



Regulación de la Potencialidad de las Células Madre Embrionarias por el Óxido Nítrico

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Reunión TerCel
Instituto de Neurociencias
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Types of Diabetes

- **IMMUNE** **5- 10%**
(JUVENILE DIABETES, TYPE 1)
- **METABOLIC** **90%**
(MATURITY ONSET, TYPE 2)

**DESTRUCTION OF PANCREATIC β -CELL BY
APOPTOSIS**

APPROACHES FOR CELL THERAPY IN DIABETES

1. TRANSPLANTATION OF PANCREAS/ ISLETS

- **Limited by the availability of organs for transplantation**
- **In the case of islet transplantation**
 - **Loss of islet material during the isolation and culture**
 - **Death of implanted islets**

APPROACHES FOR CELL THERAPY IN DIABETES

2. GENERATION OF DE PANCREATIC CELLS FROM STEM CELLS

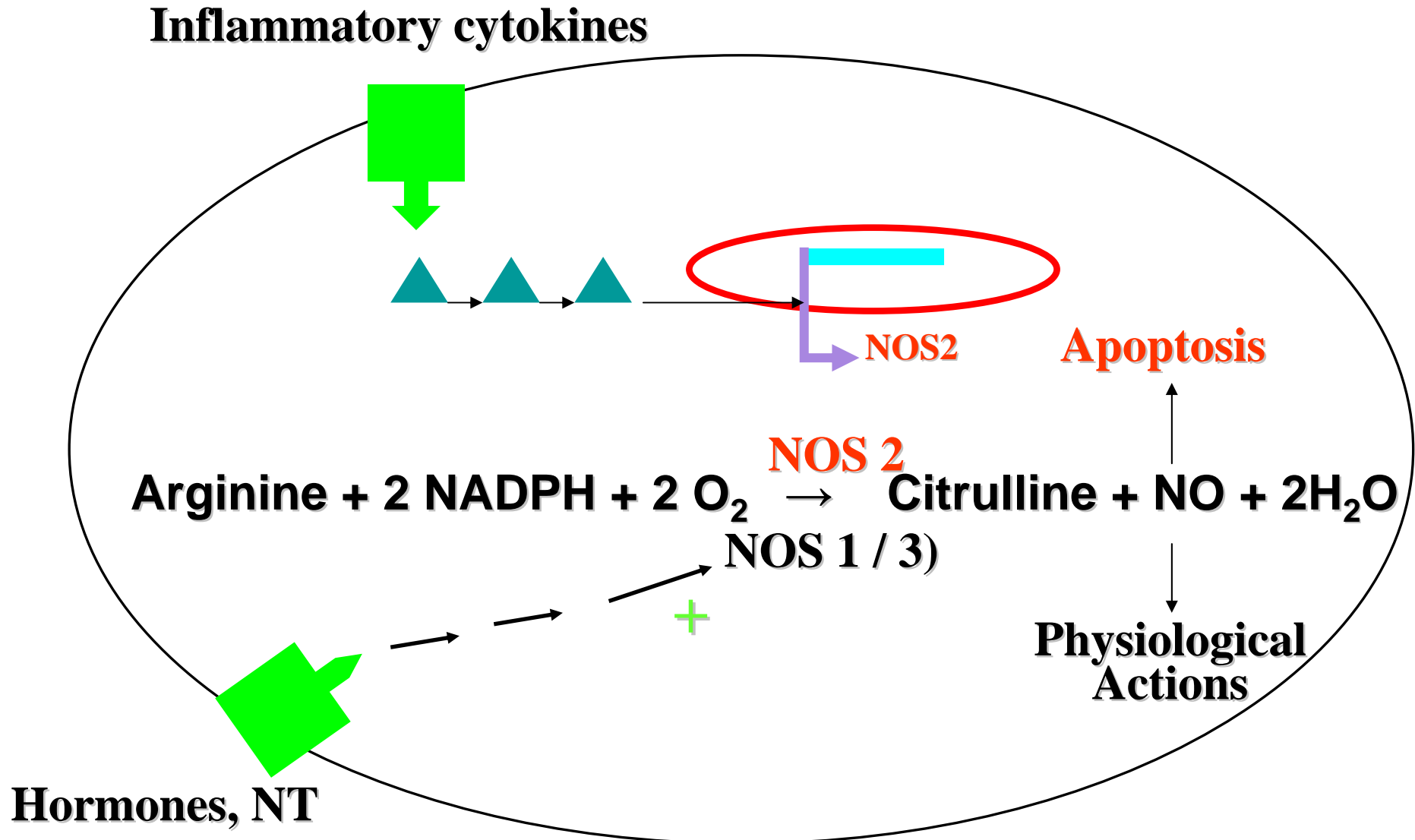
- **Potencial Sources of SC cells for Therapy**
 - SC derived from bone marrow
 - SC direct precursors of the damaged β -cell
 - SC present in blood
 - SC derived from other tissues
 - SC embryonic and fetal

APPROACHES FOR CELL THERAPY IN DIABETES

3. β -CELL PROTECTION

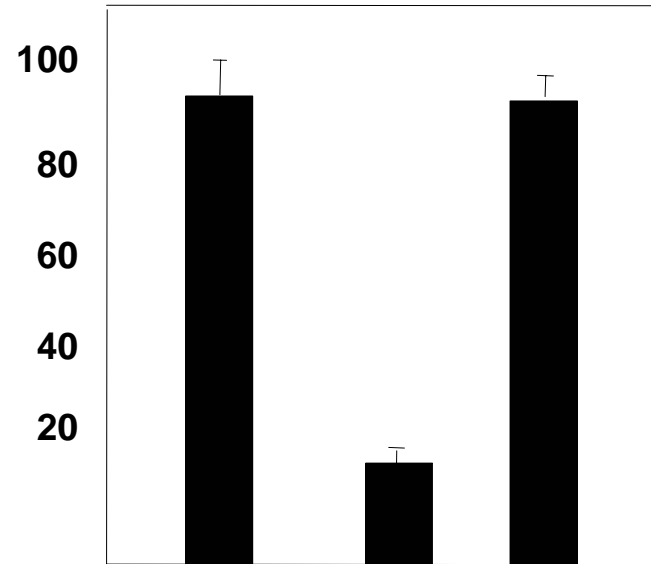
- **Identification of trophic factors that:**
 - **Protect the endocrine pancreas against the immune attack**
 - **Increase the survival of precursors during differentiation to insulin producing cells**

DUAL ROLE OF NO IN THE CONTROL OF β -CELL FATE



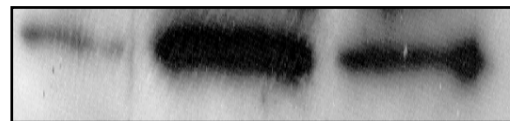
Survival Action of Nitric Oxide on β -Cells

Alive Cells, %

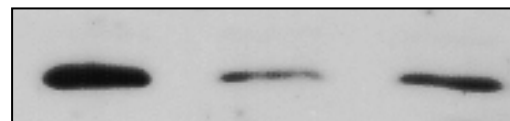


+
-
-
-
-
+

Serum
10 μ M DETA/NO



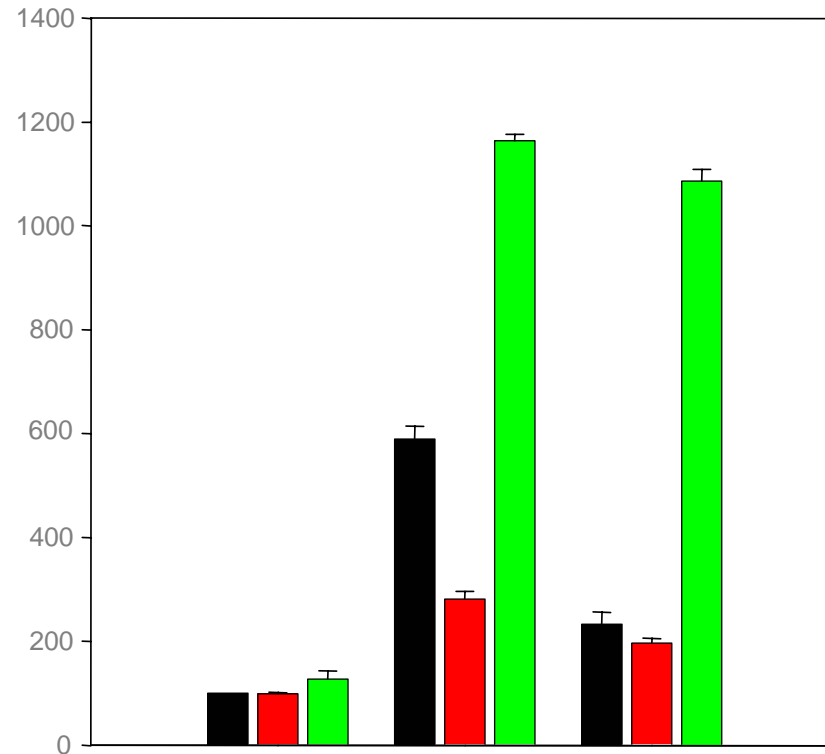
Cytochrome c



Bcl-2

Src Overexpression Confers Protection

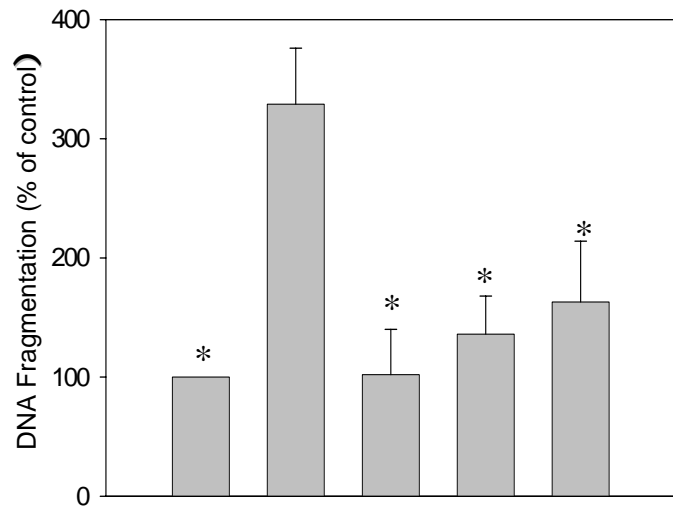
DNA
Fragmentation



v-Src: active
nd-Src: inactive

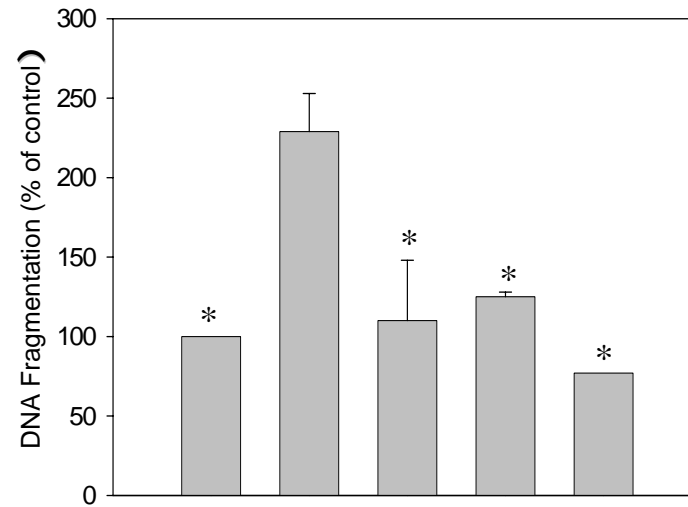
Serum	+	-	-
DETA/ NO	-	-	+

Protective action of NO, Insulin and IGF-1 in Islets



+	-	-	-	-	Serum
-	-	+	-	-	10 μ M DETA-NO
-	-	-	+	-	100 nM IGF-1
-	-	-	-	+	10 nM Insulin

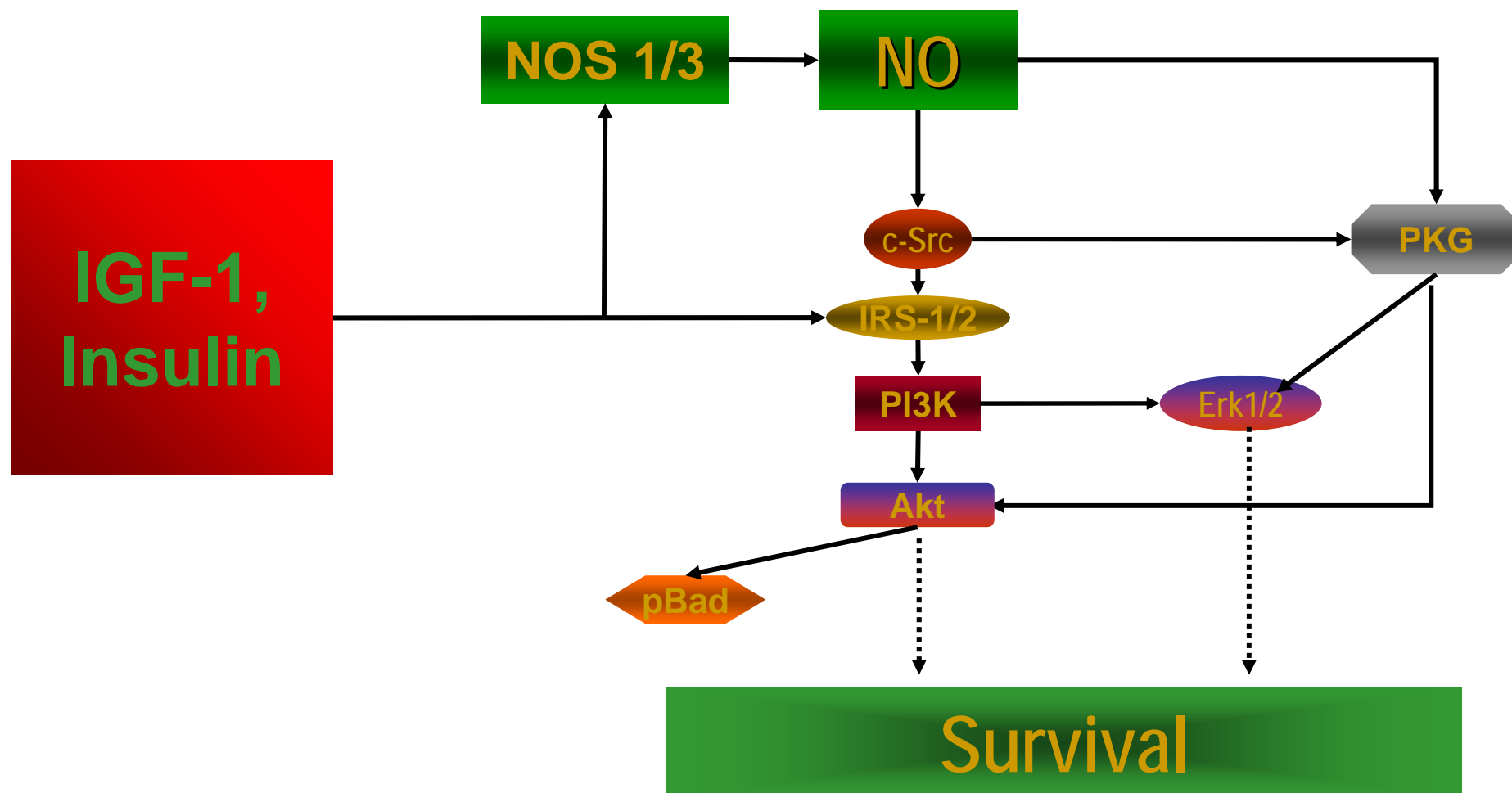
Rat



+	-	-	-	-	Serum
-	-	+	-	-	10 μ M DETA-NO
-	-	-	+	-	100 nM IGF-1
-	-	-	-	+	10 nM Insulin

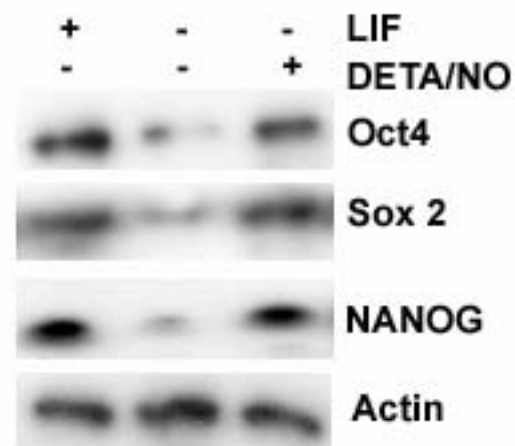
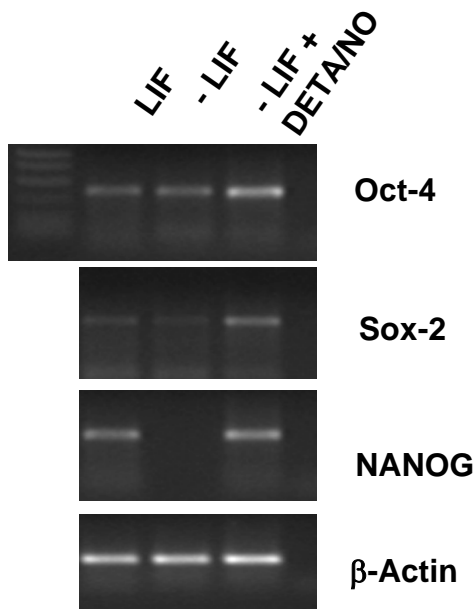
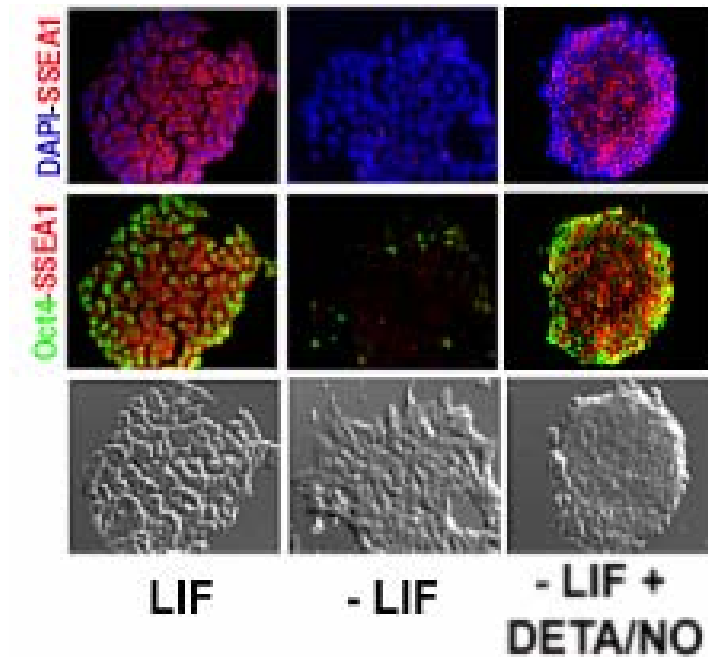
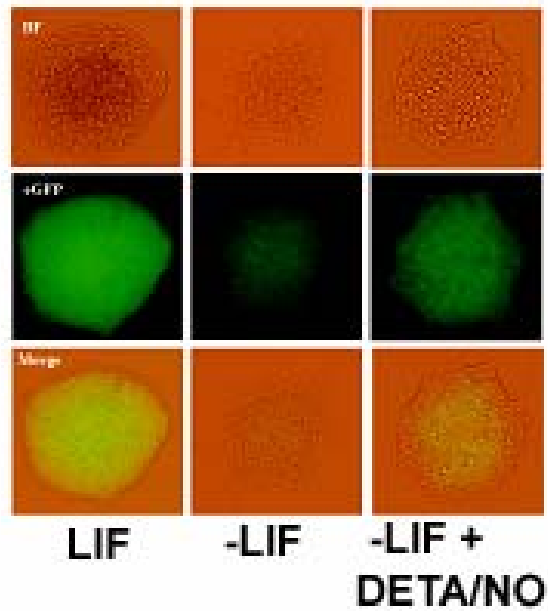
Human

Protective Signalling in the β -cell

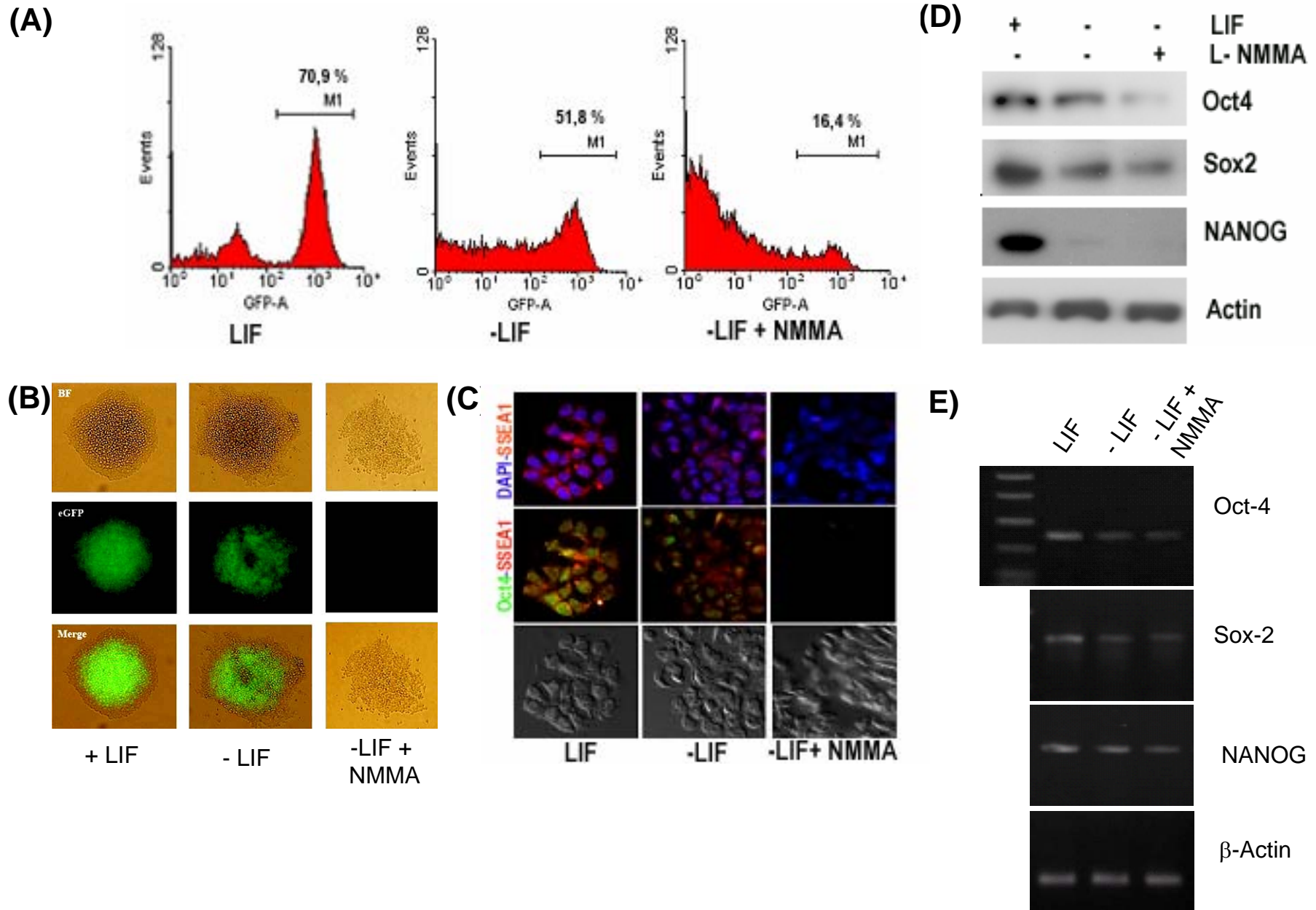


Studies with ES Cells

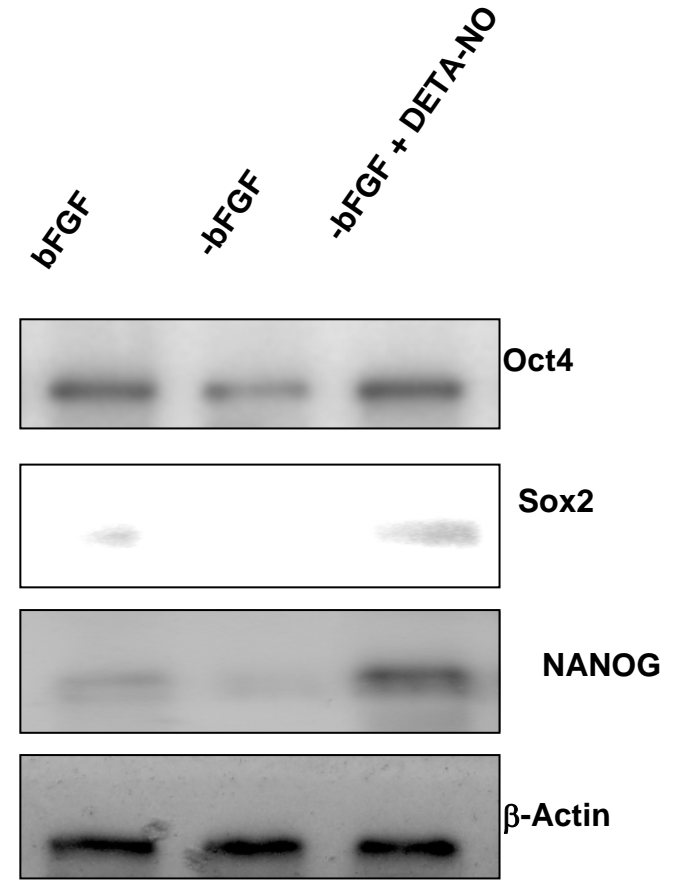
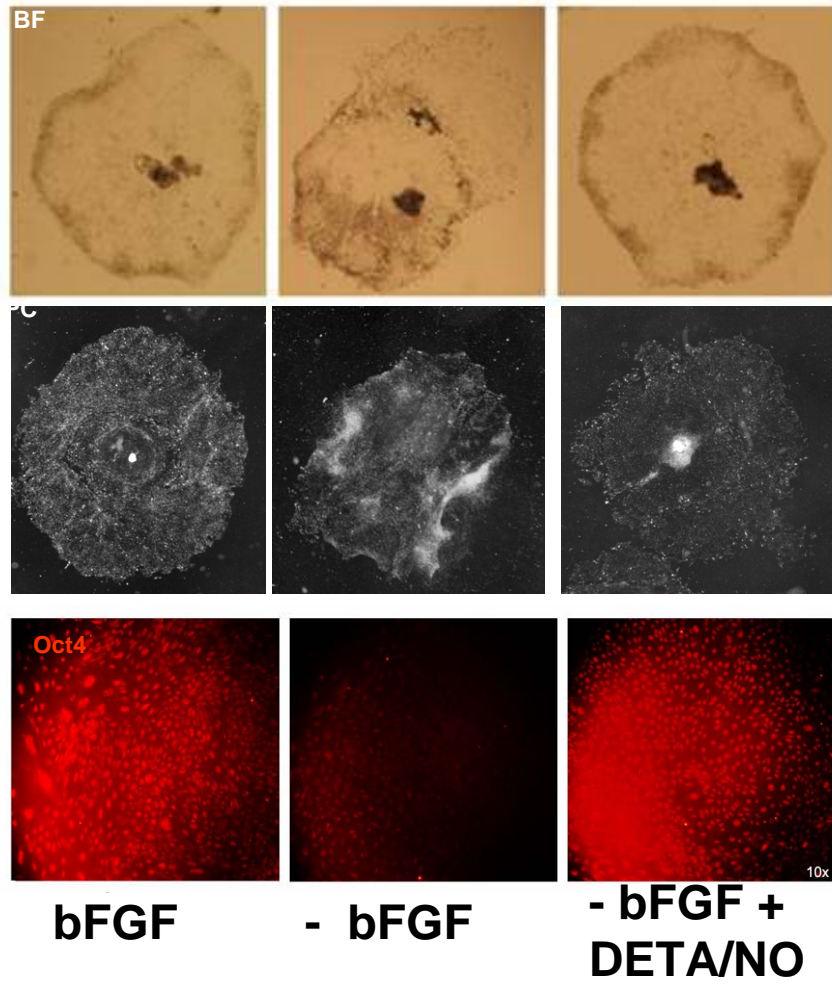
NO Promotes Undifferentiation of Embryonic Murine SC



The Inhibition of NO Production Blocks the Effect of LIF



NO Promotes Undifferentiation of Human Embryonic SC



NO Activates Src/Akt Pathway Specifically in ESC

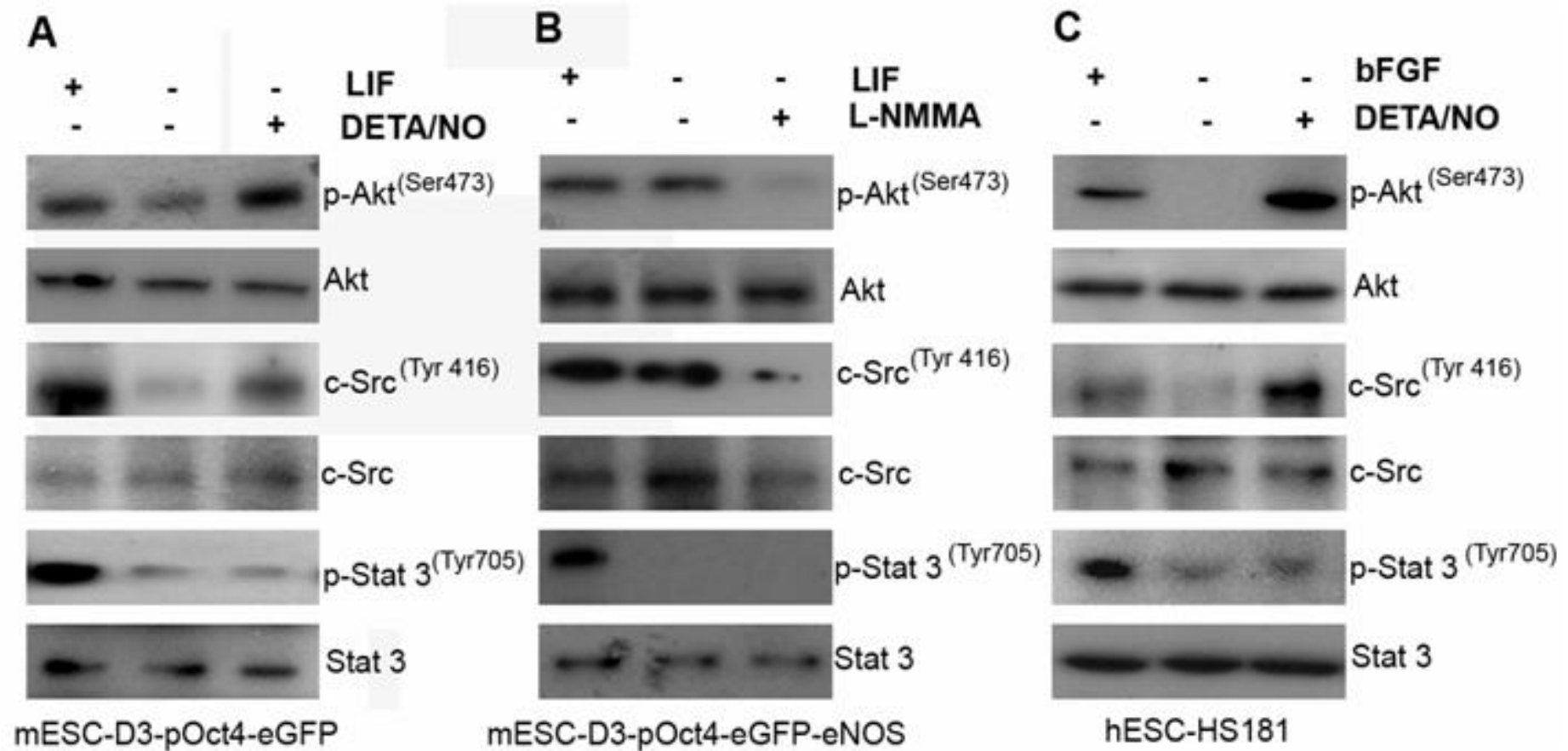
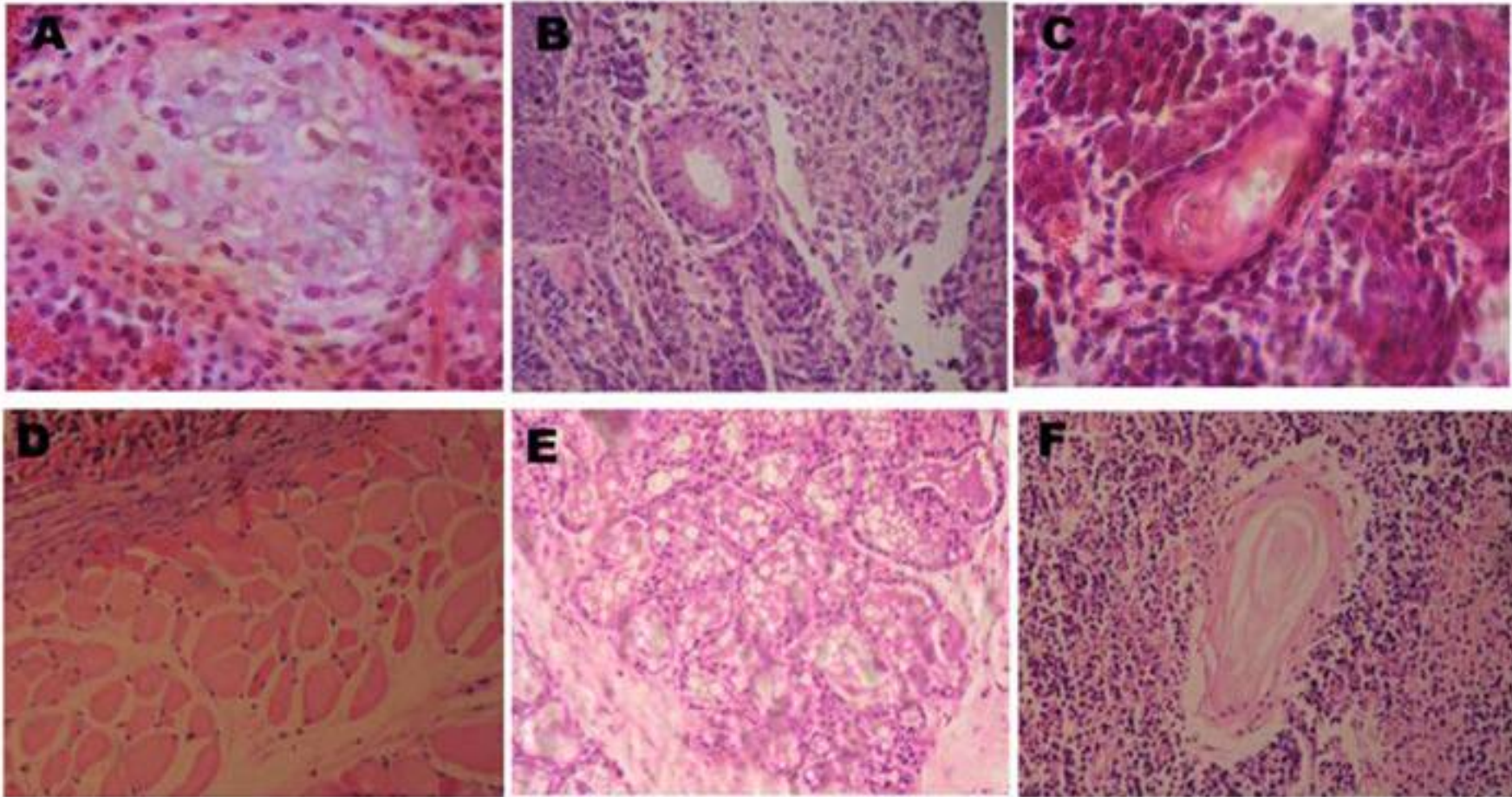


Figure 10

Teratoma formation by ESC culture in medium supplemented with NO

A, cartilage (mesoderm) B, glandular tissue (endoderm) C hair (ectoderm)



D, muscle (mesoderm)

E glandular tissue(endoderm) F keratinocyte (ectoderm)

A-C: mouse ESC

D-C: human ESC

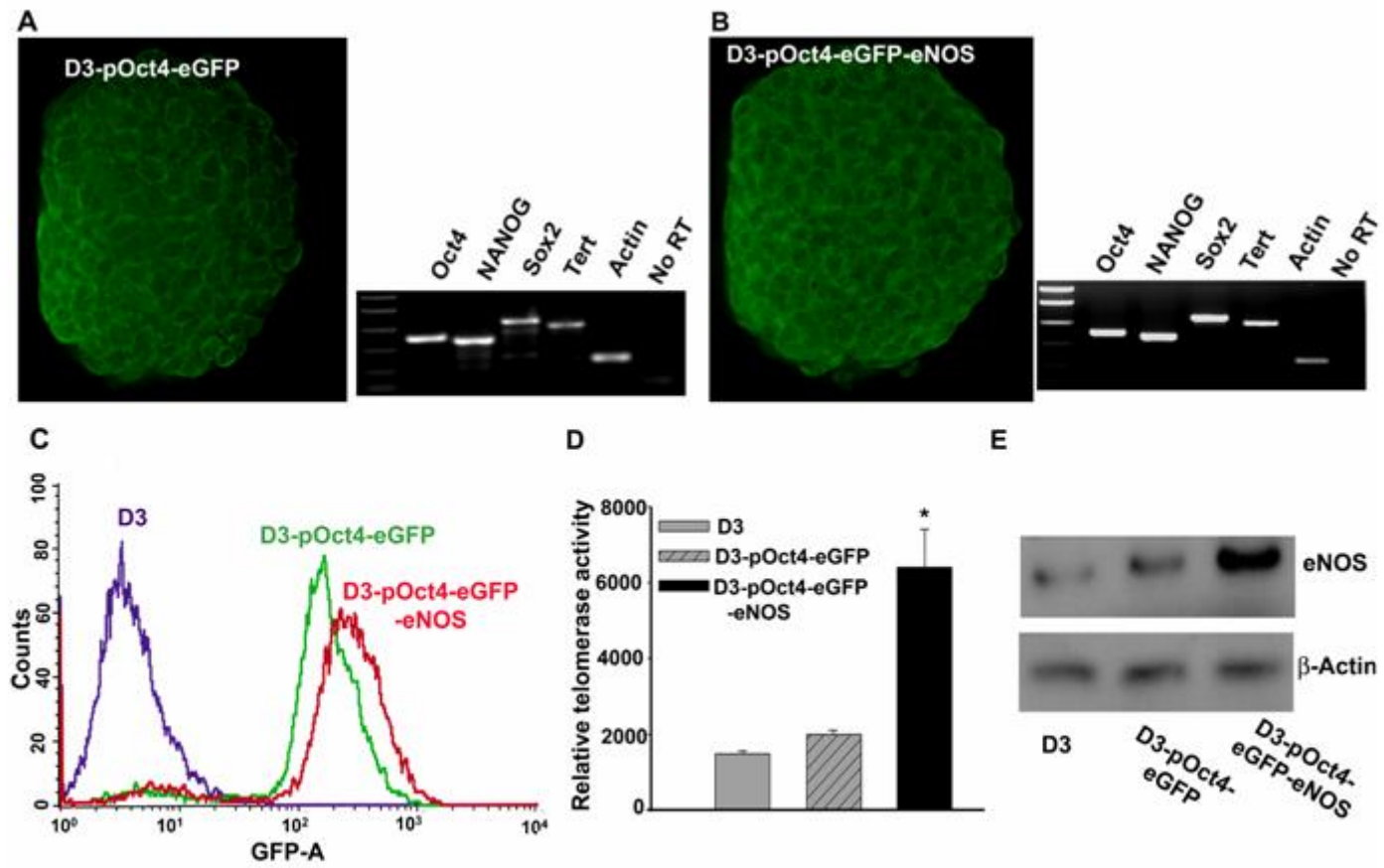
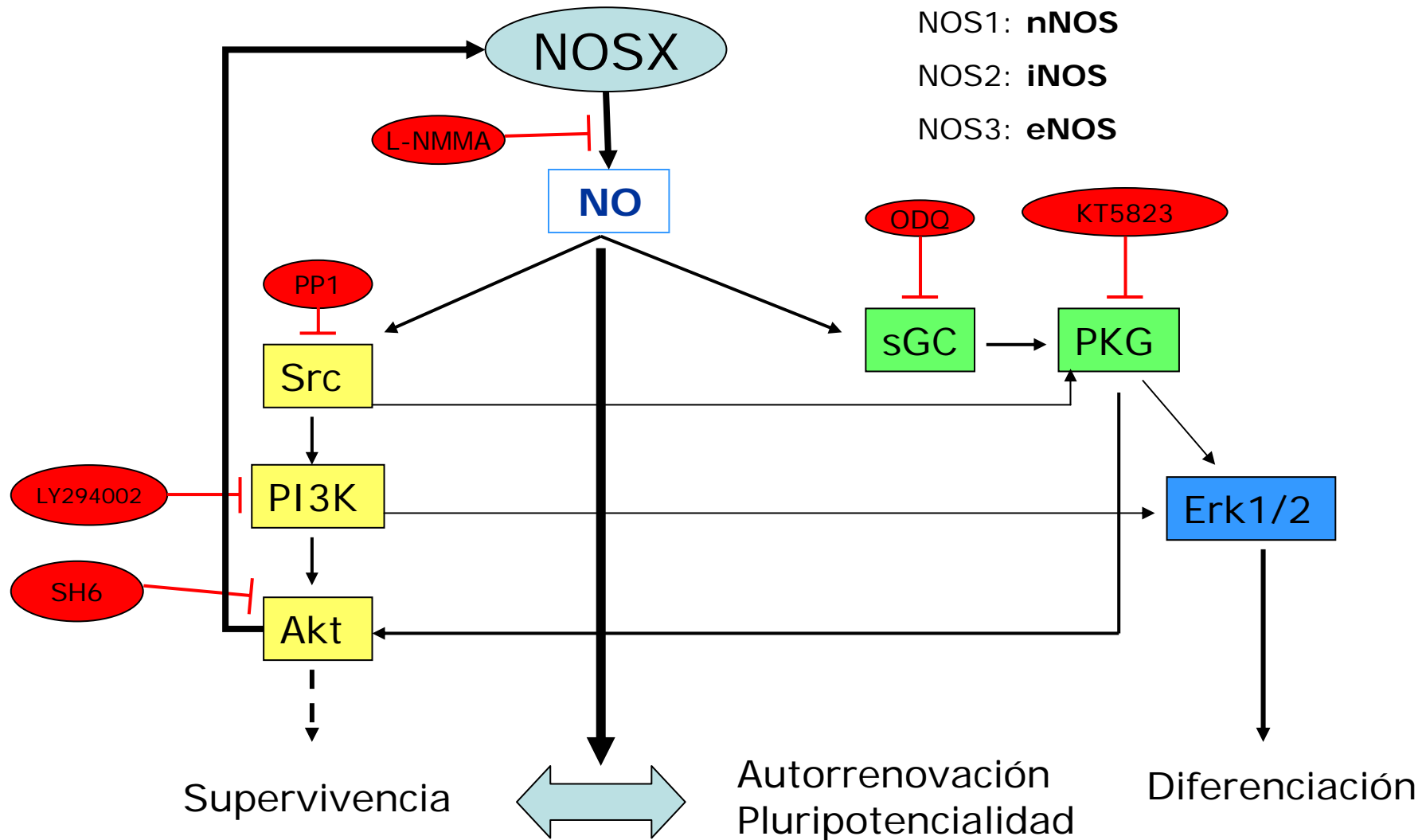


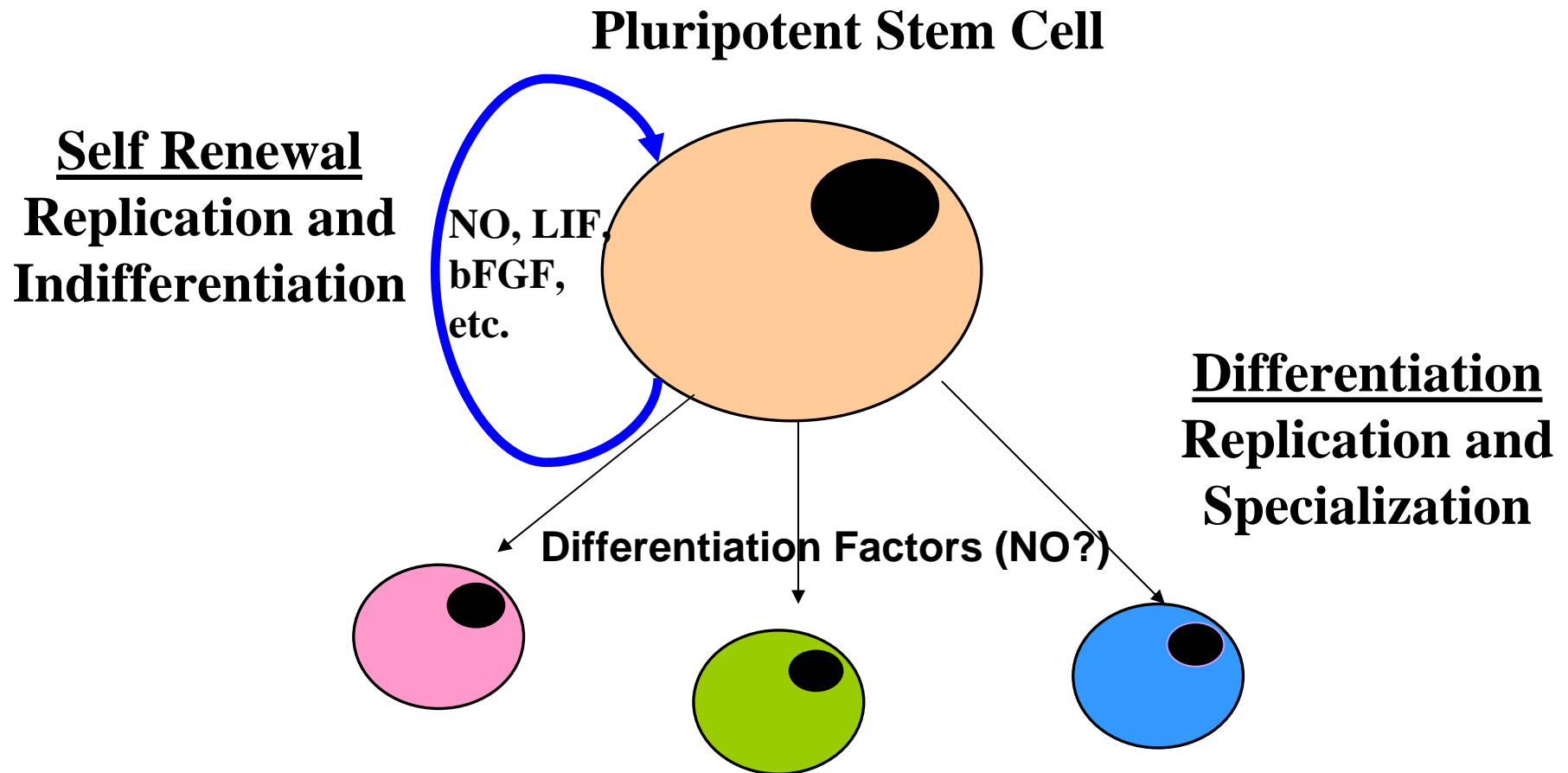
Figure 1

Papel Dual del NO en el Control del Destino Biológico de la Células Embrionarias



Adaptado de Tejedo et al. Nitric Oxide Triggers the Phosphatidylinositol 3-Kinase/Akt Survival Pathway in Insulin-Producing RINm5F Cells by Arousing Src to Activate Insulin Receptor Substrate-1. Endocrinology 145(5):2319-2327.

NO Actions in Stem Cell Biology





Grupo de Terapia Celular de la Diabetes



PROGRAMA ANDALUZ
DE TERAPIA CELULAR Y MEDICINA REGENERATIVA



"LA CÉLULA MULTIUSOS"

¡Gracias por su atención!