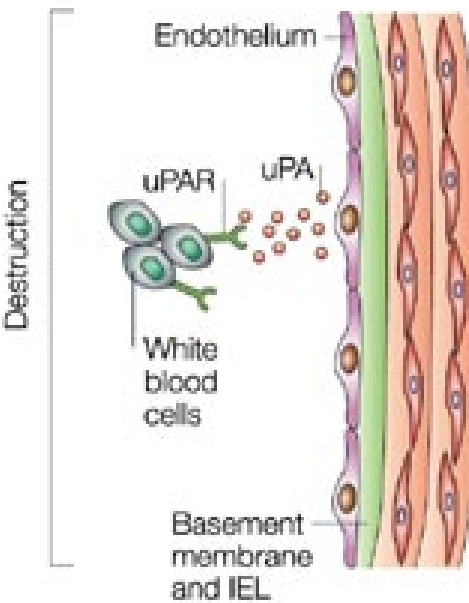
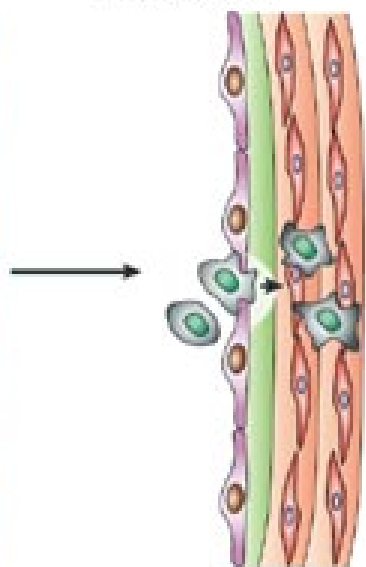


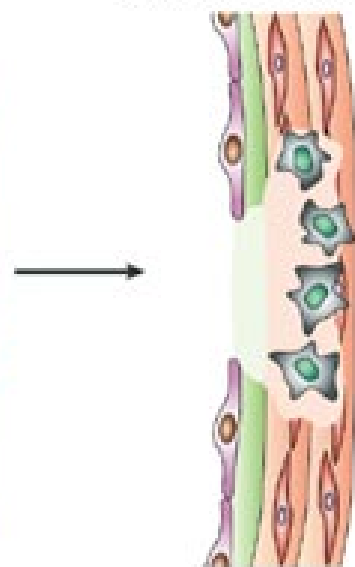
A **a Chemotaxis, adhesion**



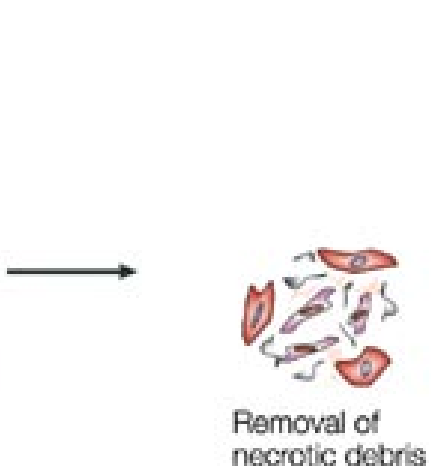
b Transmigration by basement-membrane breakdown



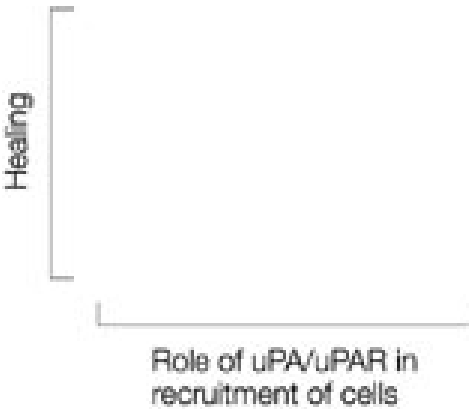
c Breakdown of interstitial ECM (collagen in heart, elastin in vessel)



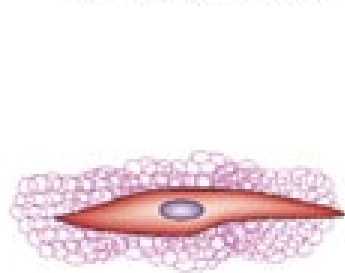
d Tissue destruction (aneurysm, rupture)



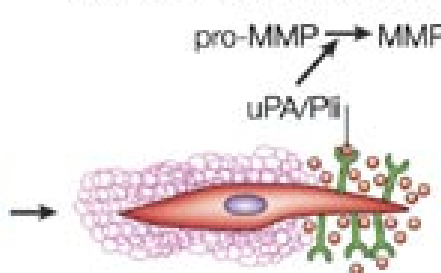
B



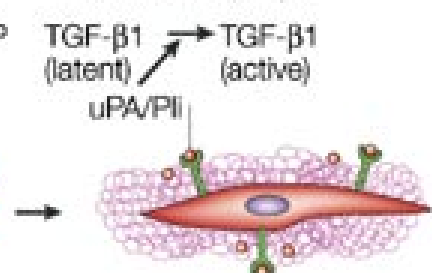
a Quiescent cell embedded in ECM



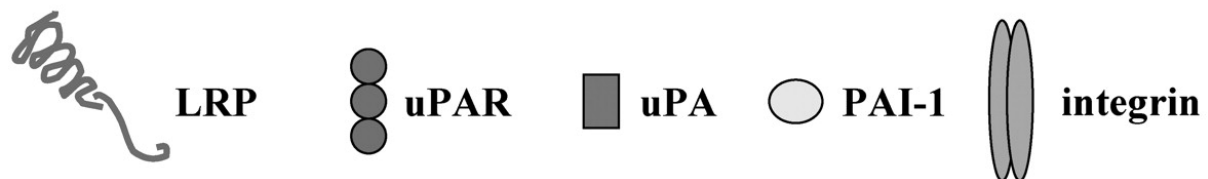
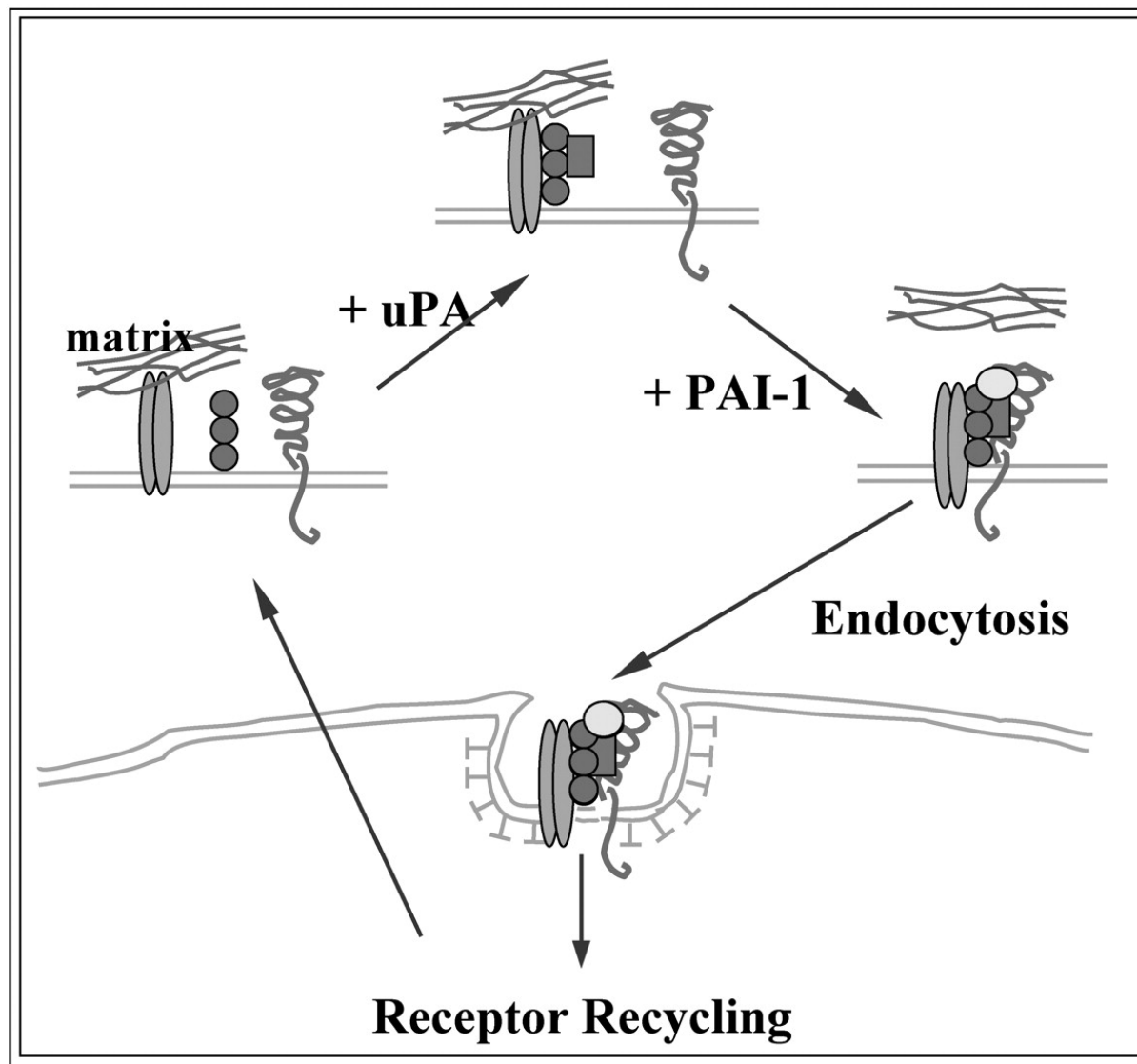
b ECM breakdown to allow migration of wound cells



c ECM repair by activation of latent TGF-β1

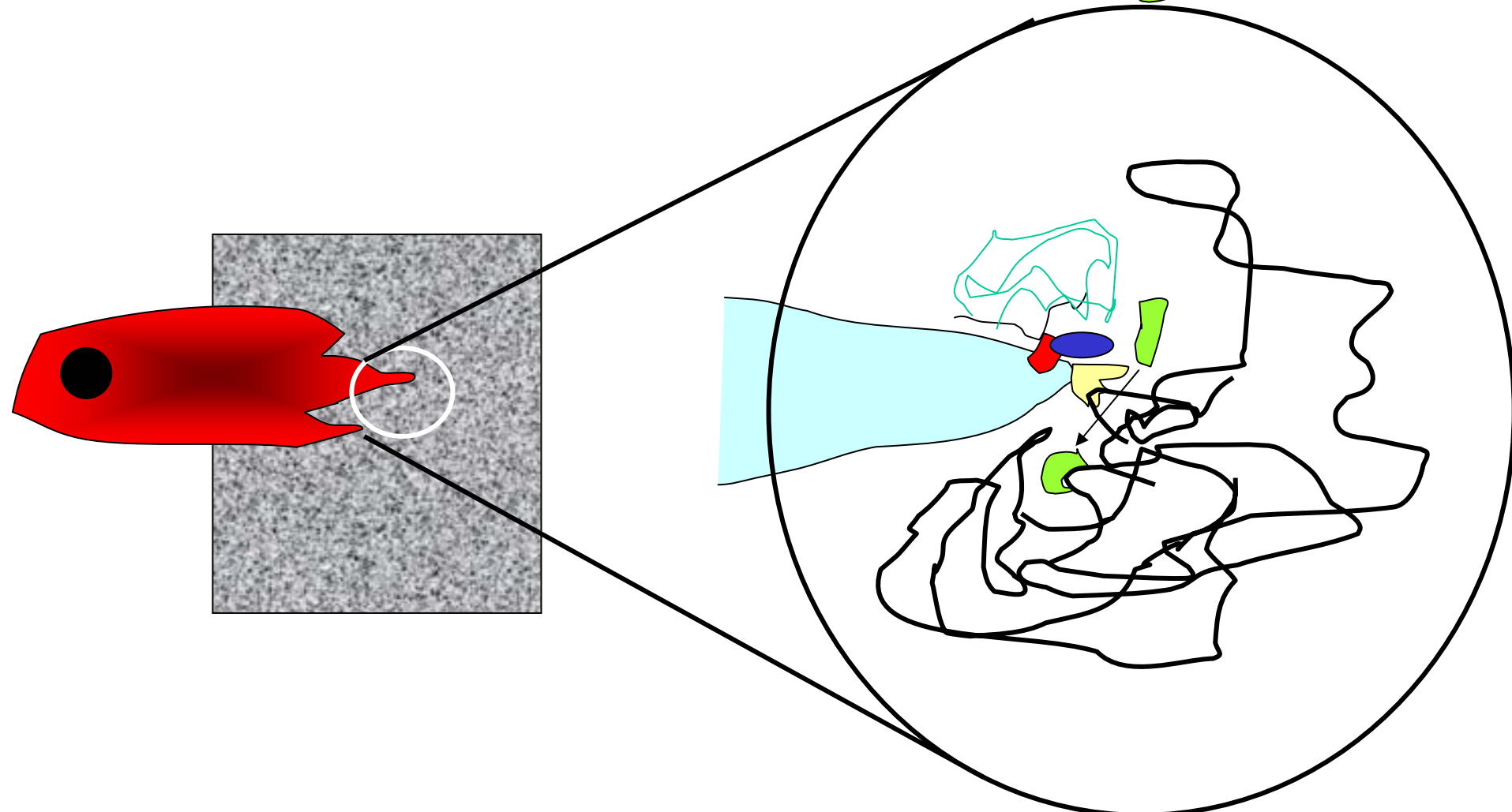
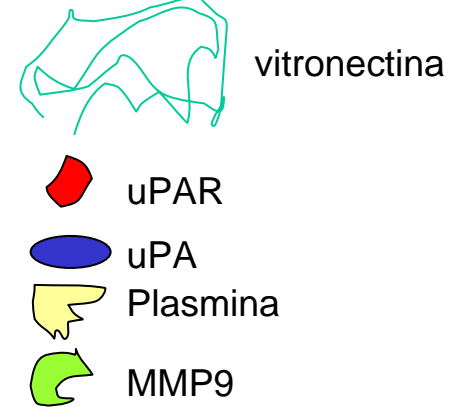


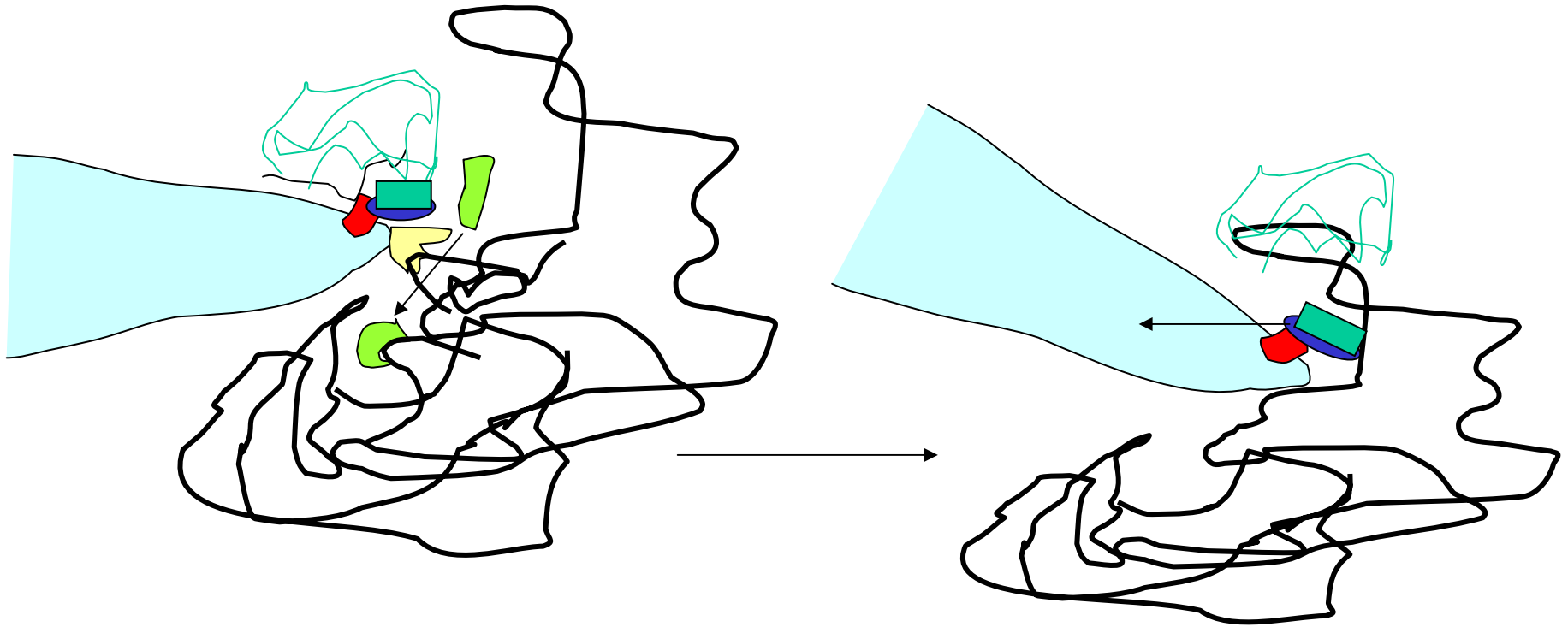
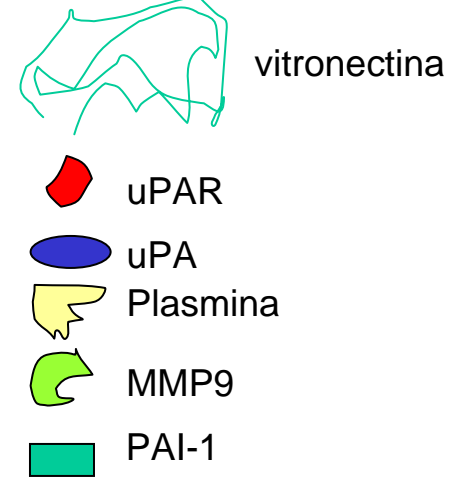
Role of uPA in proteolytic ECM remodelling and growth-factor activation

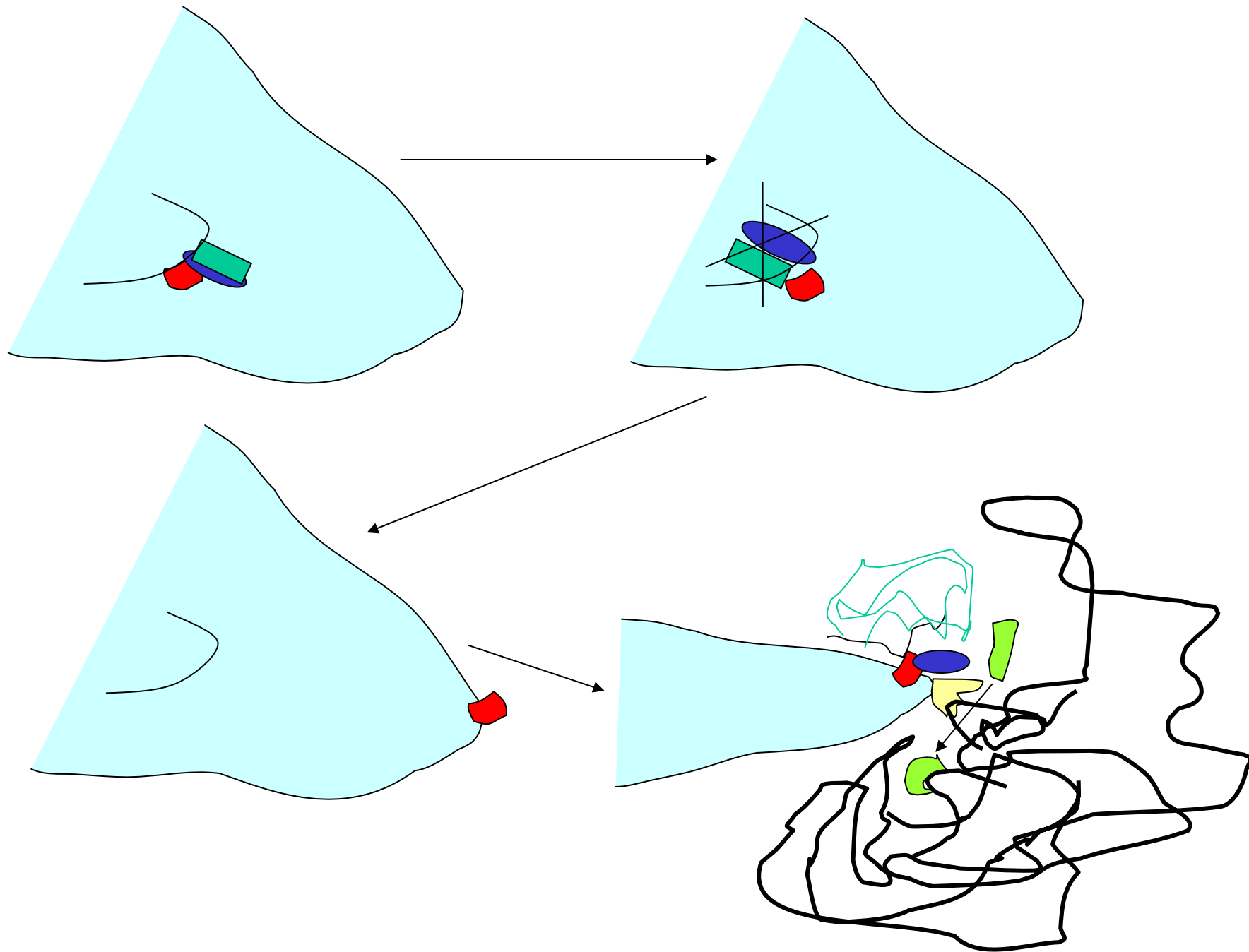


**Para una efectiva invasión tumoral, es necesaria la expresión
De uPA/PAI-1 y MMPs.**

**- Permite un control de la degradación en el frente invasivo
Y por tanto una modulación de la dinámica de degradación.**







CAMBIOS GENÉTICOS

H-Ras★

P53★



CAMBIOS BIOLÓGICOS Y QUÍMICOS

Cambios en : receptores de ME
el Citoesqueleto
Aumento de la: Motilidad
Expresión de
Proteasas
Invasividad
Pérdida de adhesión Cel-Cel.

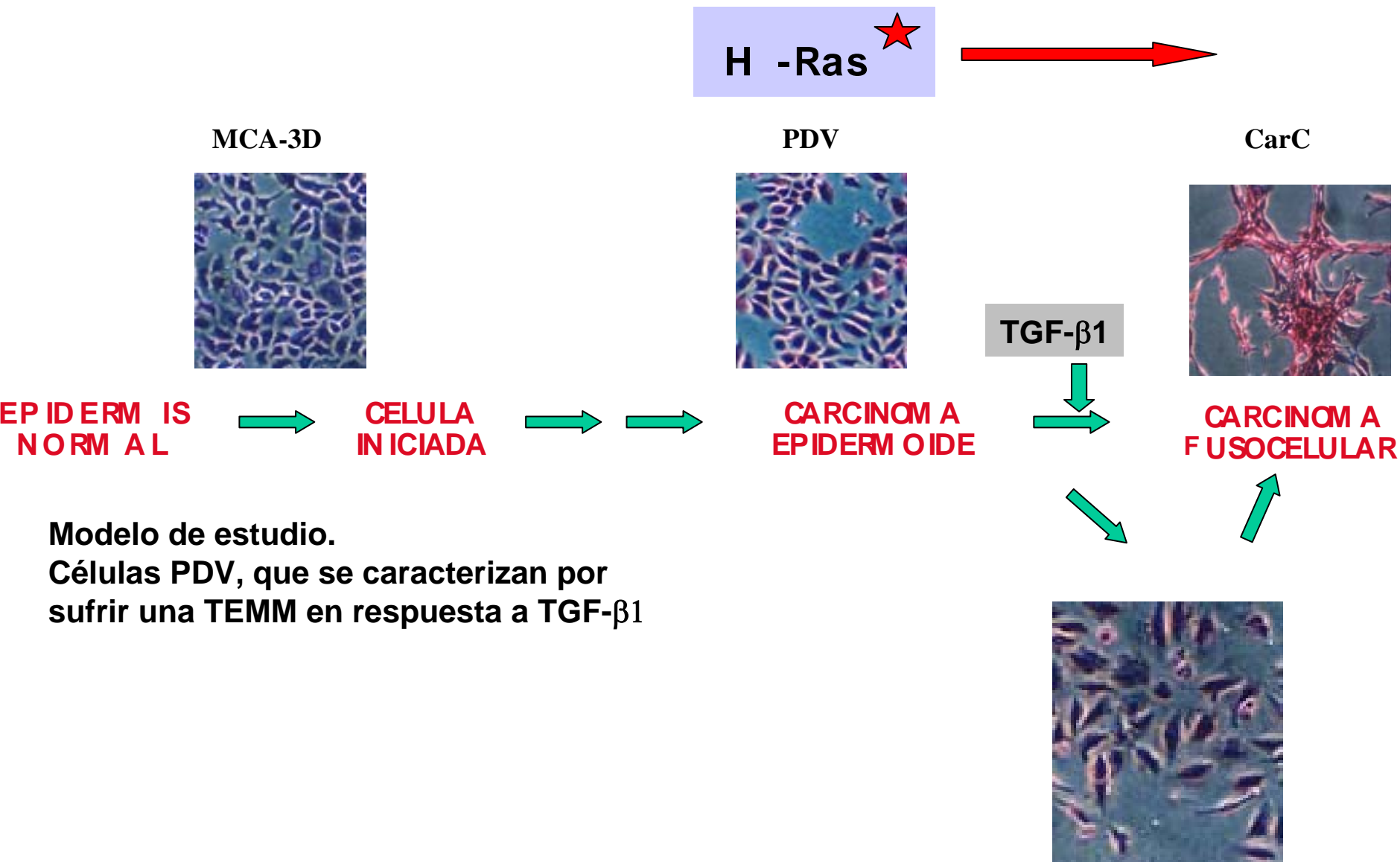
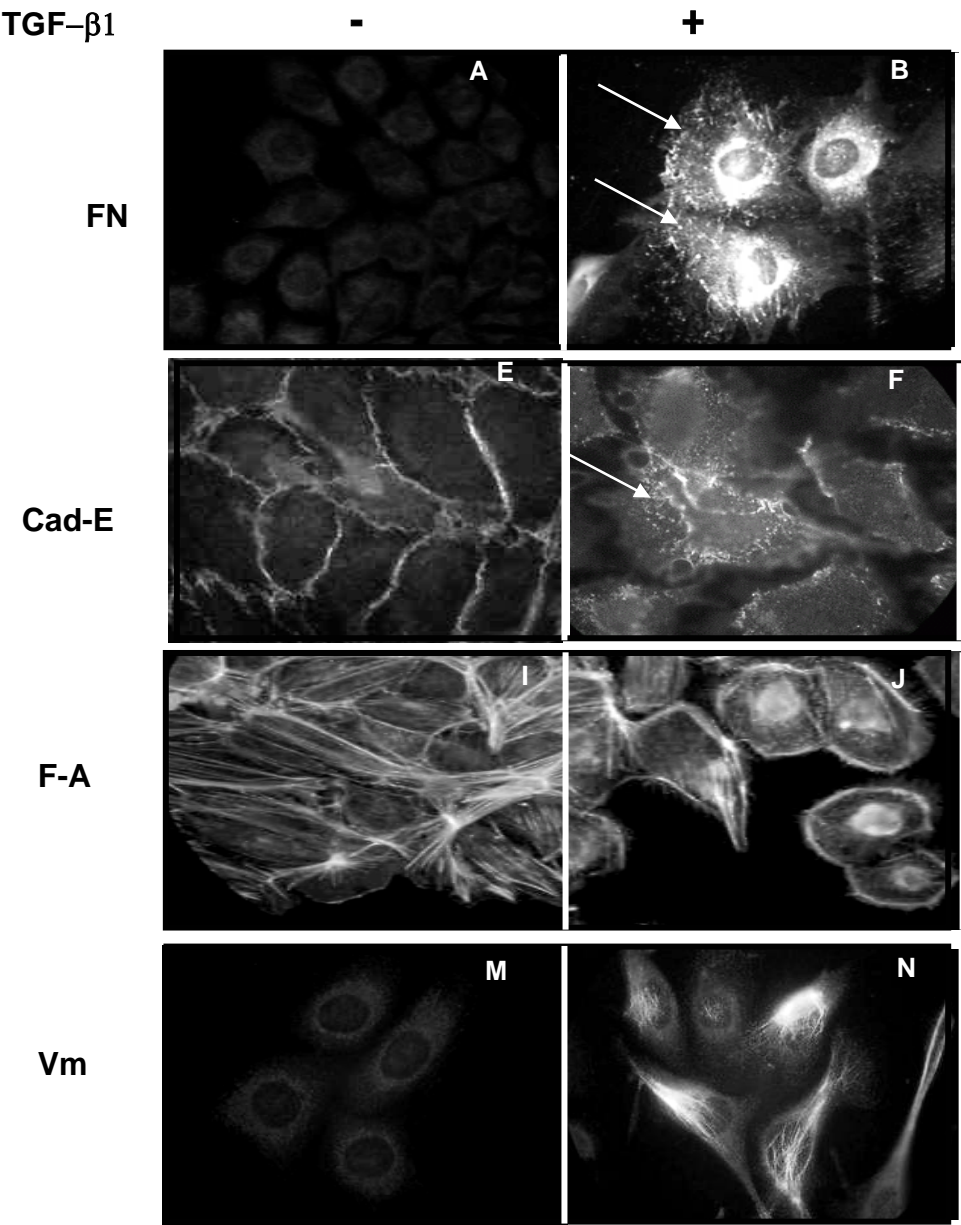


Figure 5

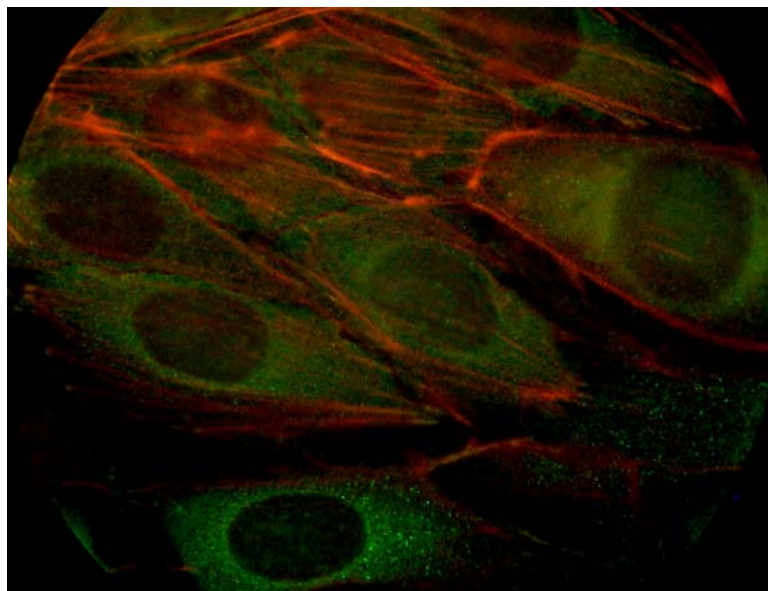
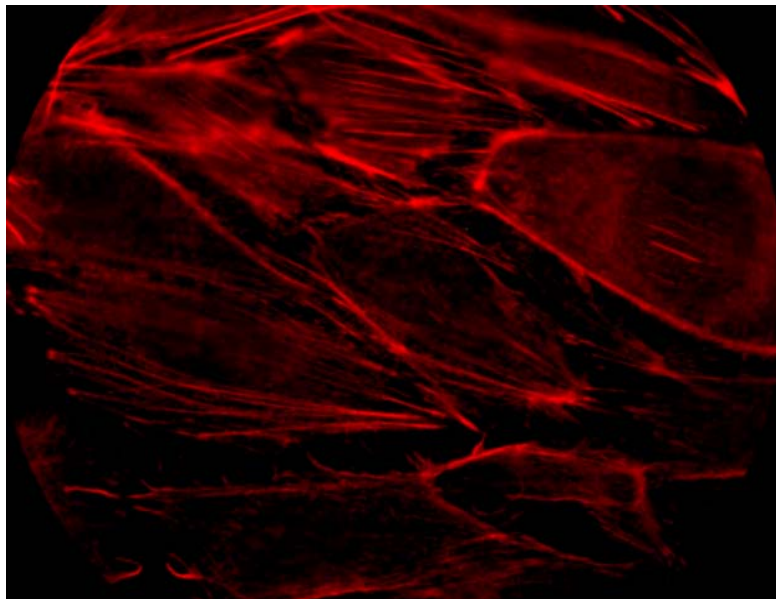


PDV

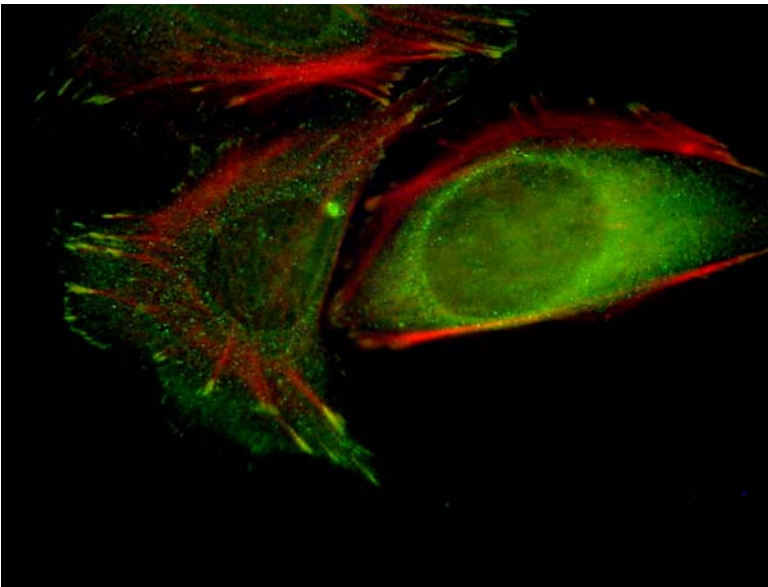
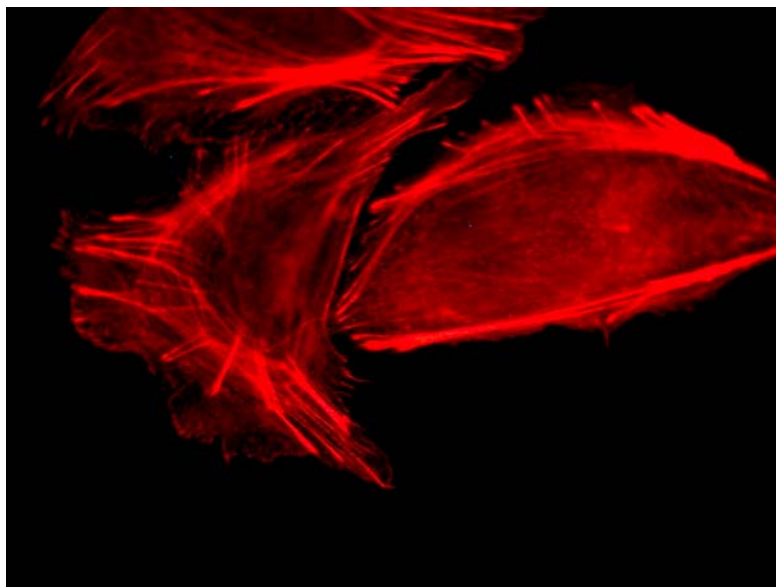
F-actin

Vinculin

S/T

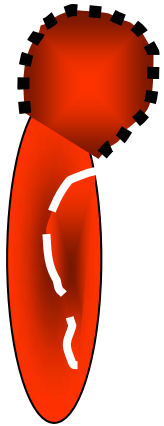


TGF- β 1



100X

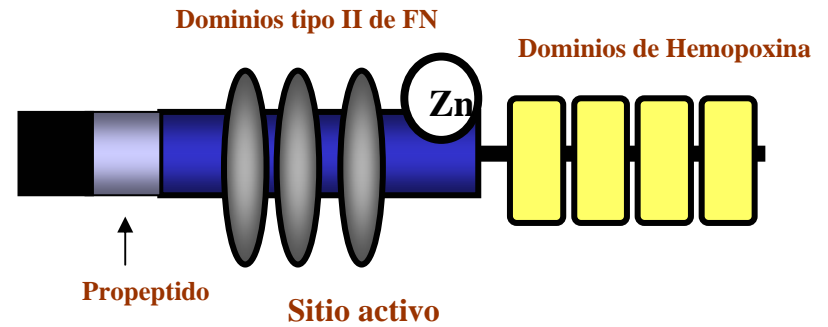
Sistema uPA-MMP-9



PAI 1

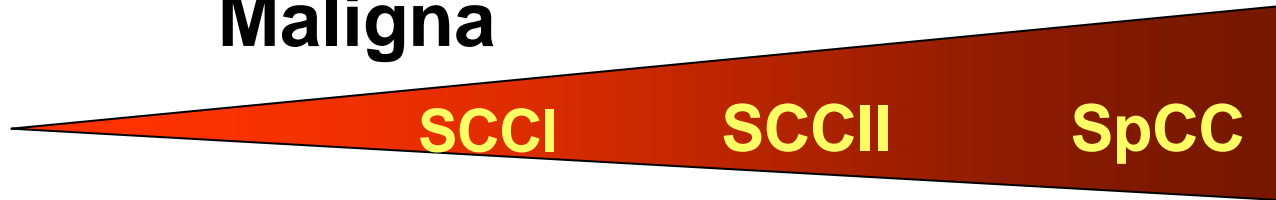


uPA

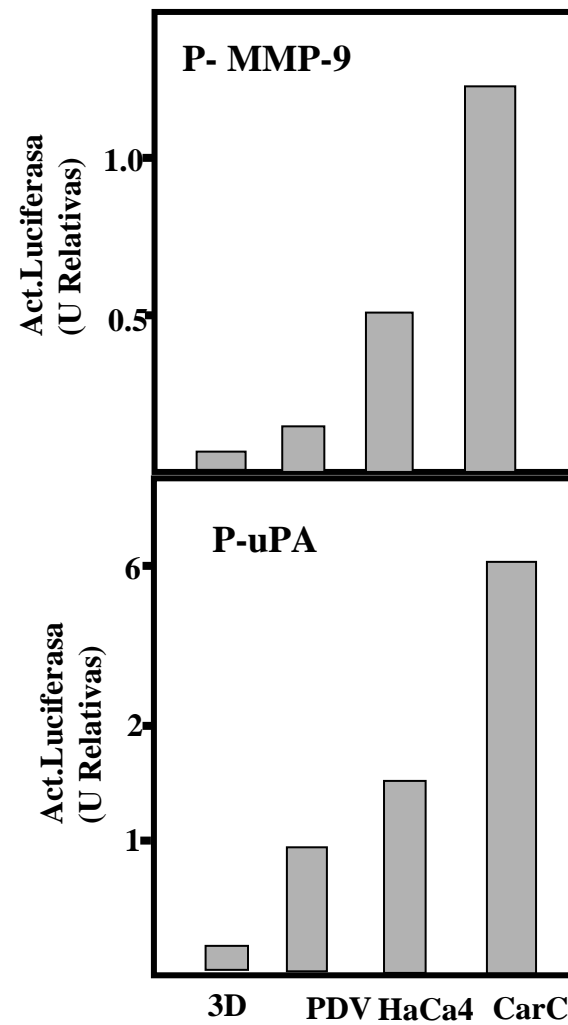
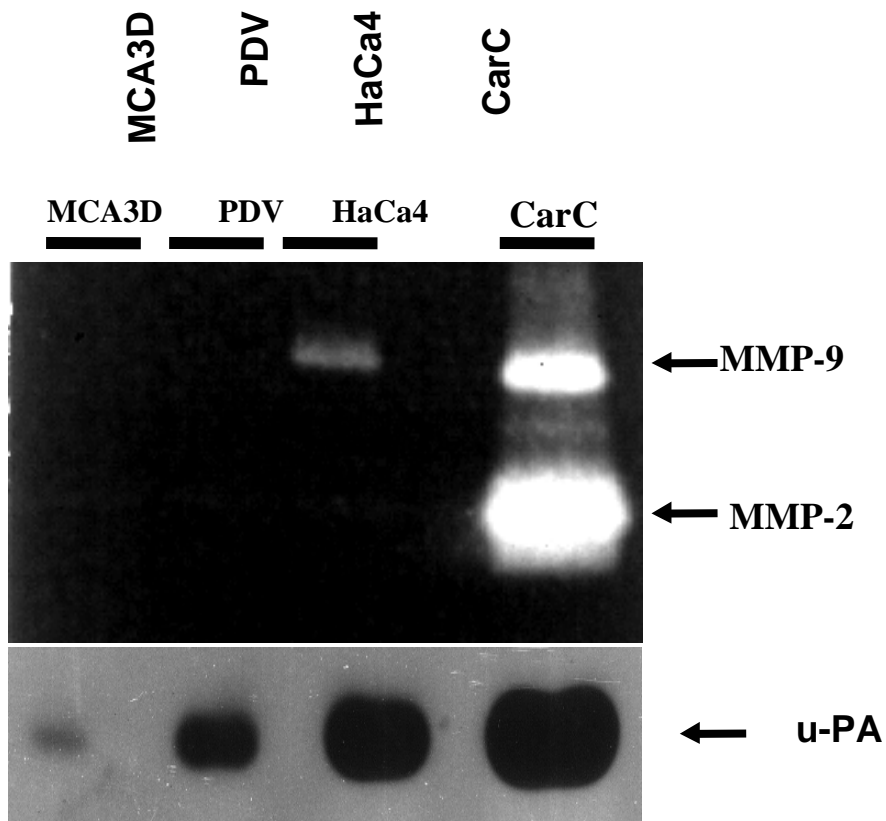


MMP-9

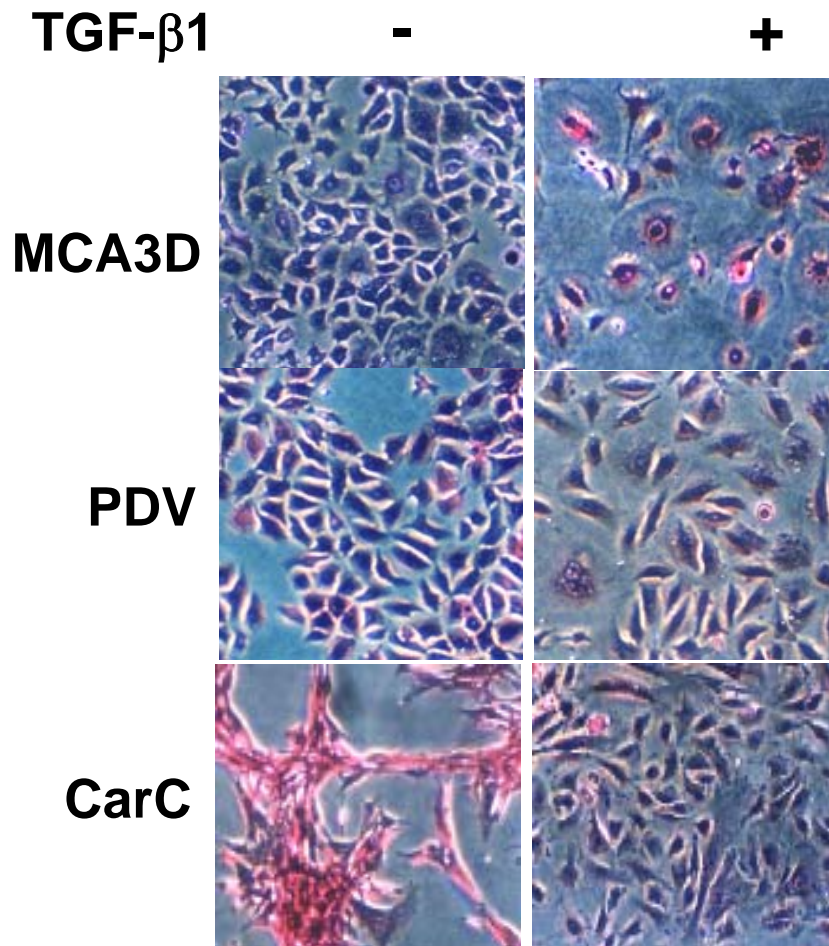
Progresión Maligna



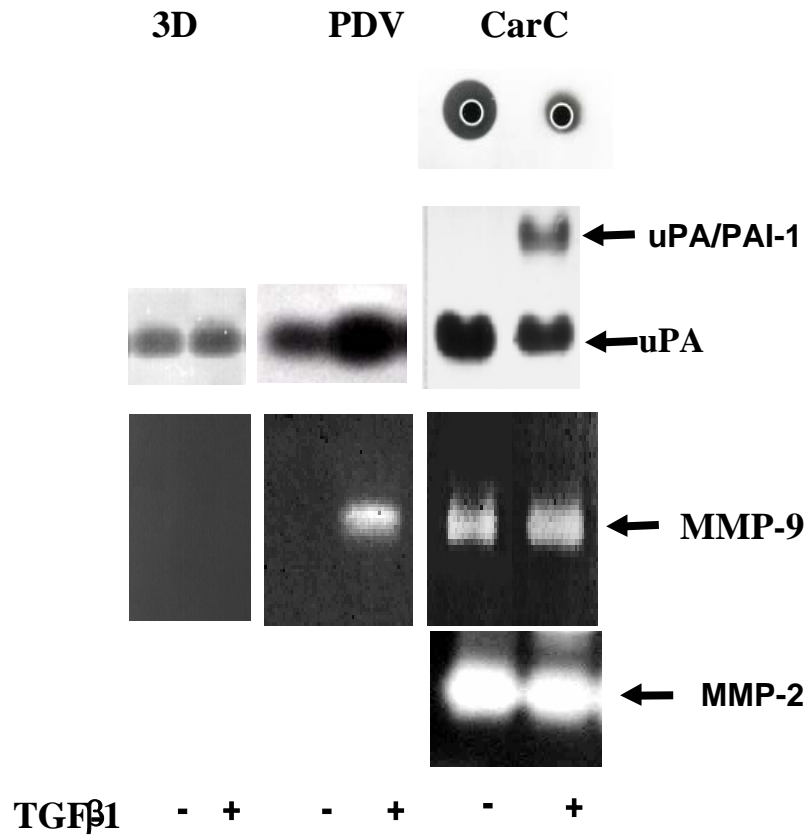
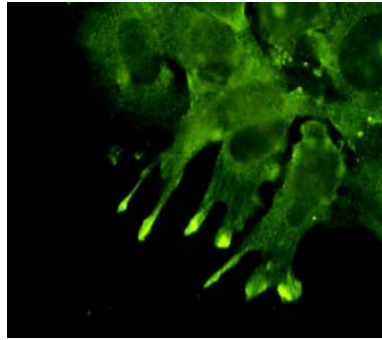
	MCA3D	PDV	HaCa4	CarC
Tumorigenicidad	-	+	++	++
Capacidad metastásica	-	-	++	++
Morfología	Epitelial	Epitelial	Epiteliode	Fusocelular
H-Ras	Normal	Mutado 1:2 con normal	Viral	Mutado, pérdida del alelo normal
Cadherina E	+	+	-	-
Queratinas	+	+	+	-/+
Vimentina	-	-	+	+



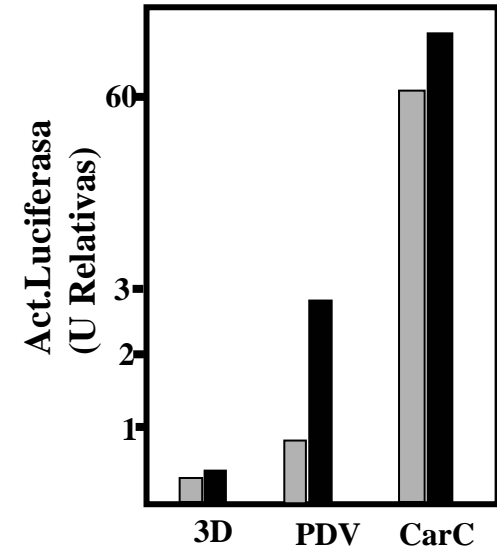
Efecto de TGF- β 1 sobre el fenotipo celular



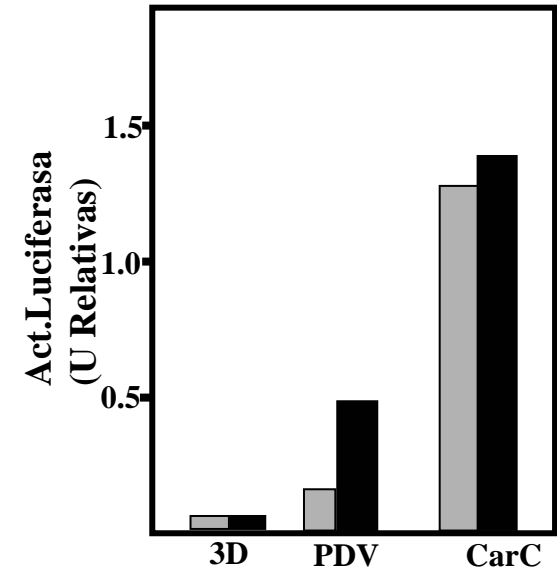
TGF- β 1- uPA/MMP-9



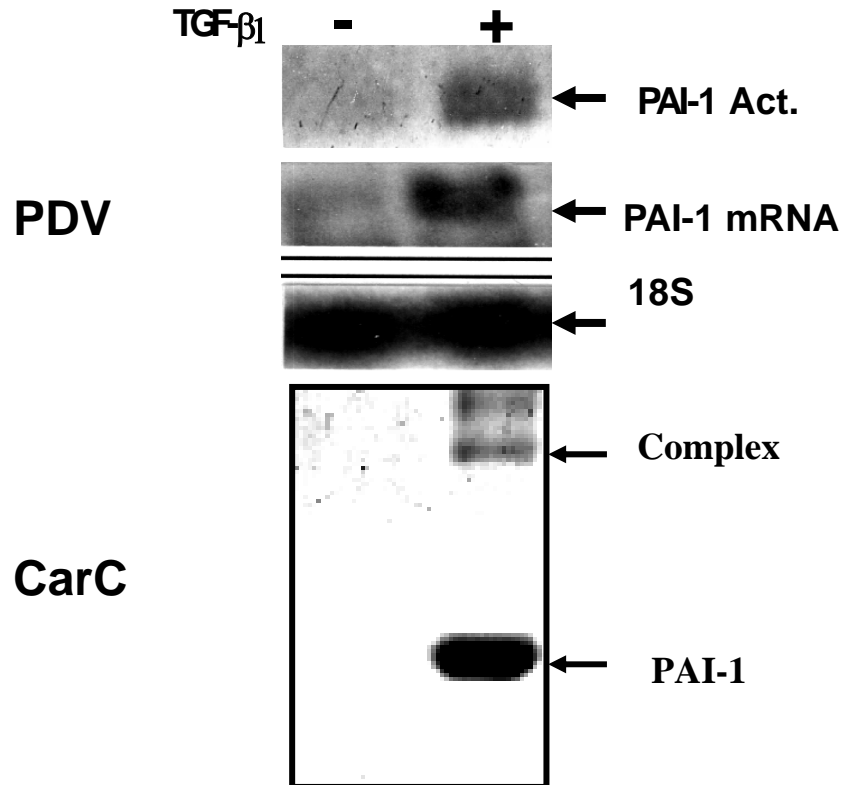
Promotor uPA



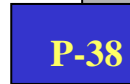
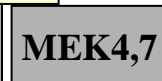
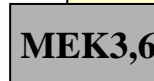
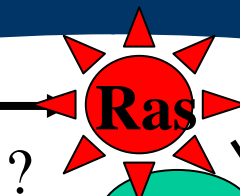
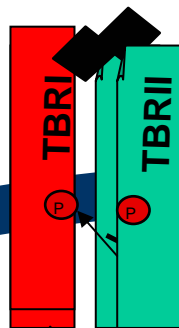
Promotor MMP-9



Efecto de TGF- β 1 sobre PAI-1



TGF β 1



SMAD2,3



CITOPLASMA

Respuesta Biológica

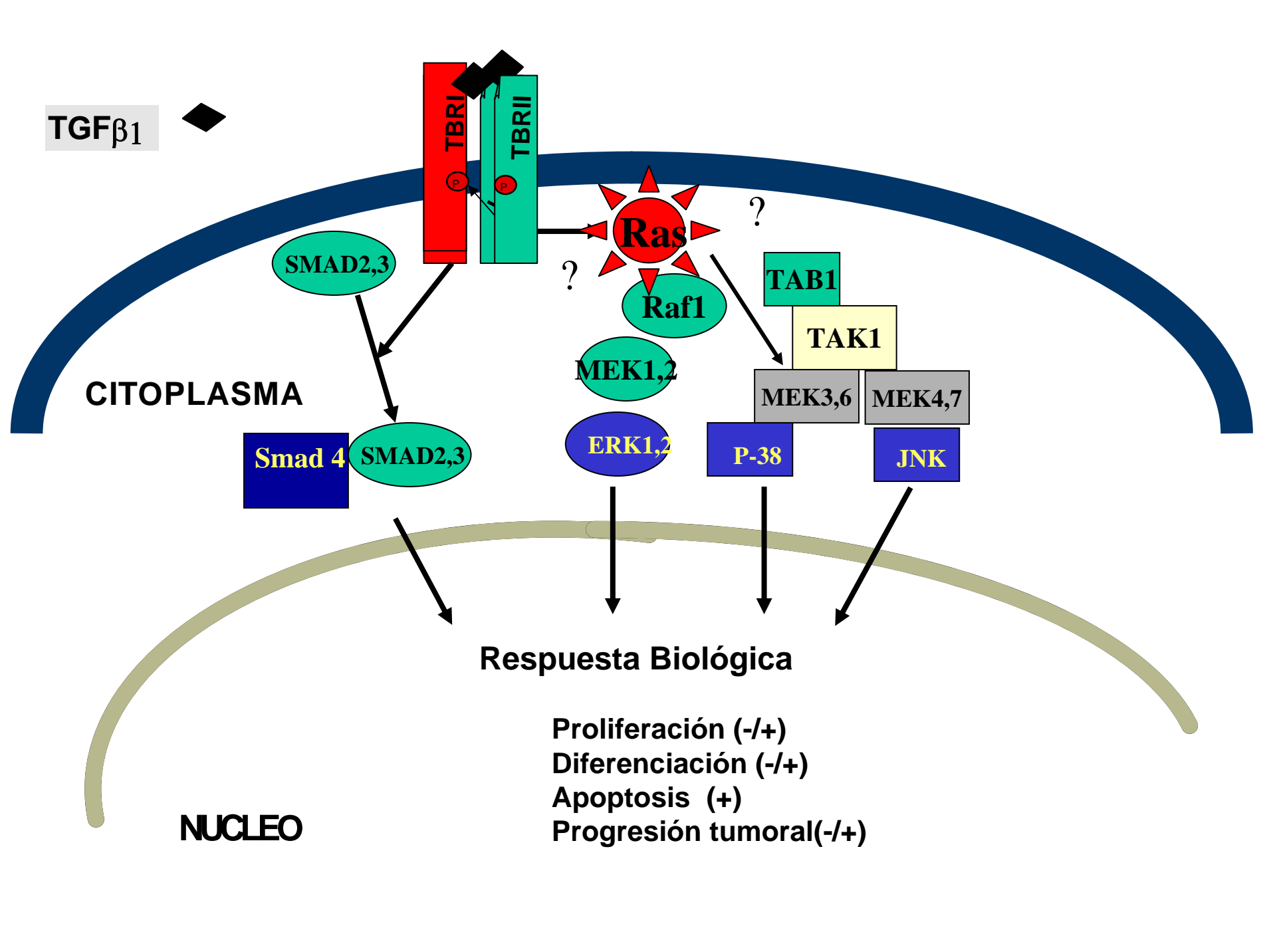
Proliferación (-/+)

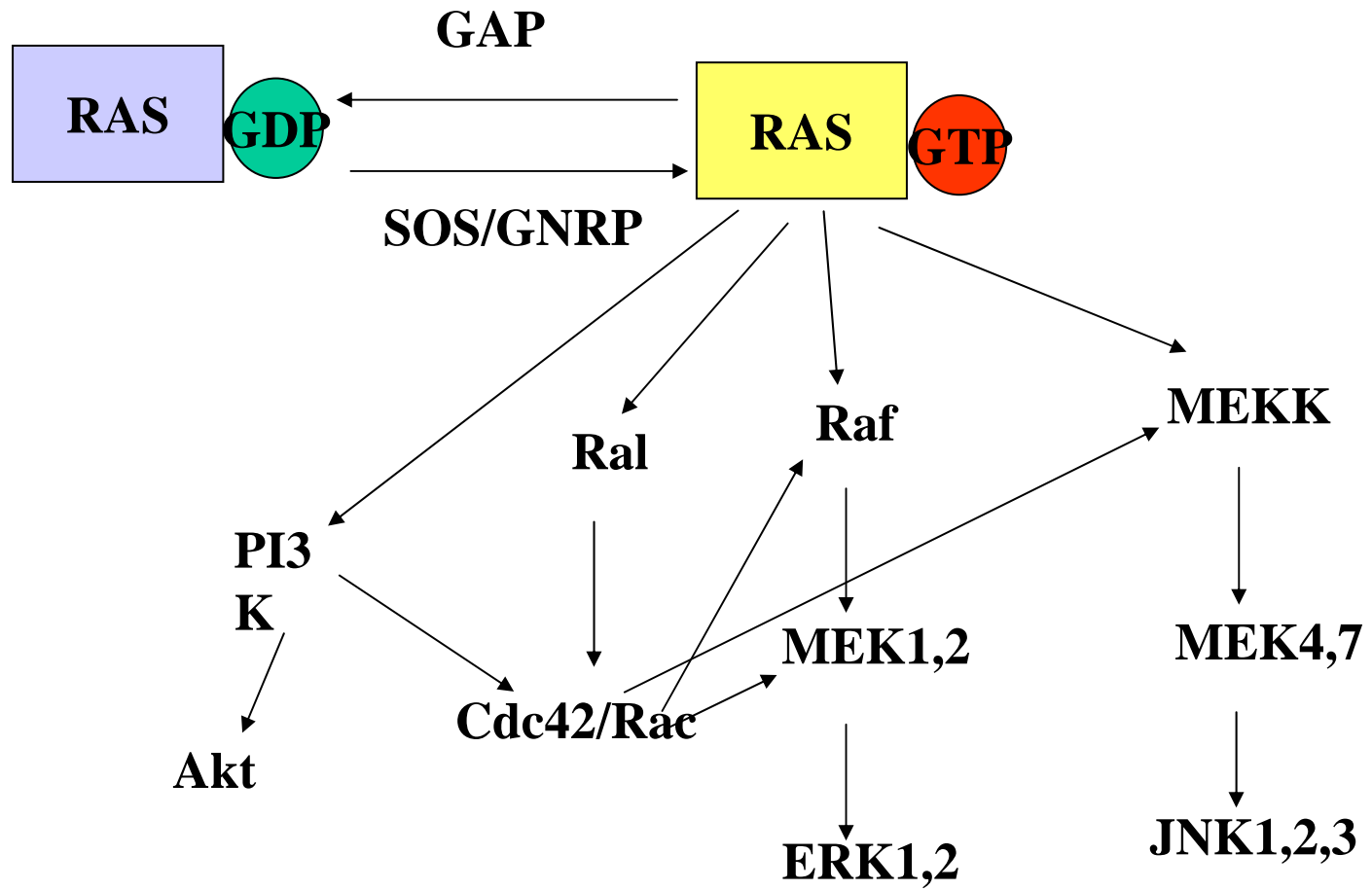
Diferenciación (-/+)

Apoptosis (+)

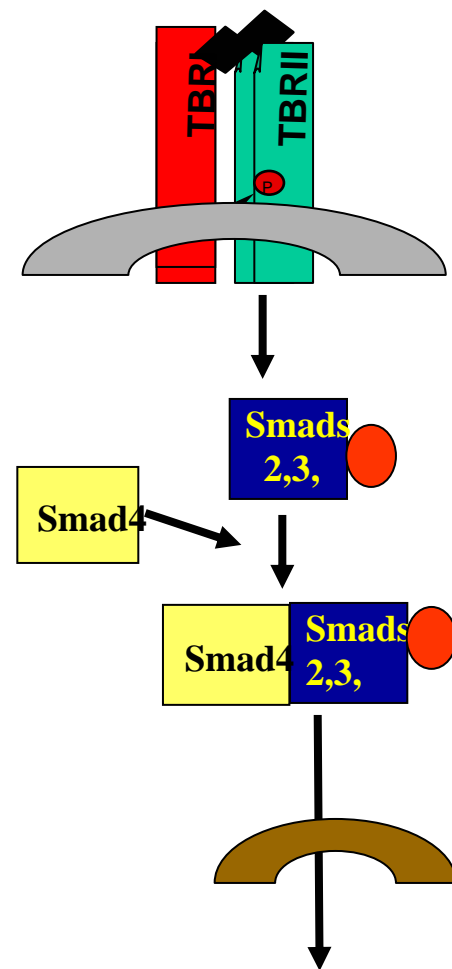
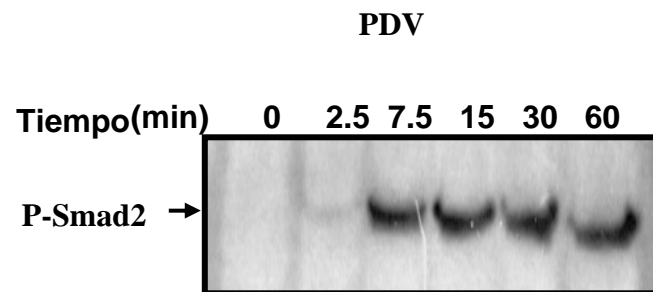
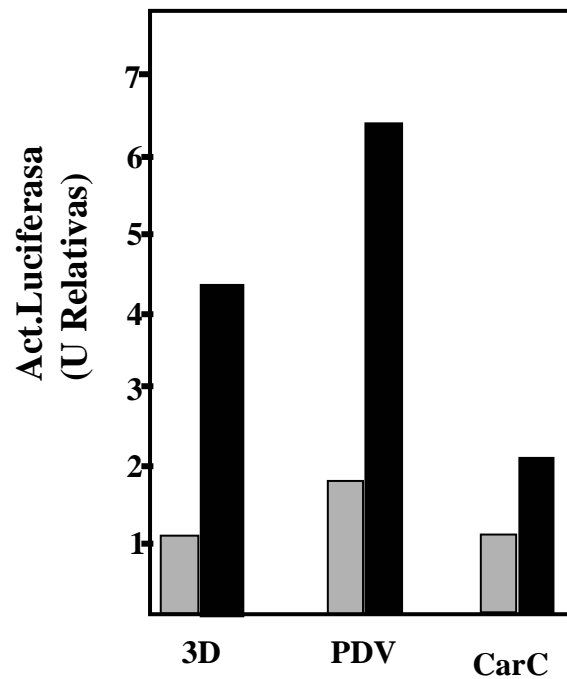
Progresión tumoral(-/+)

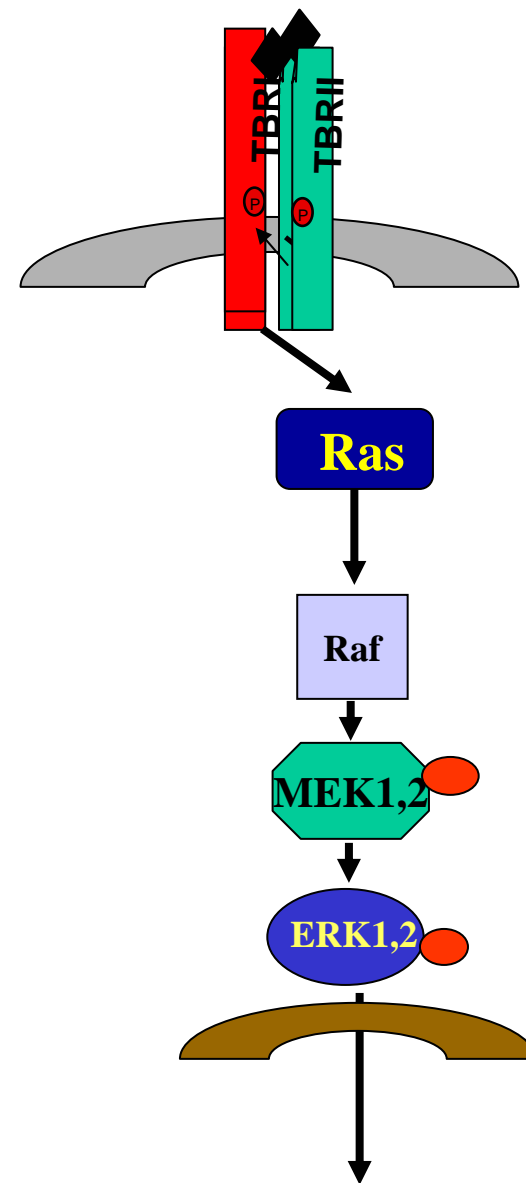
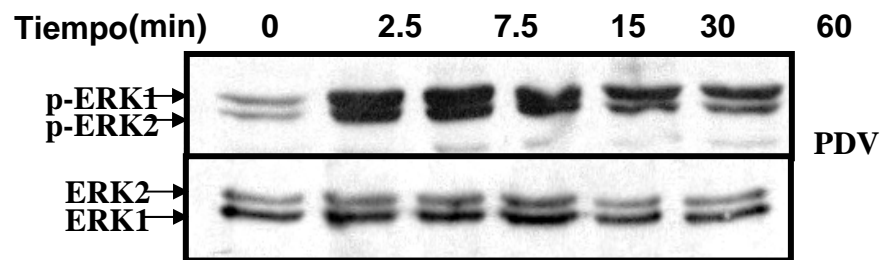
NUCLEO

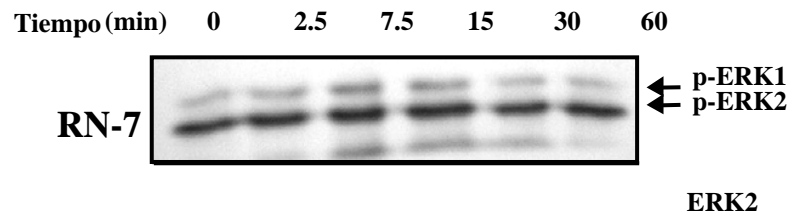
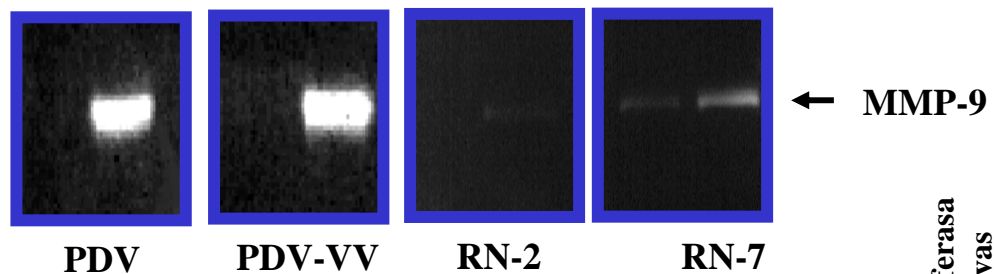
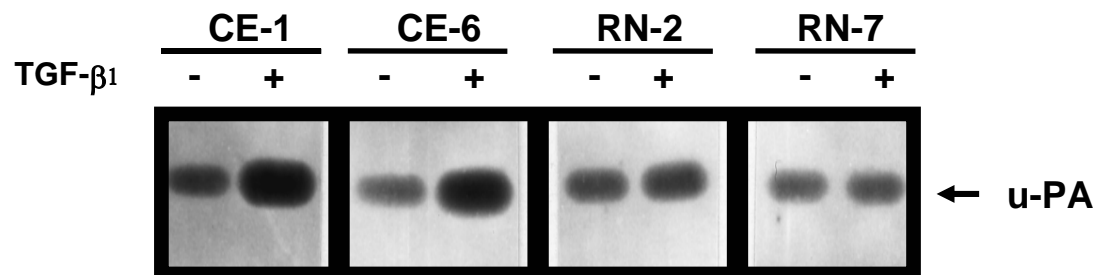




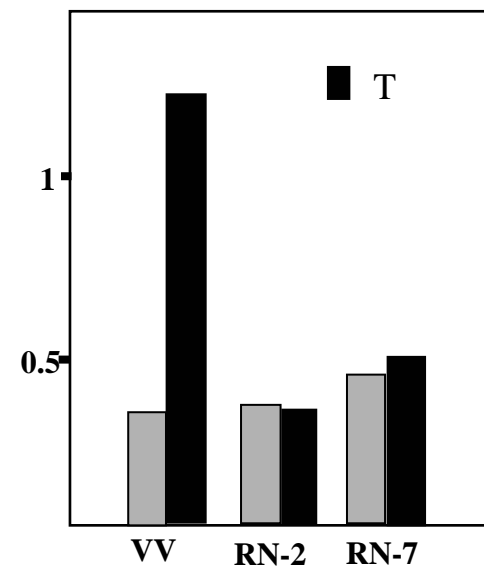
Promotor 3TPlux





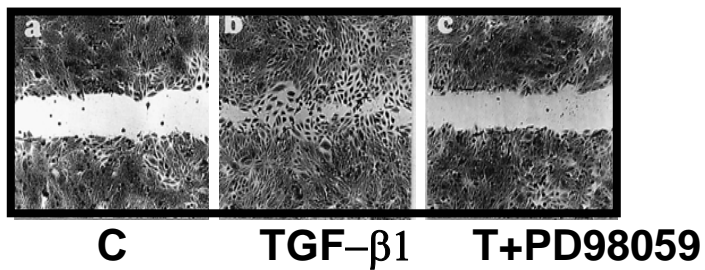
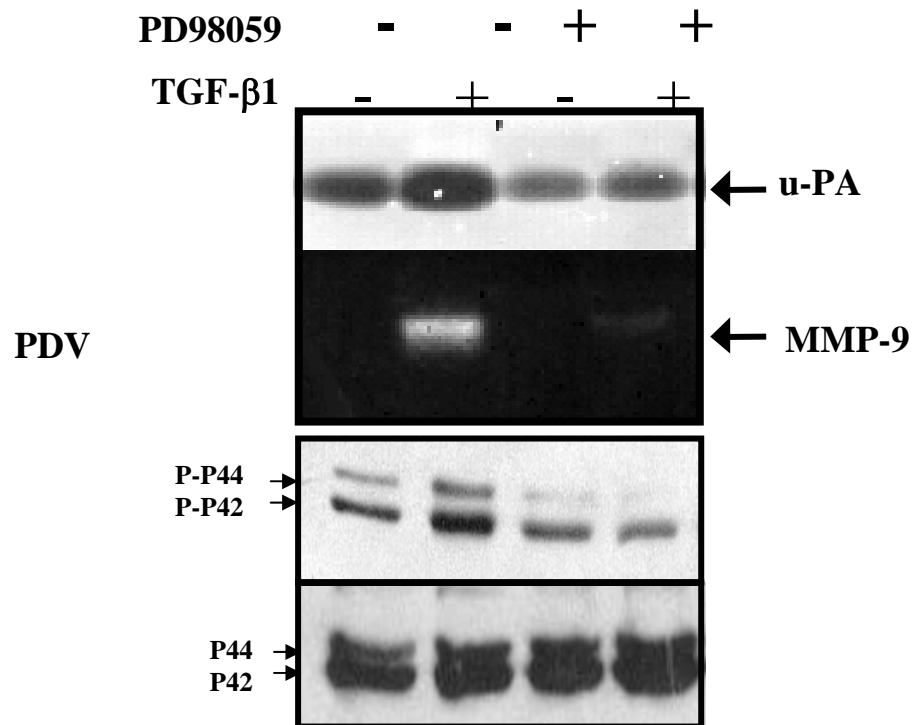


Promotor MMP9, .

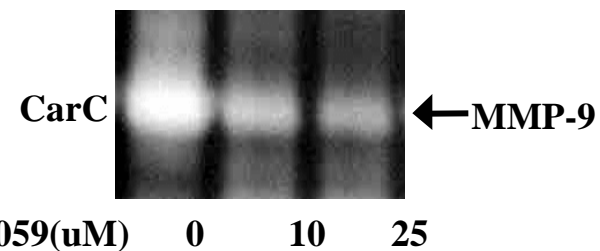
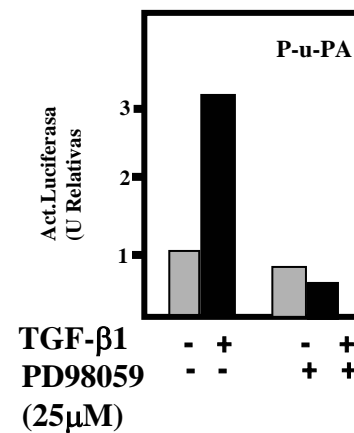
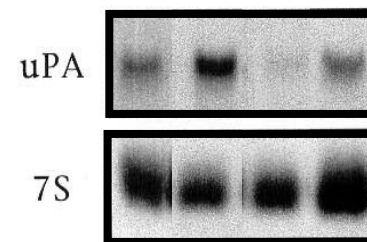


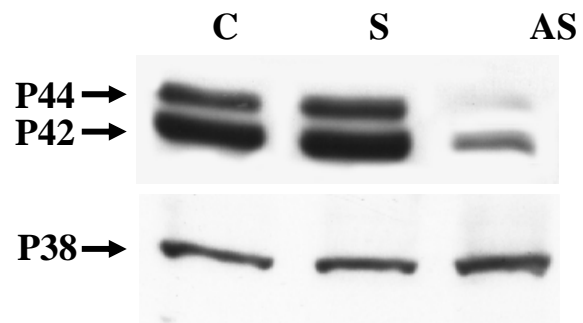
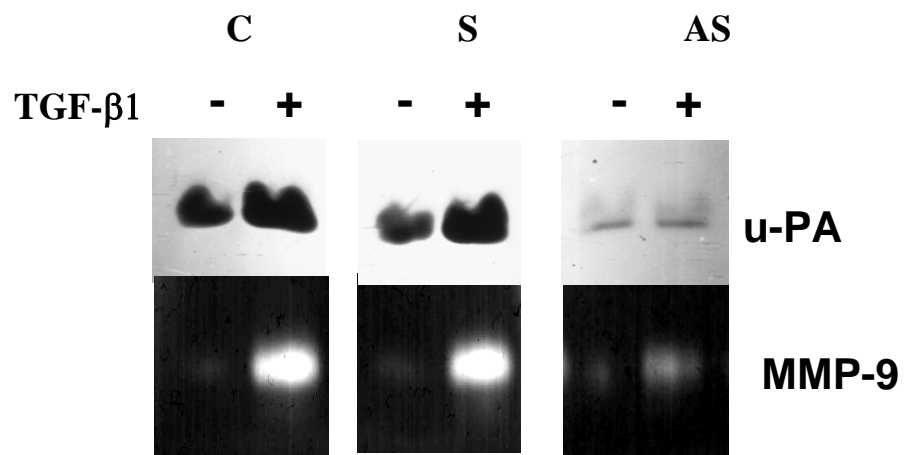
Papel de H-Ras

Papel de MEK1,2

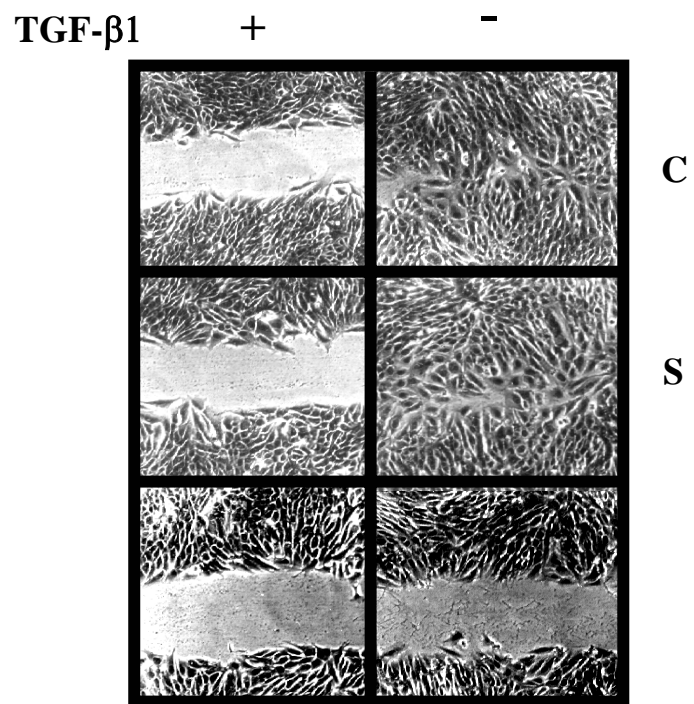


TGF- β 1	-	+	-	+
PD98059 (25 μ M)	-	-	+	+



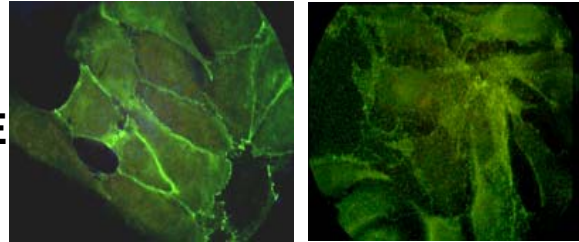


Papel de ERK1,2

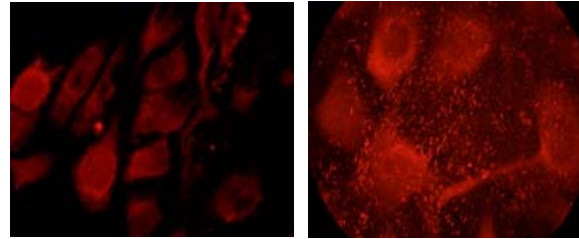


(A)

Cad-E



Fn



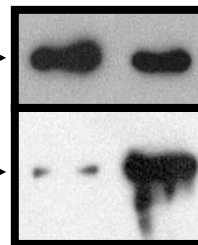
PVV

P-Ras3

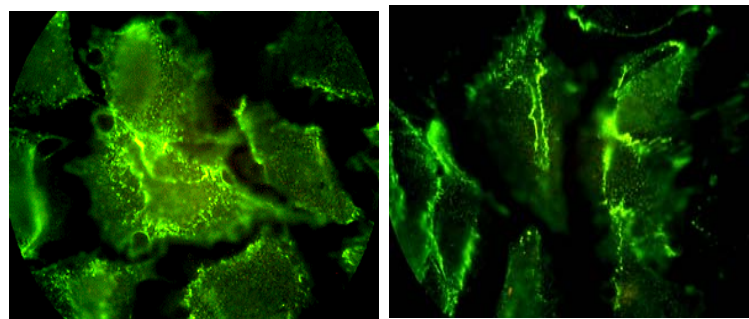
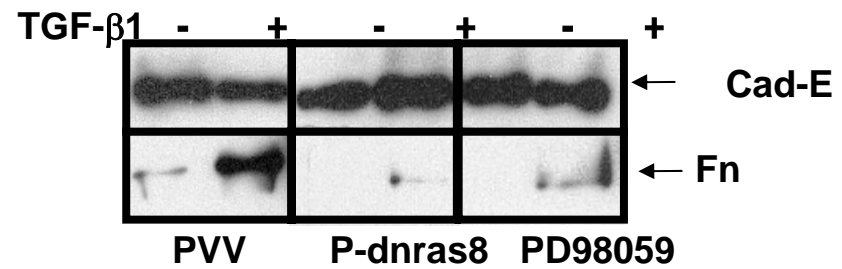
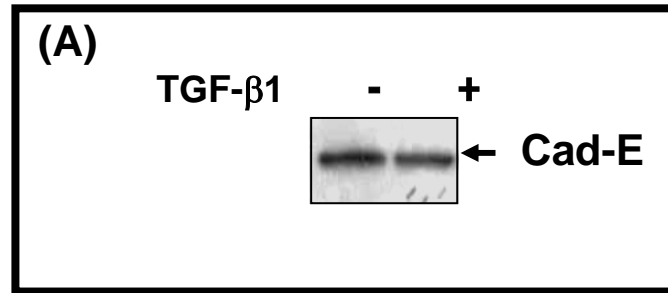
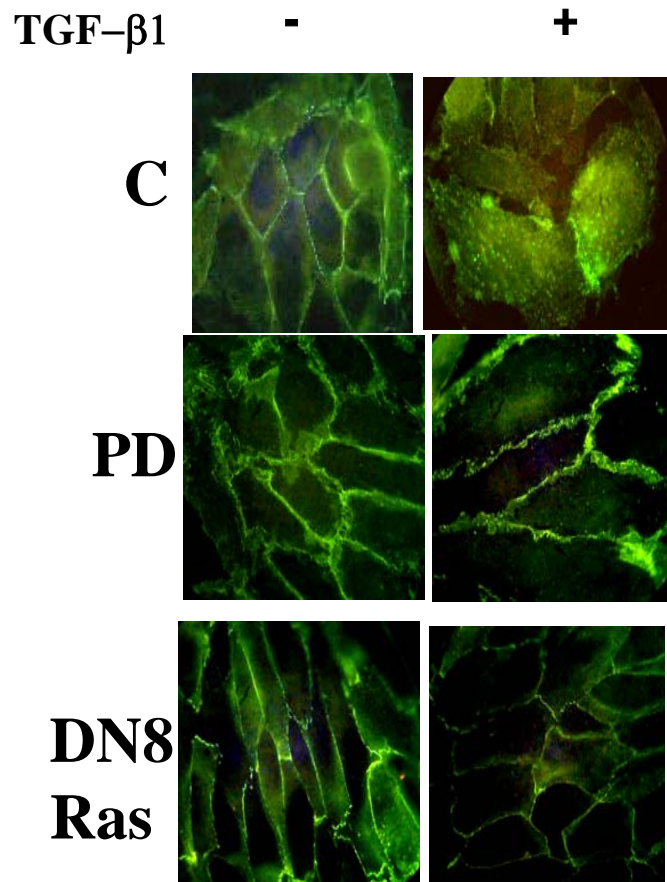
(B)

Cad-E →

Fn →



PVV P-Ras3

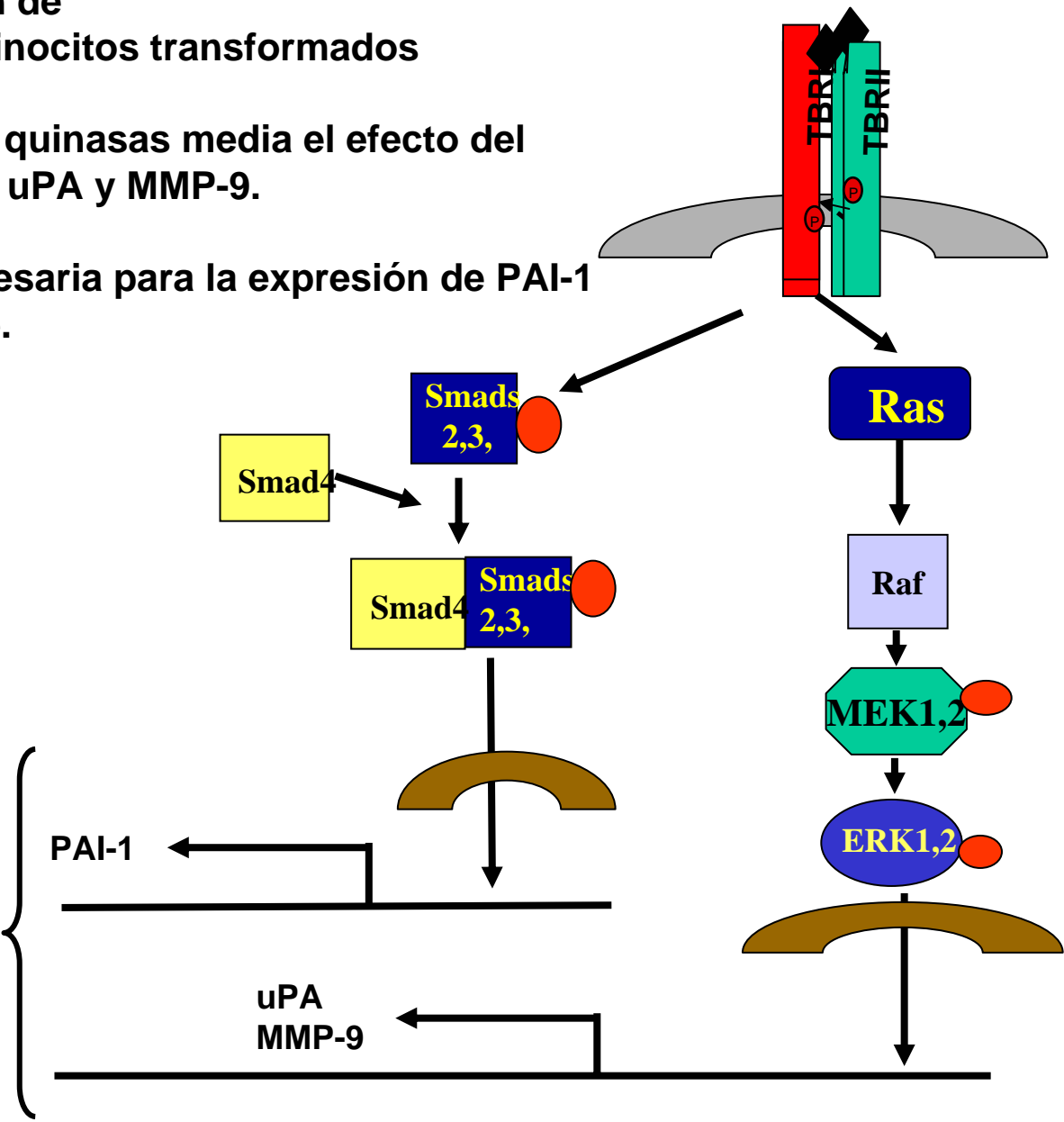
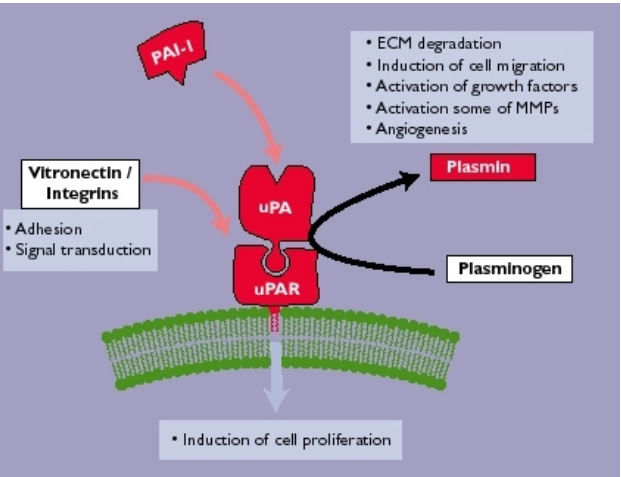


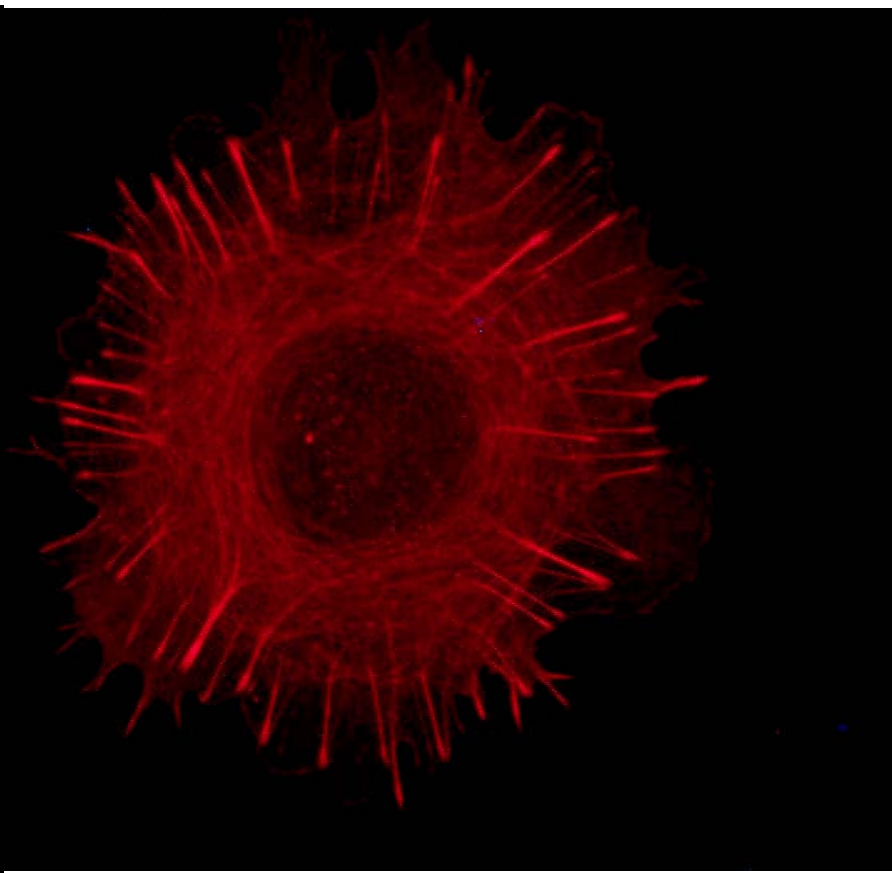
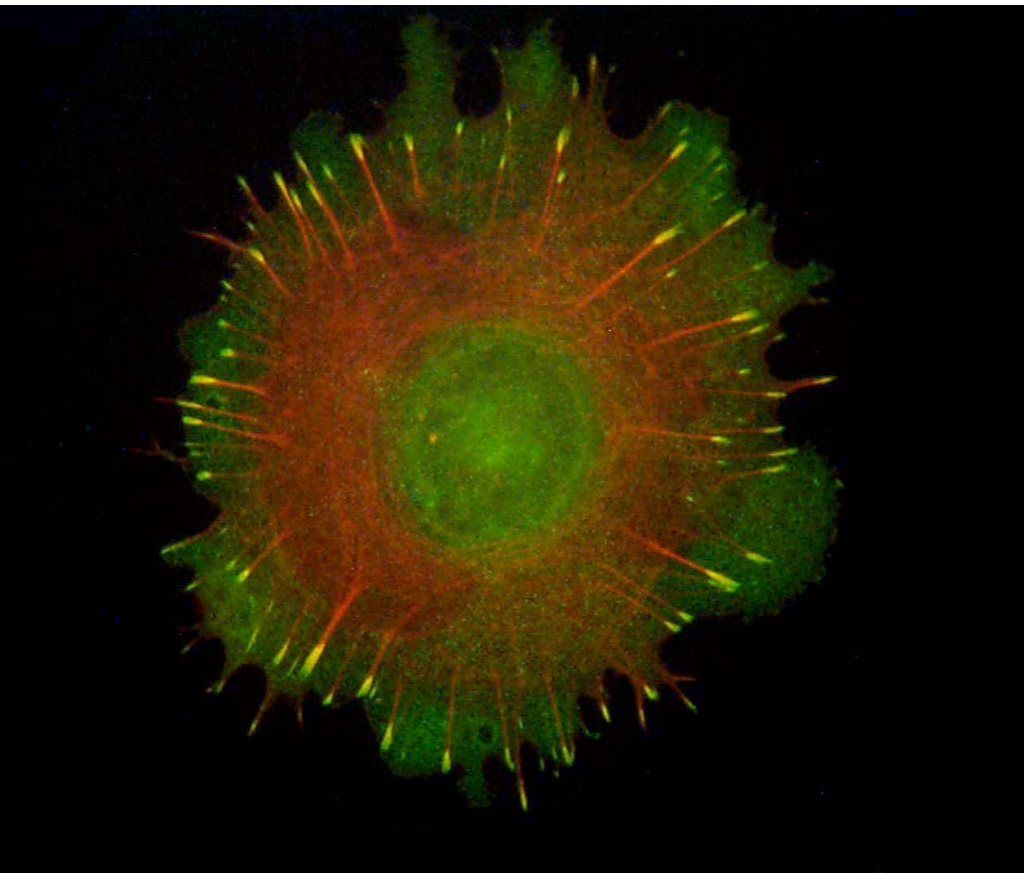
TGF-β1 estimula la producción de uPA, PAI-1 y MMP-9 en queratinocitos transformados

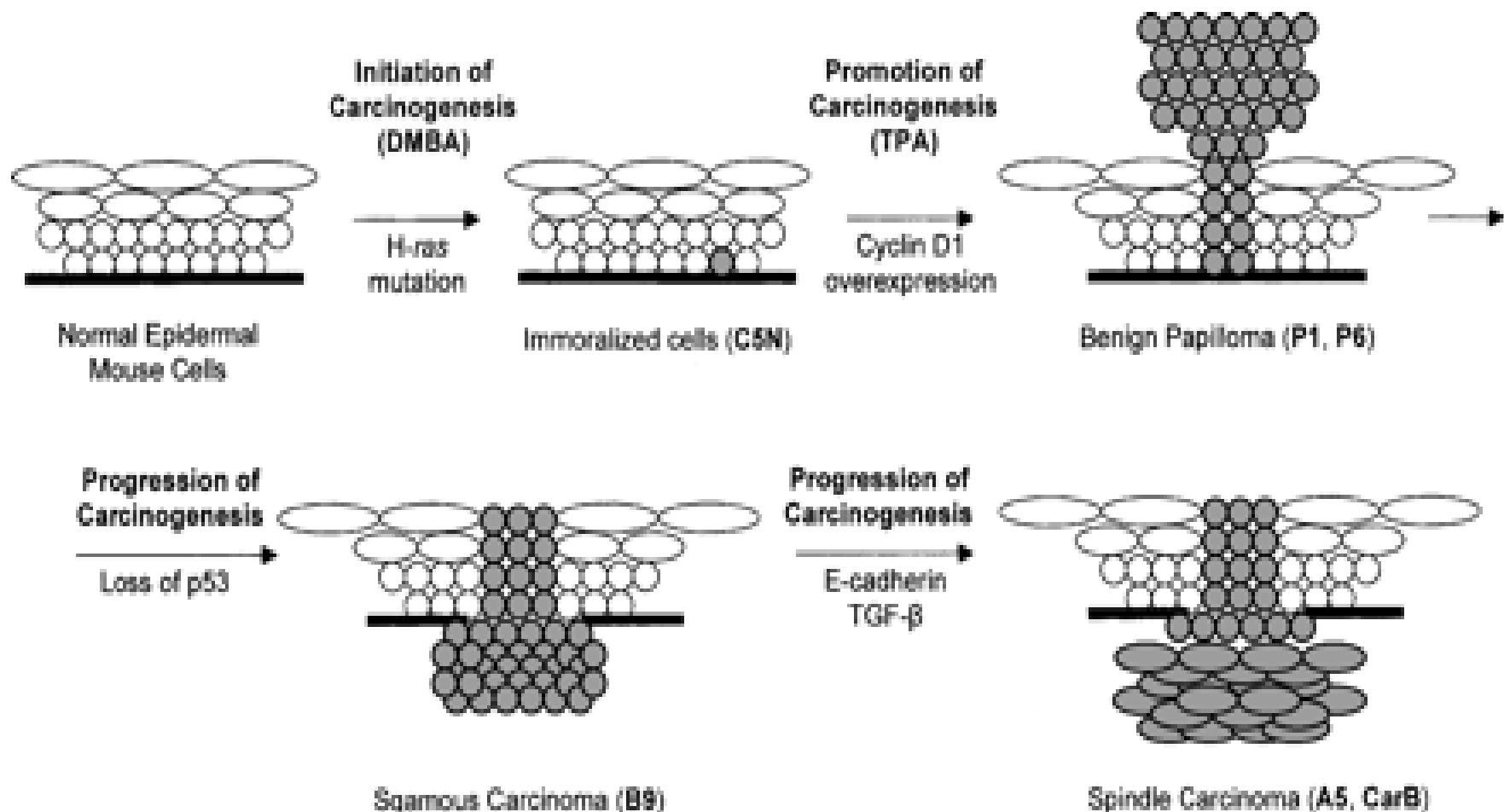
La ruta de H-Ras-ERK1,2 MAP quinasas media el efecto del Factor sobre la producción de uPA y MMP-9.

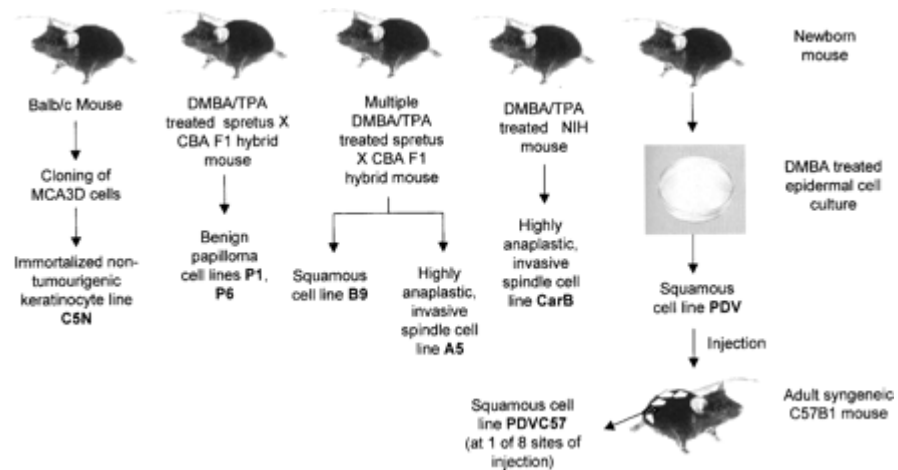
En PDV la vía de Smad es necesaria para la expresión de PAI-1
Iglesias y col. 2000, Oncogene.

Invasión y migración tumoral









TGF- β

Superfamilia de TGF- β

- TGF β 1-5
- BMPs
- Activinas

Receptor de TGF- β

- T β RI
- T β RII
- T β RIII

The physiological inhibitor PAI-1 plays an additive role in metastasis: The enzymatic activity of uPA is controlled by a number of inhibitors. One of these inhibitors, PAI-1, inhibits uPA when it is bound to its cell surface receptor uPAR. After PAI-1 binds to the uPA/uPAR complex, the cell internalizes all three molecules. uPA and PAI-1 are degraded and uPAR is recycled to the cell surface ready to bind another uPA molecule. Thus, there is a positive correlation between high PAI-1 expression and tumor metastasis.

The binding of uPA to uPAR transduces growth promoting signals in tumor cells, events which are separate from its enzymatic activity. In addition, uPAR interacts with vitronectin and integrins, which are involved in cell adhesion and signal transduction.

Thus, tumor cells acquire growth and survival advantages by overexpressing the uPA system, which promotes the growth, invasion, and metastatic spread of tumor cells via multiple mechanisms. This makes the uPA system an attractive target for the development of cancer drugs which attack cancer by acting at multiple points of the metastatic process.