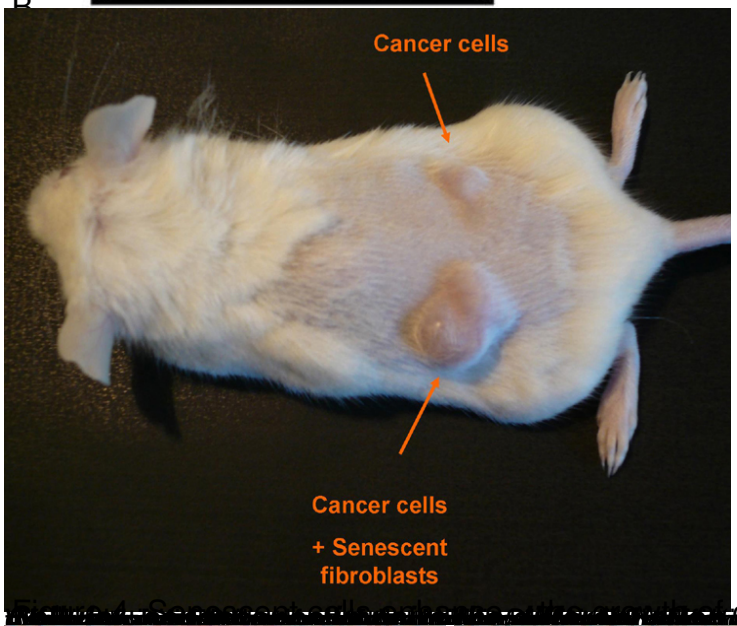
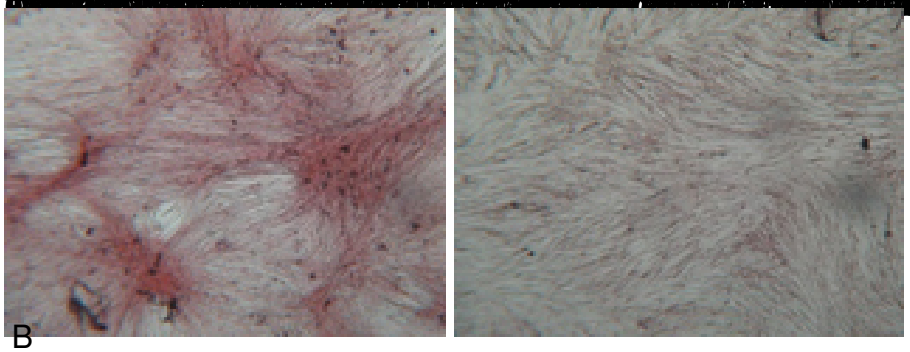
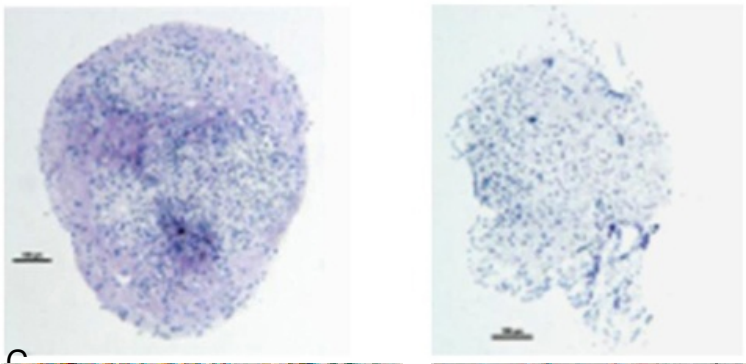


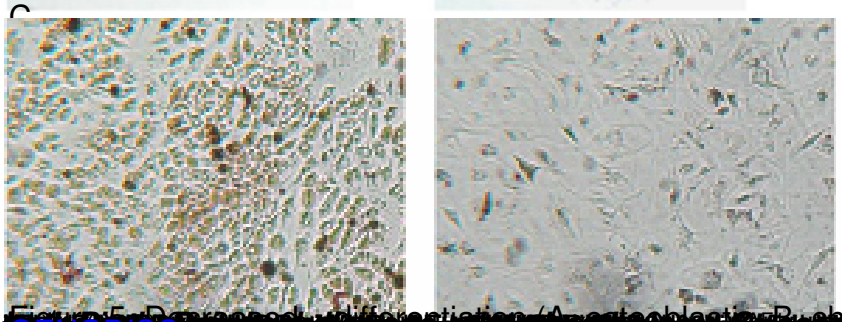

Figure 4 - Senescent cells enhance the growth of cancer cells in vitro (A) and in vivo (B).



B

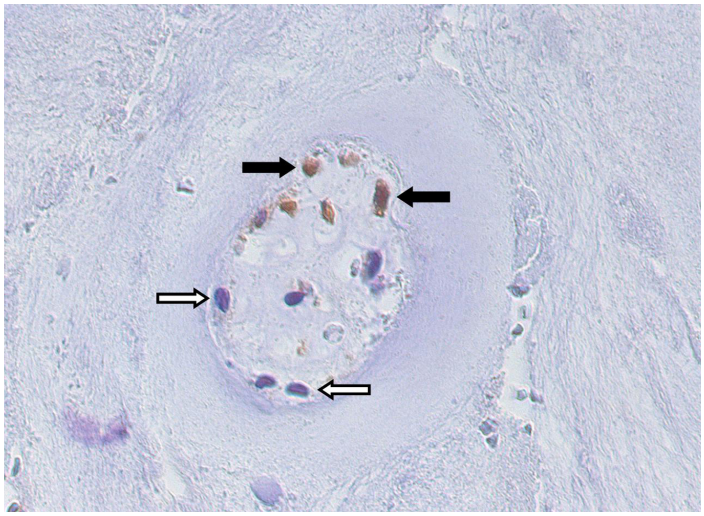


C

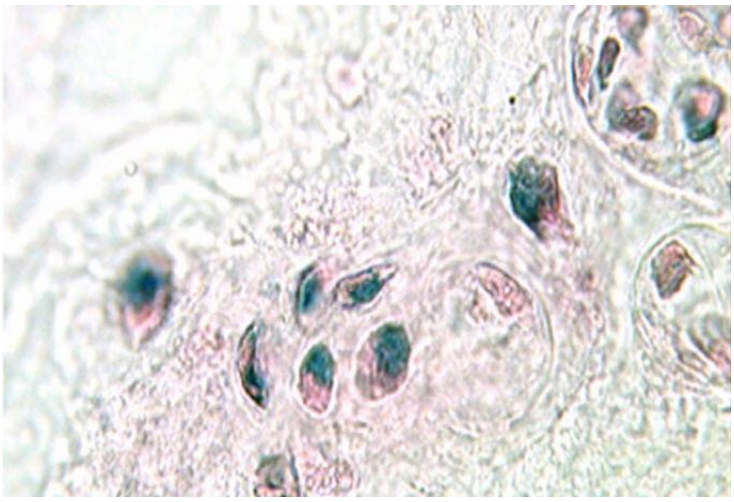


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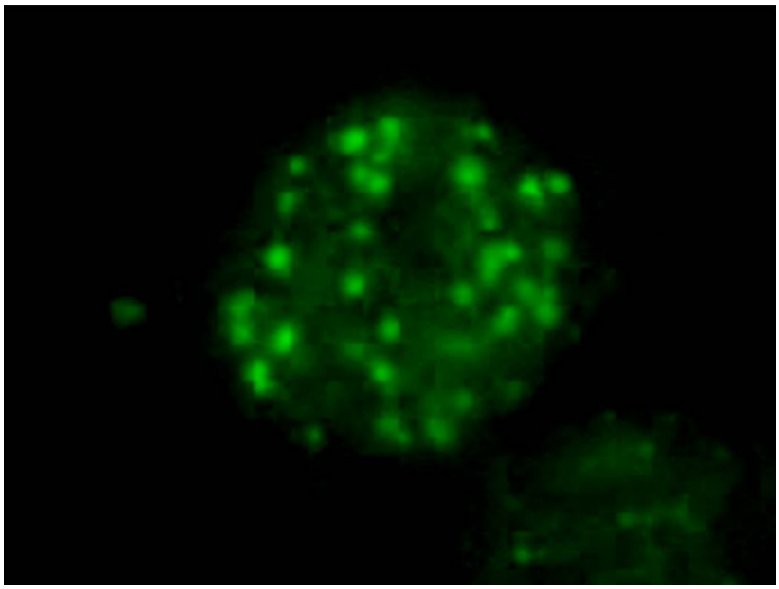
A



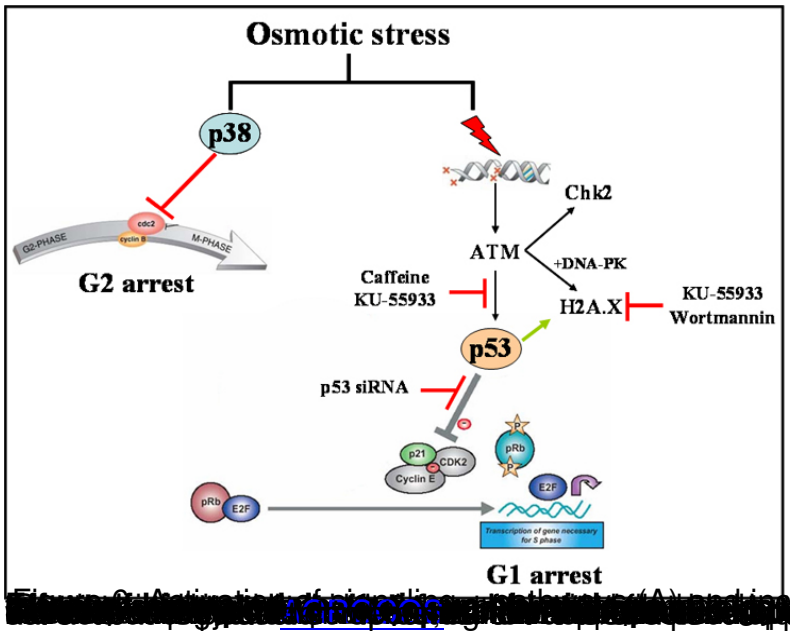
B



C



D


Osmotic stress
p38
Chk2
ATM
+DNA-PK
Caffeine
KU-55933
H2A.X
KU-55933
Wortmannin
p53
p53 siRNA
p21
CDK2
Cyclin E
pRb
E2F
G2 arrest
G1 arrest

ed IVD.