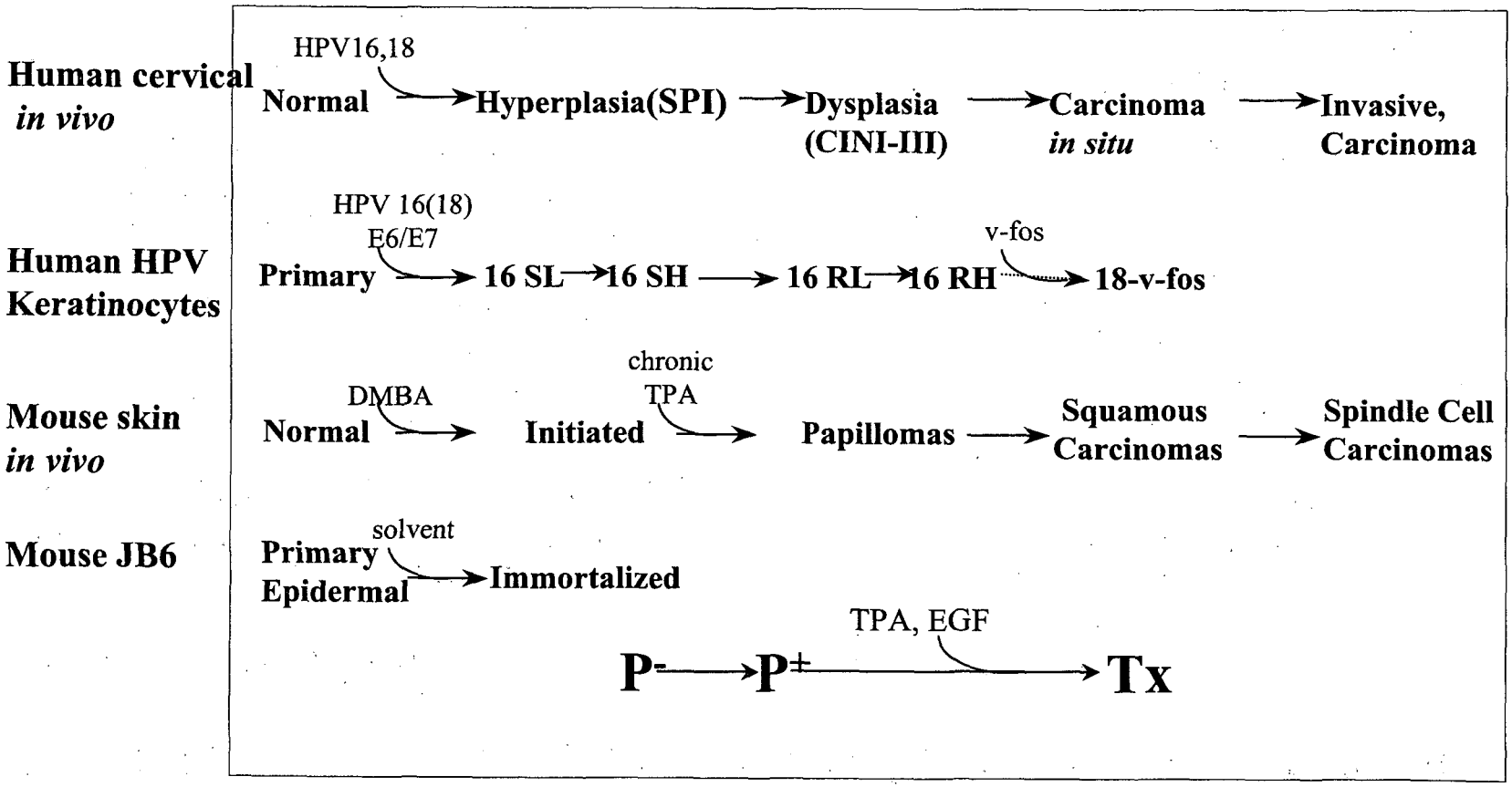
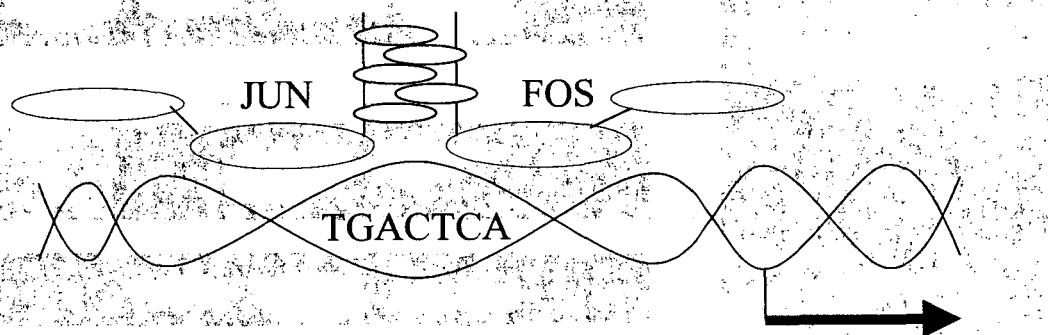
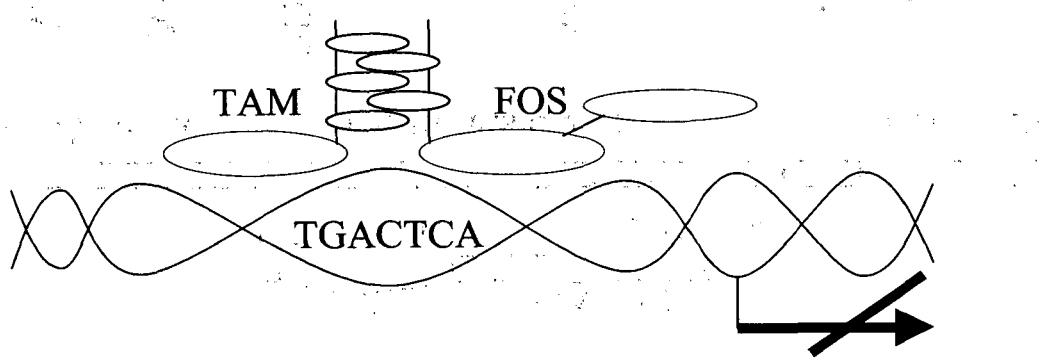
Multistage Carcinogenesis: What is the Molecular Basis of the Rate-limiting Steps?



MILESTONES: AP-1 and Tumor Promotion/Progression

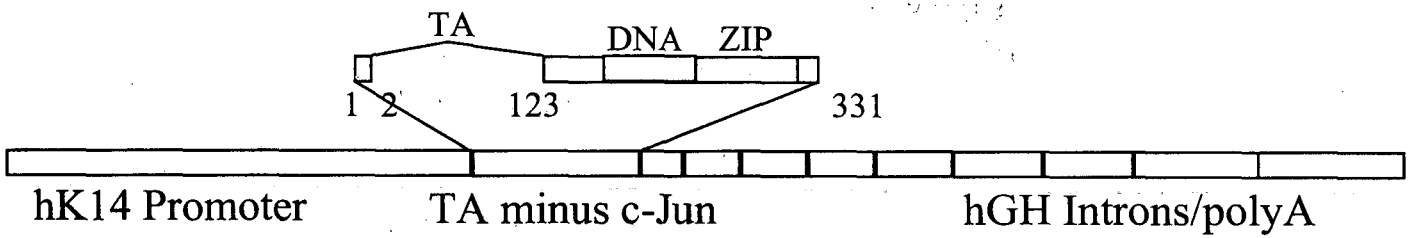
- **Transformation Resistant Variants Fail to activate AP-1**
  - Bernstein and Colburn, Science, 1989
- **Suppression of AP-1 by dominant negative jun (TAM 67) suppresses mouse keratinocyte tumorigenicity**
  - Domann et al Cell Growth and Diff, 1994
- **Tumor promoter induced AP-1 is required for JB6 cell transformation**
  - Dong et al PNAS 1994
- **cFos is required for skin tumor progression but not tumor promotion**
  - Saez et al CELL, 1995
- **Transformation and AP-1 nonresponsive variants owe their resistance to insufficient MAP kinase Erk 1 & 2**
  - Huang et al, PNAS 1998
- **Suppression of AP-1 and NFkB by TAM 67 in human keratinocytes suppresses tumor phenotype**
  - Li et al Oncogene 1998
- **K14-TAM 67 transgenic mice demonstrate that tumor promoter induced AP-1 is required for papillomagenesis, but not for hyperplasia**
  - Young et al PNAS 1999

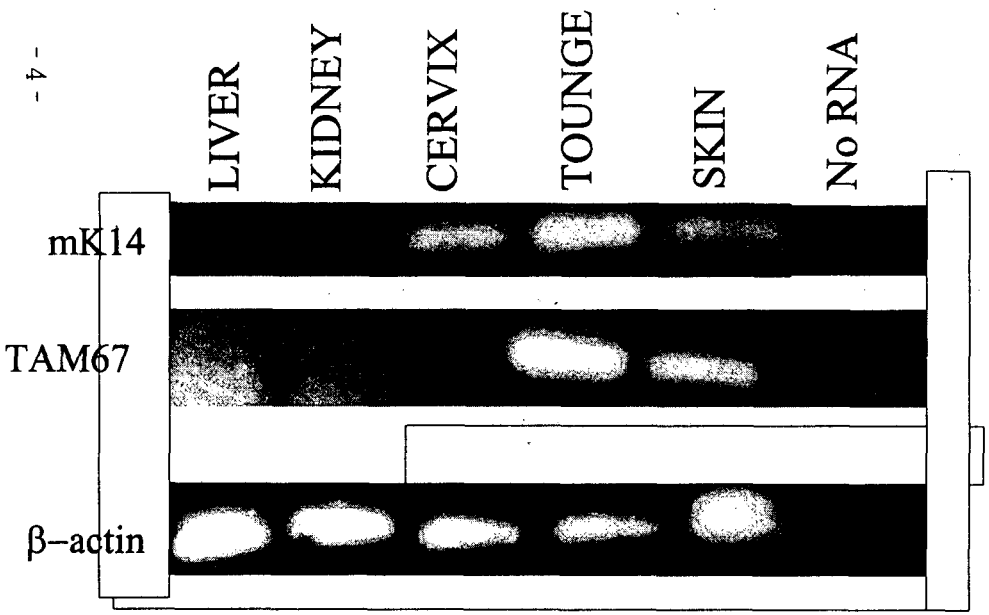


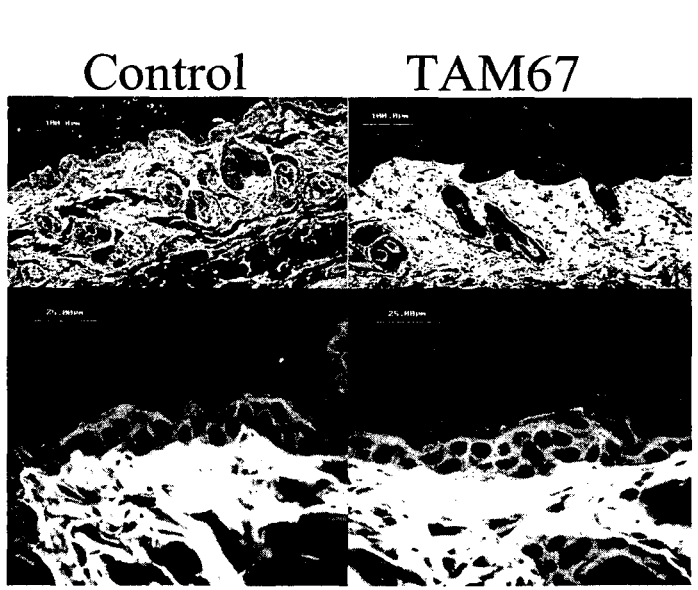


YOUNG & COLBURN 1998

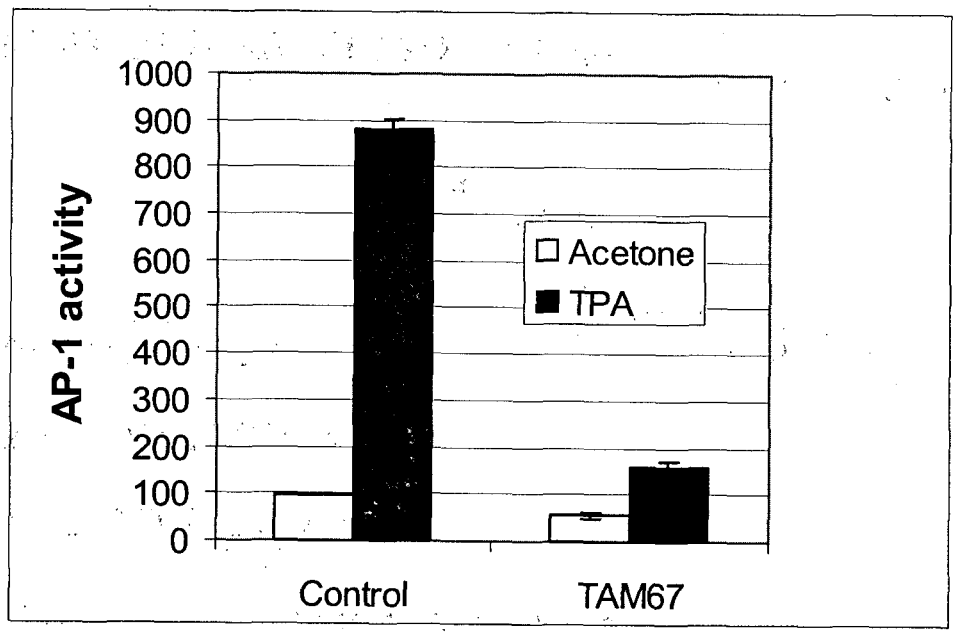
TAM67 is expressed in the skin, tongue and cervix with no effect on the morphology of these tissues



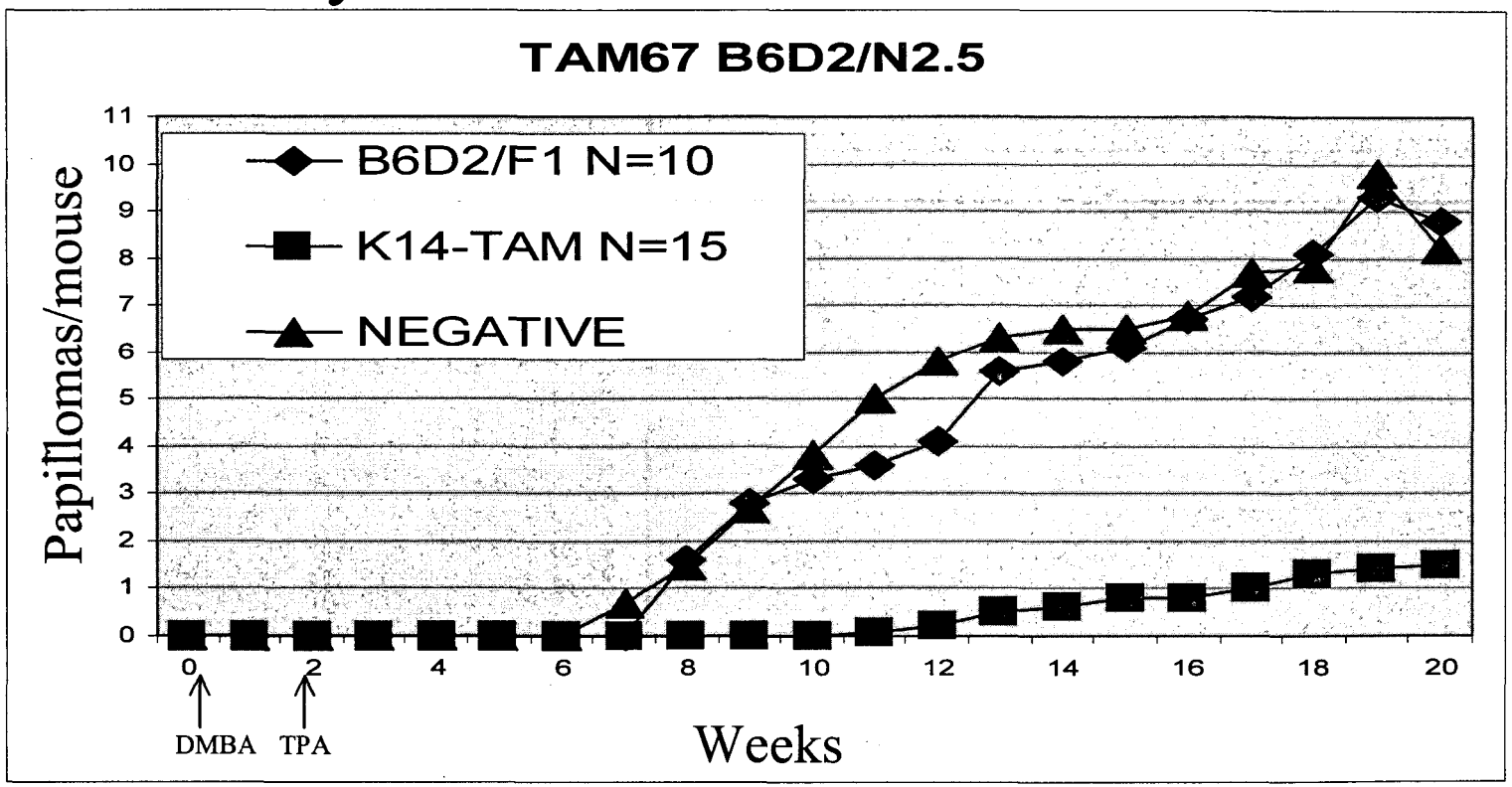




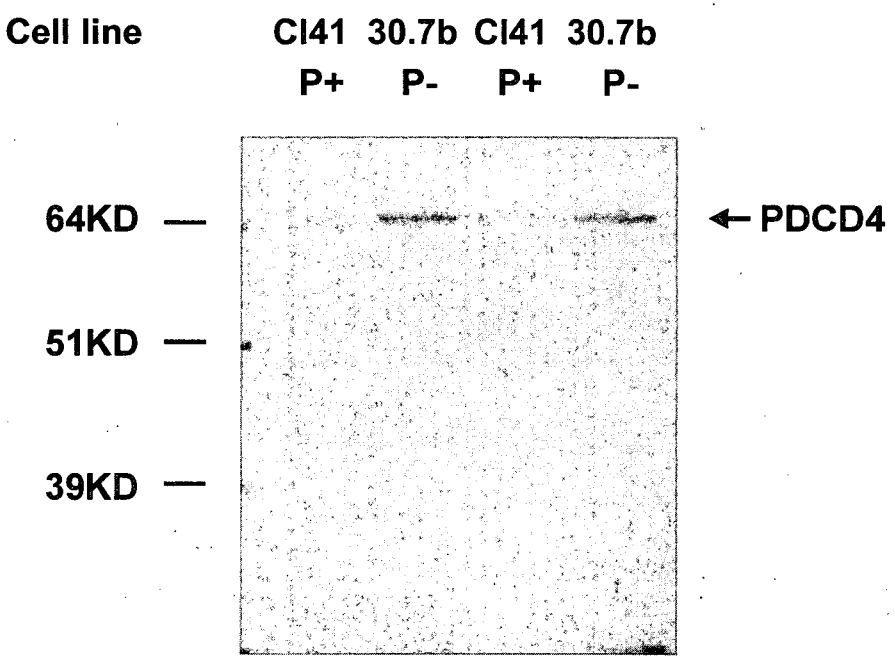
Dominant Negative Jun Expression Inhibits AP-1 Transactivation



Papillomagenesis Is Markedly Inhibited by TAM67 in B6D2/N2.5 Mice



Preferential expression of Pdcd4 protein in P- cells



What is the biological function of Pdcd4?

If Pdcd4 functions as a transfomation suppressor

→ lowering Pdcd4 in P- cells ➡ **P+ phenotype**

→ increasing Pdcd4 in P+ cells ➡ **P- phenotype**

Pdcd4 inhibits TPA-induced neoplastic transformation

Western blot:

Anchorage-independent transformation assay:

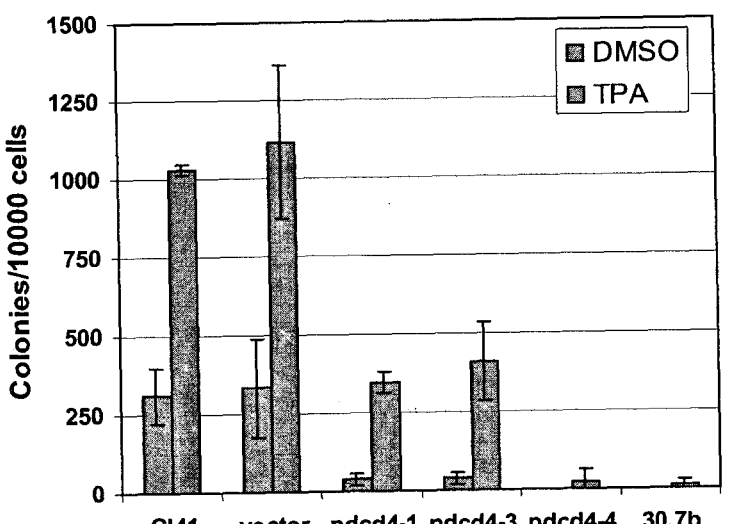


Table 1 *EVENTS REQUIRED FOR TRANSFORMATION*

Event	**Higher in**
Elevation of superoxide anion/ Antioxidant protection	**P+**
Activator protein-1 (AP-1) activation	**P+**
Extracellular regulated kinase (ERK1/2) expression	**P+**
Nuclear factor-kB (NF-kB) activation	**P+**
Phospho-inositol-3-kinase activation	**P+**
Tissue inhibitor of metalloproteinase-3 (TIMP-3) downregulation and transcriptional silencing	**P-/P+ vs. Tx**
Activation of ornithine decarboxylase (ODC) activity	**P+=P-**

Pdcd4 inhibits AP-1 dependent transcriptional activity