

CARCINOMA FARINGEO

“Dime con quién andas y te diré quién eres”

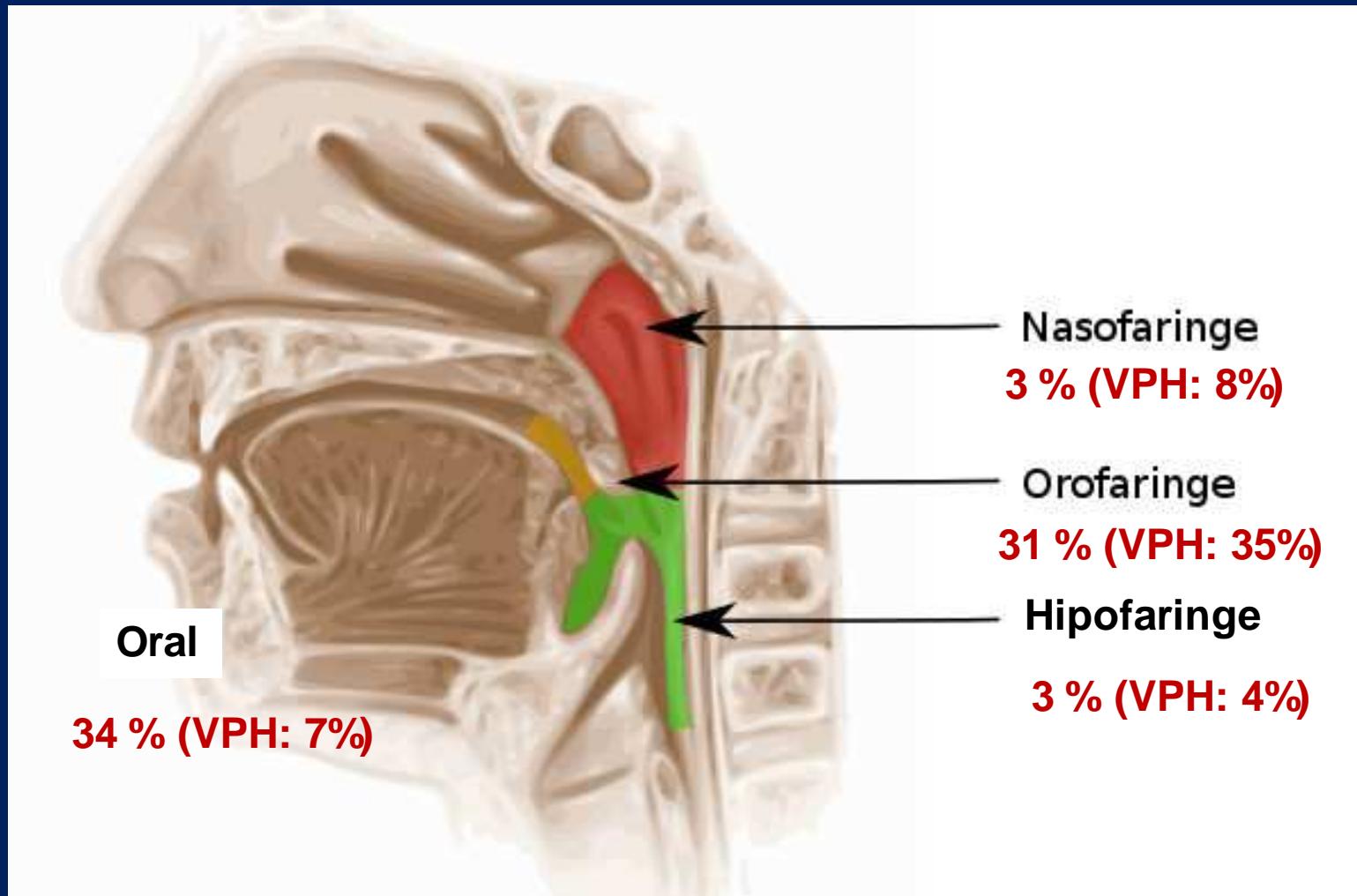
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Laboratorio Anatomoclínico Romea *

Servicios de Anatomía Patológica /Unidad de Virología **

Hospital Clínico Virgen de la Arrixaca

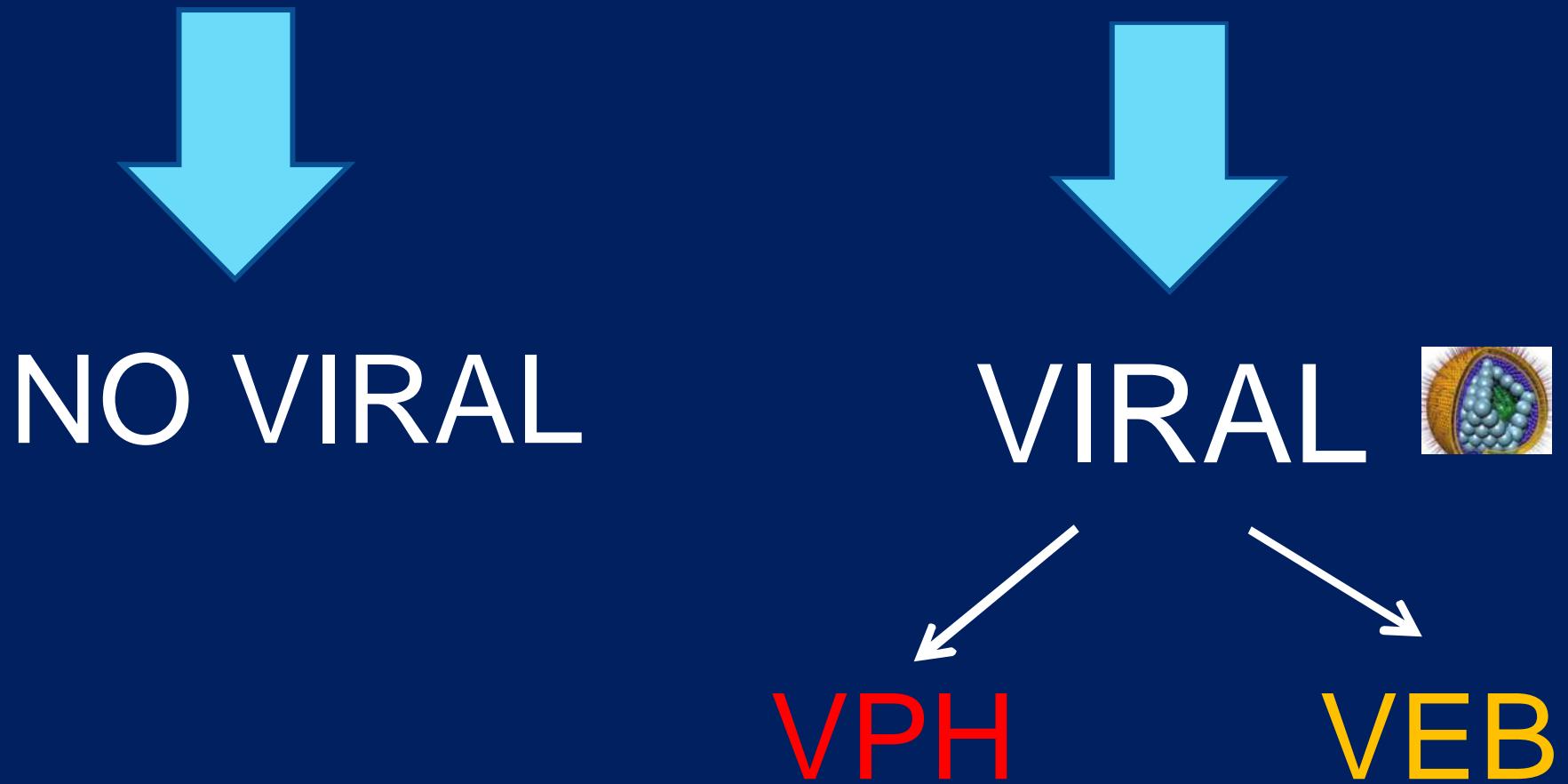
CARCINOMA FARINGEO



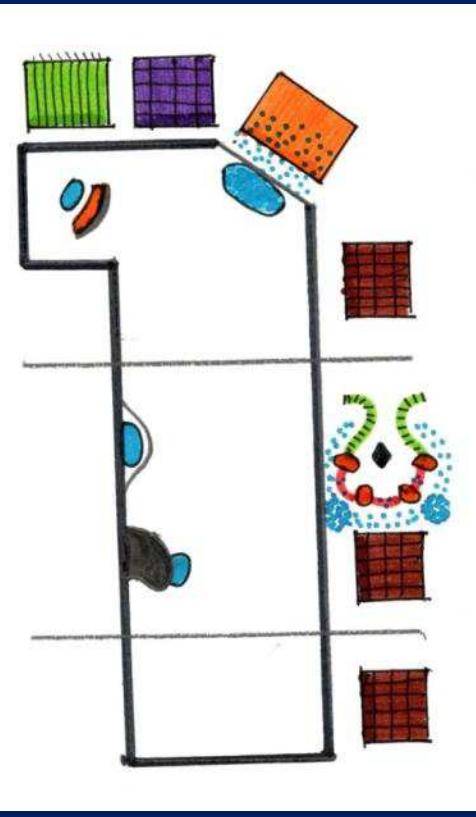
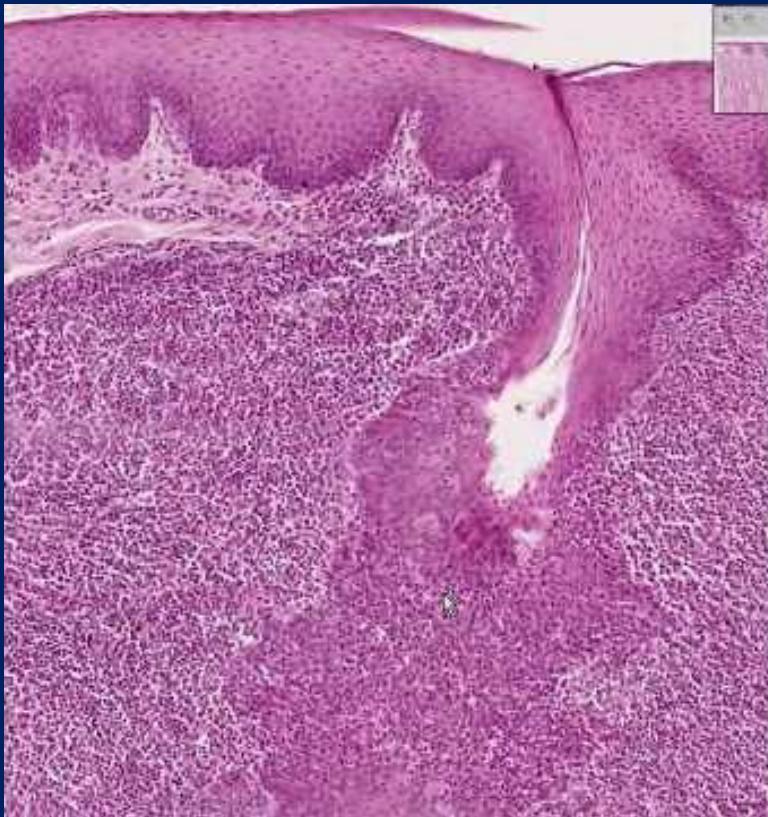
3680 pacientes

X. Castellsagué et al. 2016
J Natl Cancer Inst 2016; 108(6):djv403

CARCINOMA FARINGEO

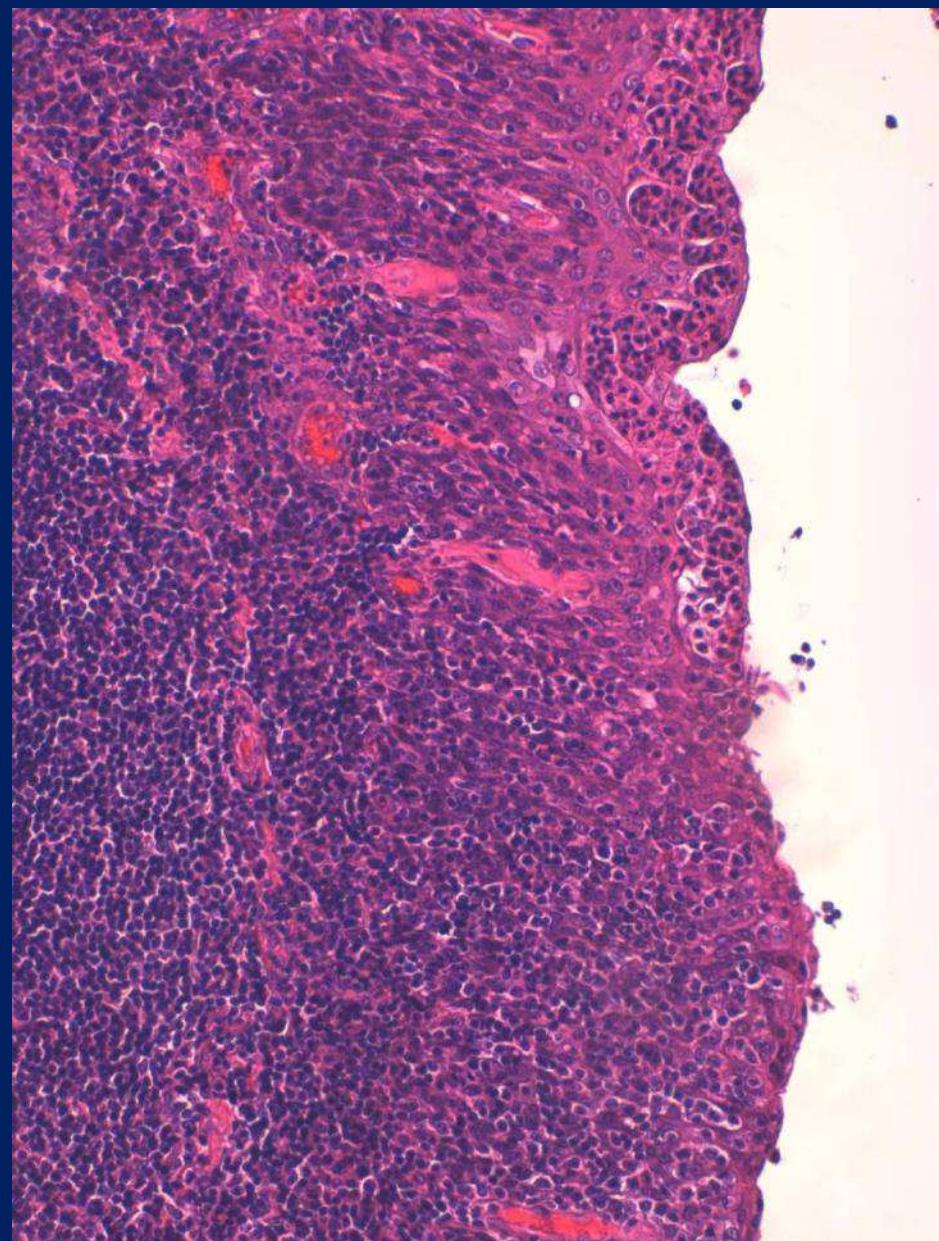


Tipos de tejidos



Epitelial

TIPOS DE EPITELIO



CARC. NASO/OROFARÍNGEO

Tipo 1. (tóxicos)

Carc. esc. Queratinizante
(23%)



NF: 26%

OR: 24%

Tipo 2. (virus)

Carc. esc. no queratinizante
(70%)



2a. Forma diferenciada (basaloide)

NF: 15% OR: **75%**

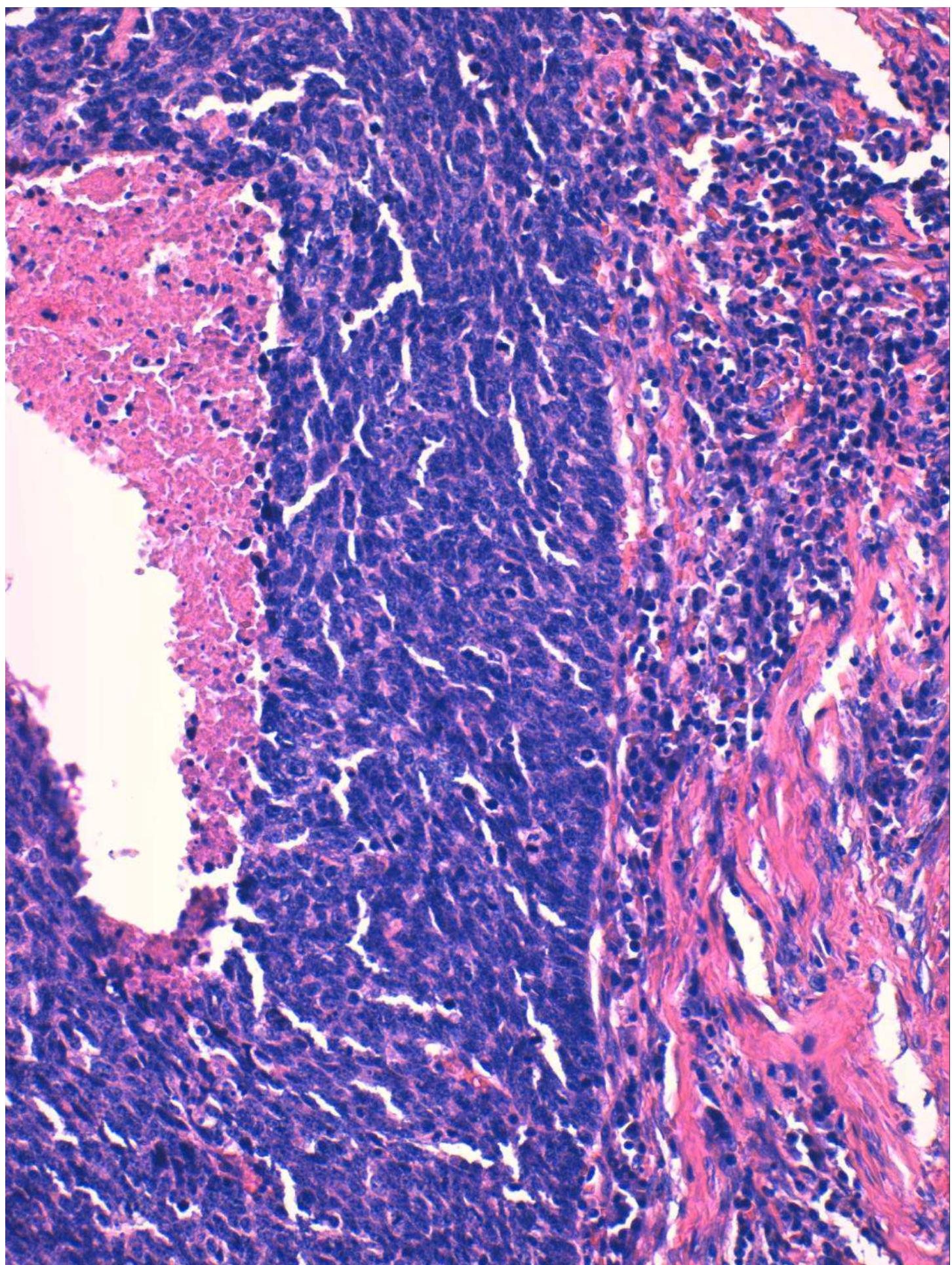
2b. Forma indiferenciada (infoepitelial)

NF: **70%** OR: 15%

2c. Forma híbrida (3%)

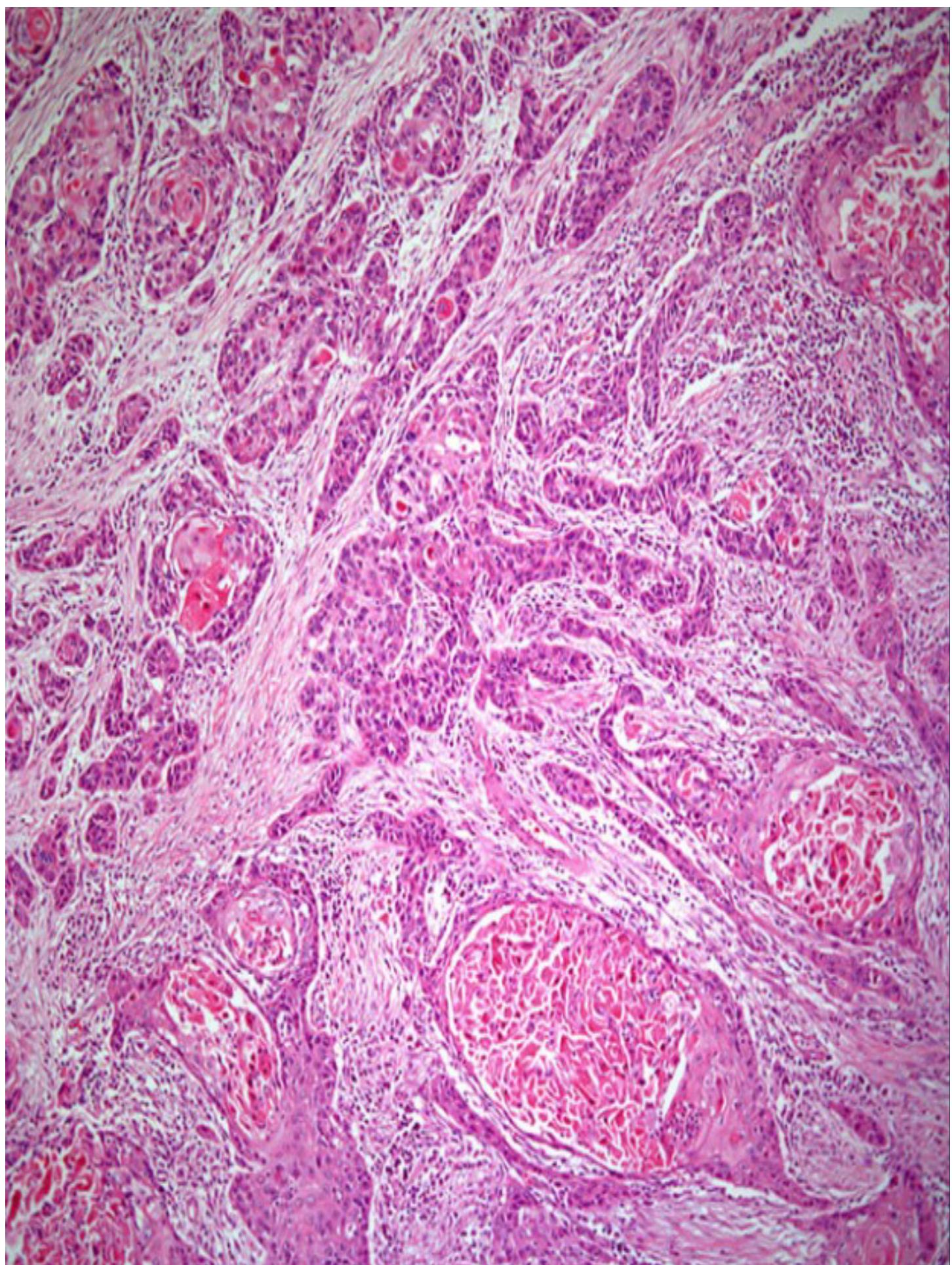
VARIANTES (4%)

(Basaloide, papilar, adc, células pequeñas, etc)



NO VIRAL / CONVENCIONAL

- Epitelio de superficie
- Lesiones preneoplásicas
- Cordones y nidos queratinizantes
- Bien a pobemente diferenciado
- Reacción estromal desmoplásica
- Tabaco, alcohol, etc
- Mal pronóstico
- Metástasis ganglionares sólidas

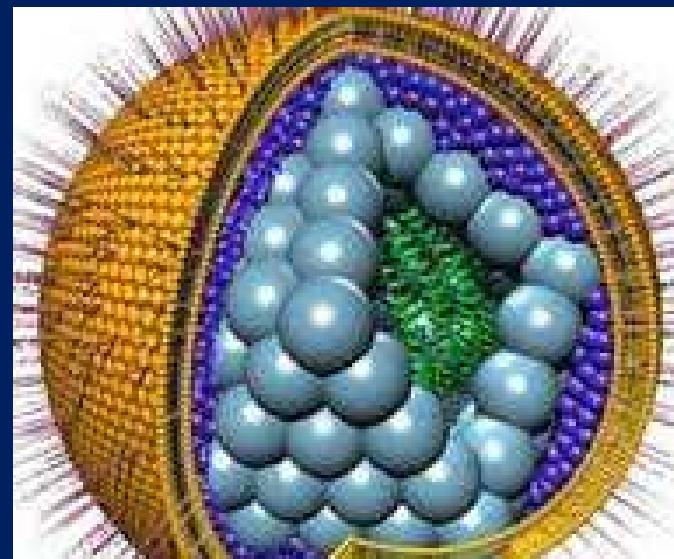


CARCINOMA CONDUCIDO POR VEB

MA Epstein



Genoma



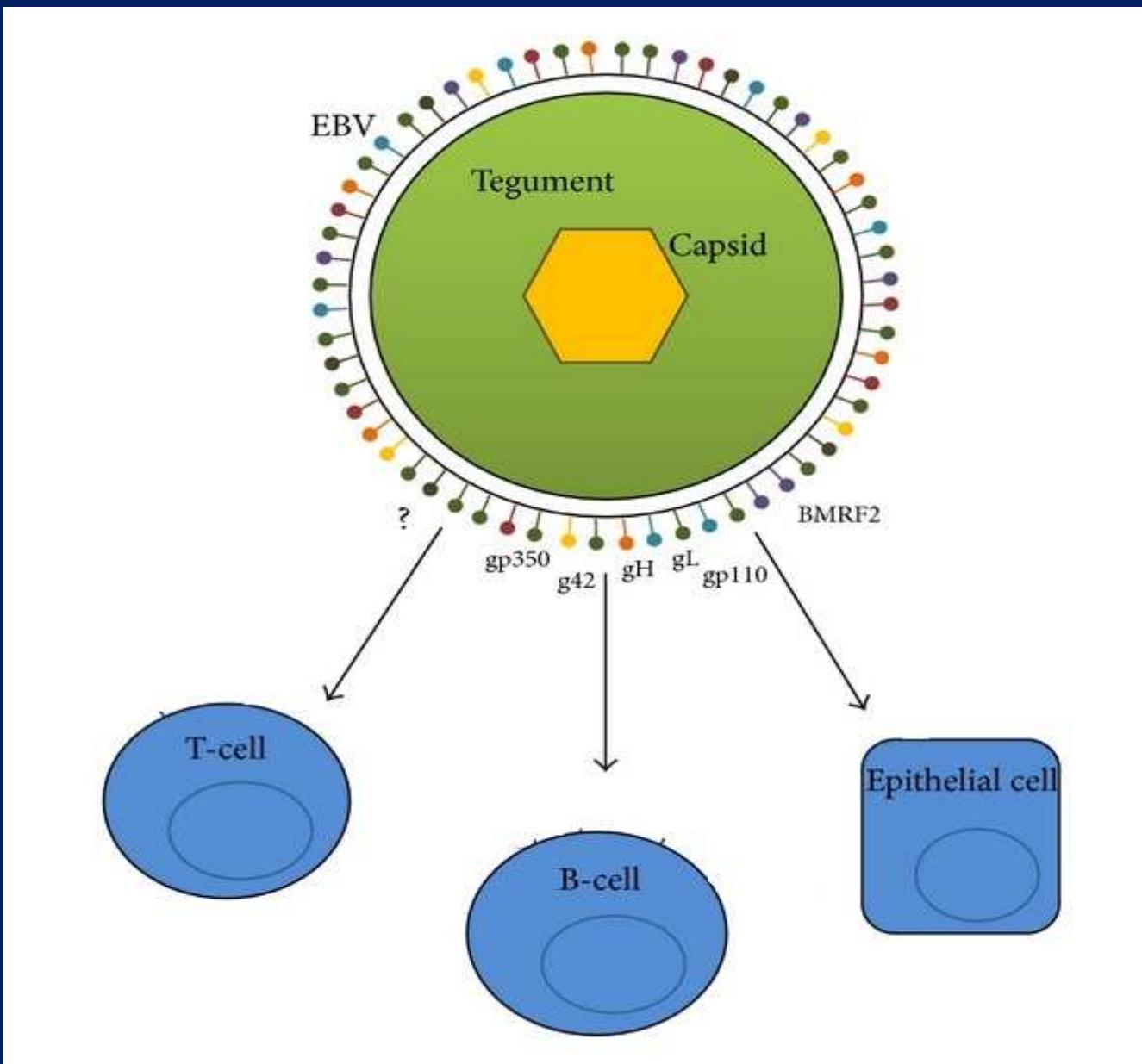
Antecedentes VEB

- MA Epstein and M Barr 1964 (linfoma)
- Herpesviridae
- Muy frecuente en población (90% episómico)
- Transmisión por saliva
- Relación carcinoma nasofaríngeo con VEB (1966 Old)
- Relación con alimentos ahumados y salados
- Susceptibilidad genética

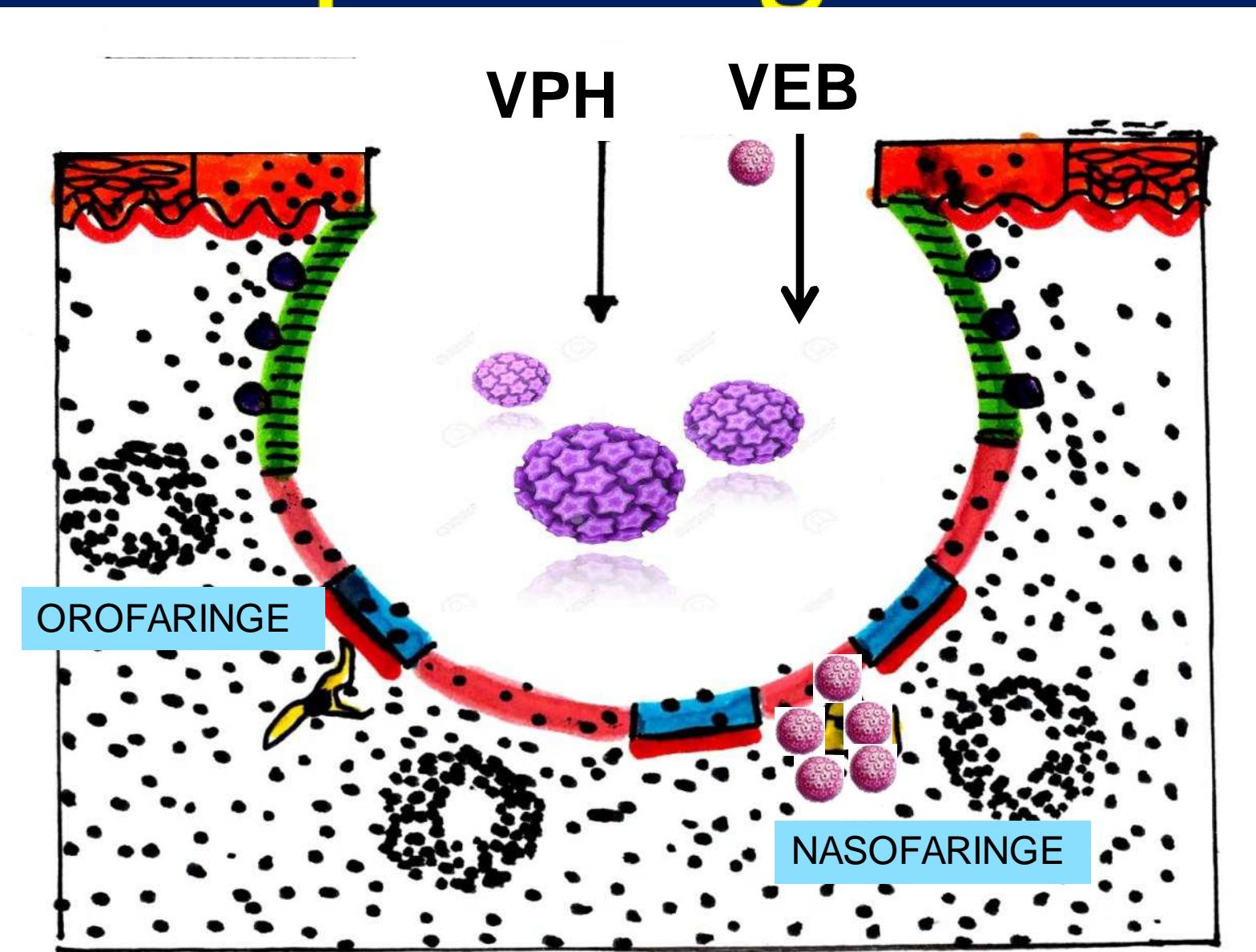
CARCINOMAS - VEB

- 5-10 % carcinomas cabeza-cuello
- Edad 50-60 años y en hombres
- Factores ambientales y genéticos
(“*tumor Canton*”)
- Localización más frecuente (Fosa de Rossemüller)
- Histología: carc.esc.no queratinizante
(forma linfoepitelial)
- Tinción p16 -, p53 +, EBER +
- Buen pronóstico
- Metástasis ganglionares sólidas

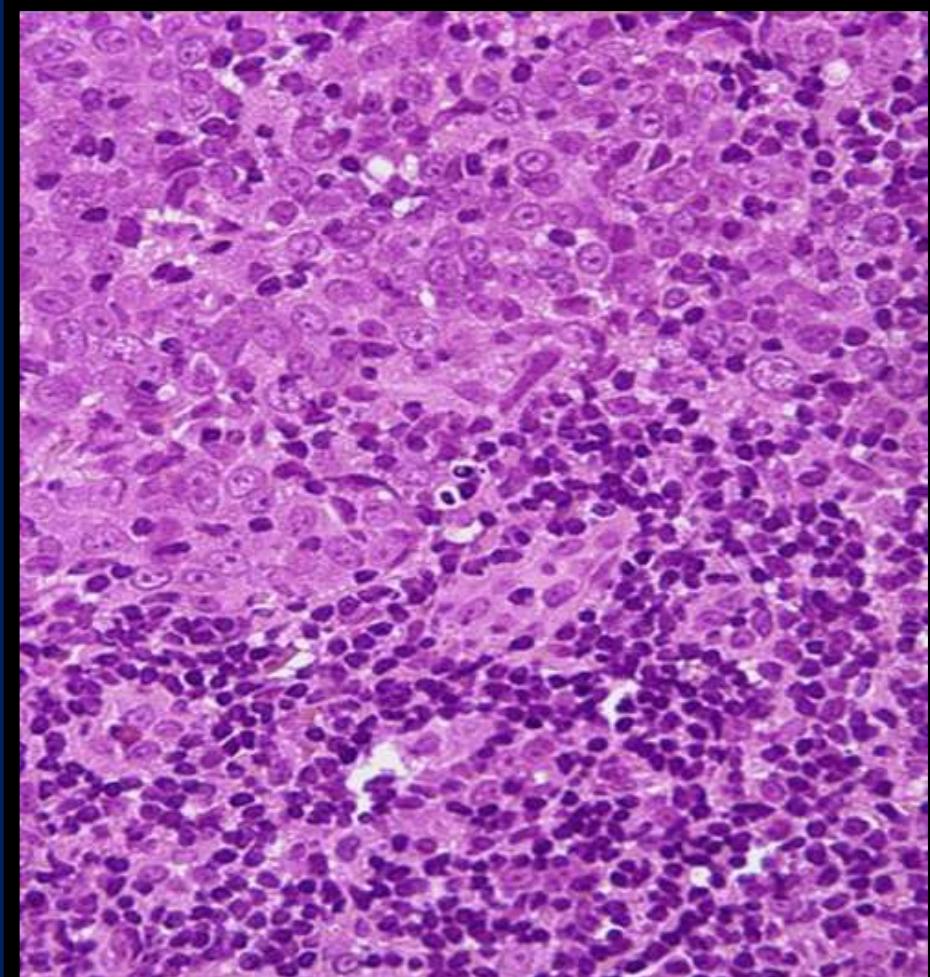
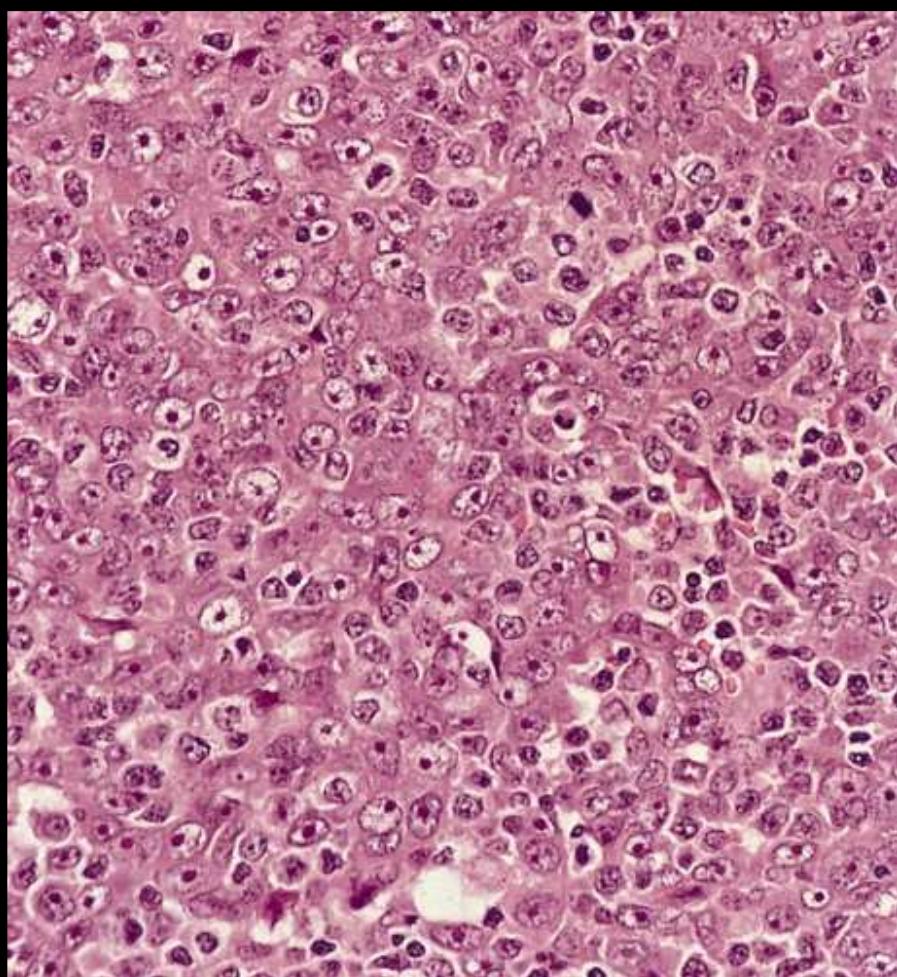
Genoma VEB



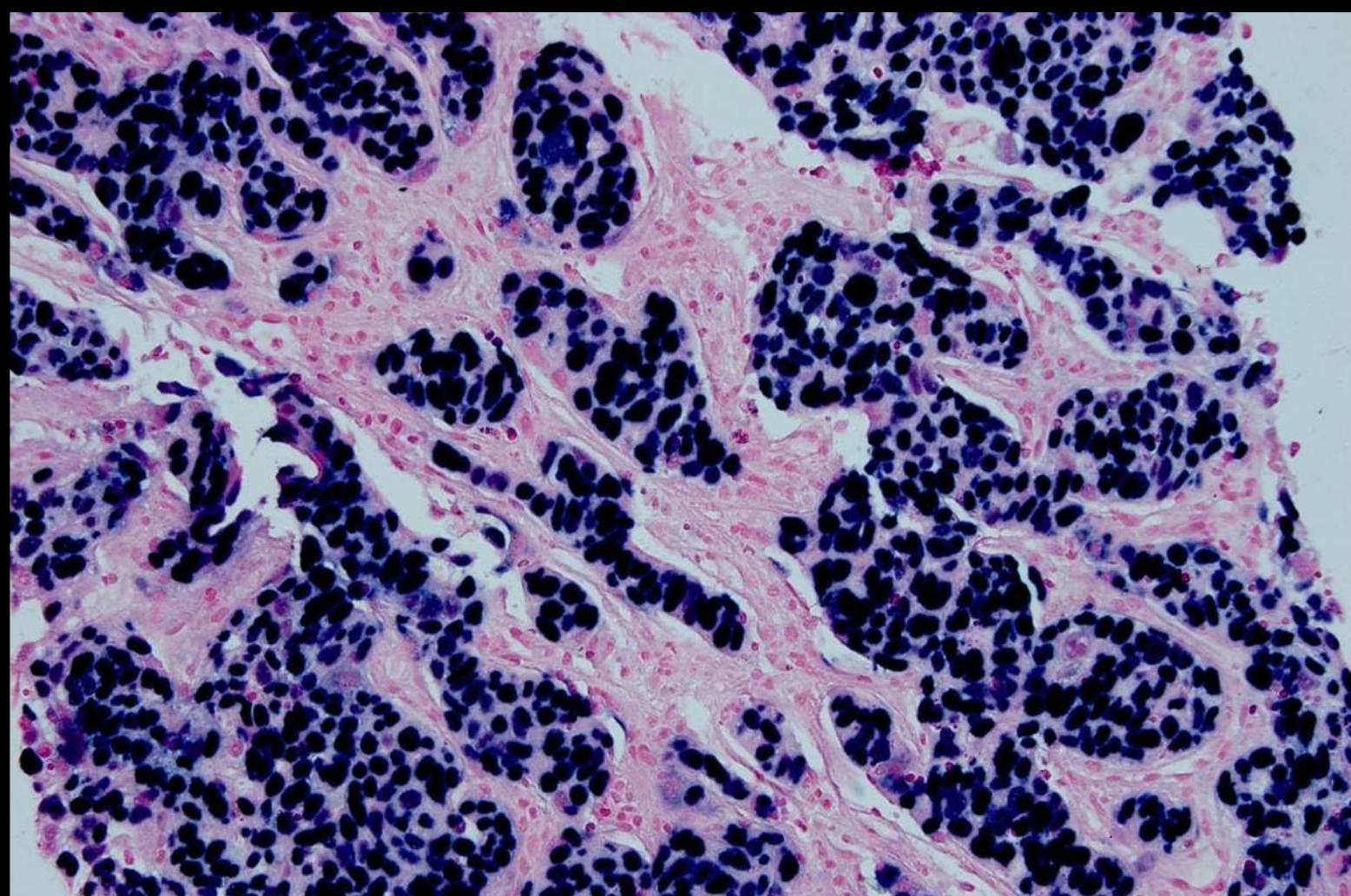
Cripta amigdalar



CARCINOMA ESCAMOSO NO QUERATINIZANTE (forma linfoepitelial)



Hibridación in situ (EBER)



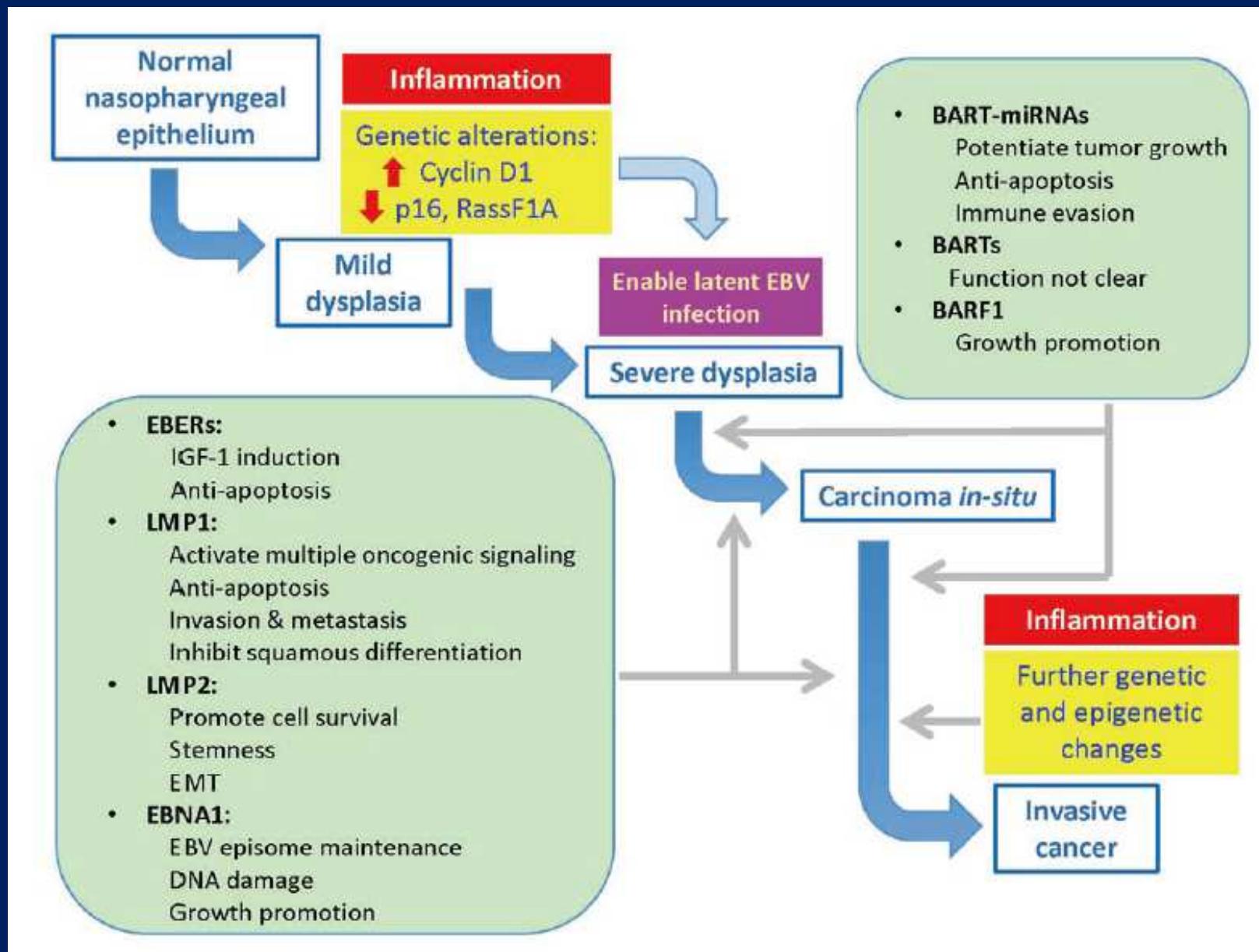
CARCINOMA NASOFARÍNGEO

TIPO	QUERATINIZANTE	NO Q. DIFEREN.	NO Q. INDIFEREN.
Frecuencia	25%	15%	70%
Sexo	H>M	H>M	H>M
Edad	Raro <40 años	4 ^a -6 ^a década	4 ^o - 6 ^o década Niños
Asociación EBV	Débil	Estrecha	Estrecha
Tto	Rx	Rx	Rx
Pronóstico > 5 años	20- 40%	75%	75%

EN CRIPTA: Comportamiento epitelial especializado

- Mayor contacto de las células linfoides con los antígenos
- Transporte directo de los antígenos
- Contiene inmunoglobulinas

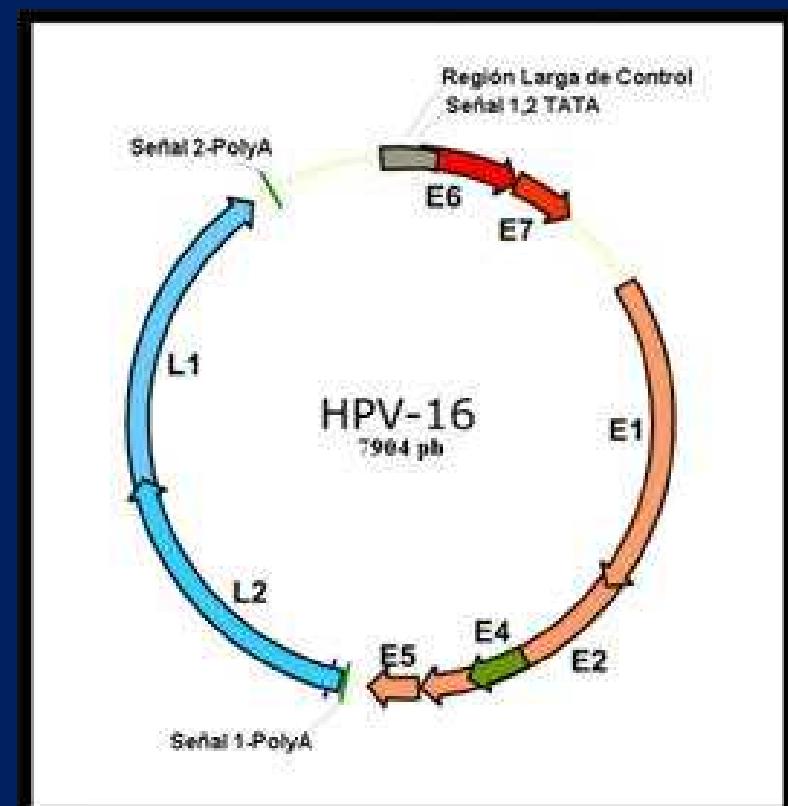
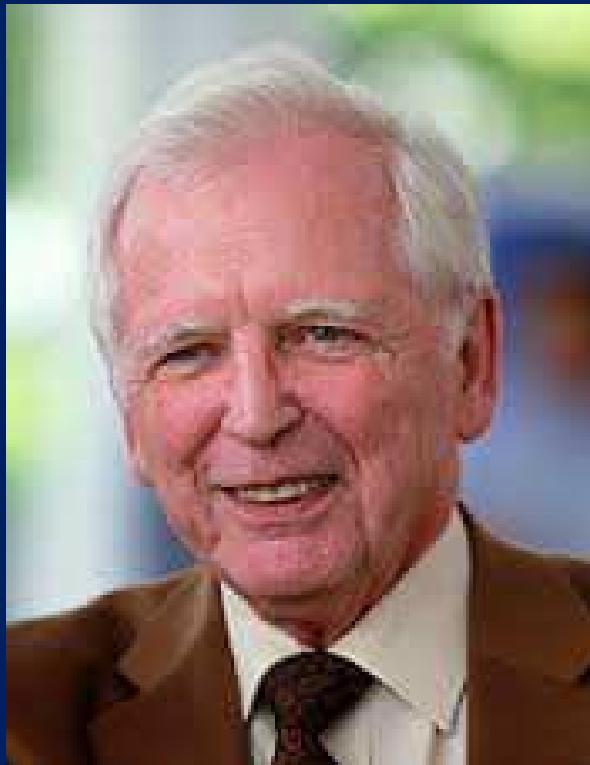
Carcinogénesis VEB



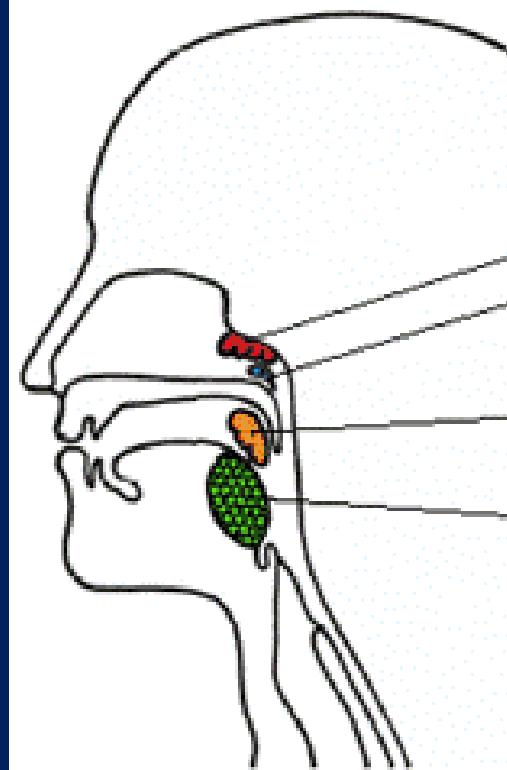
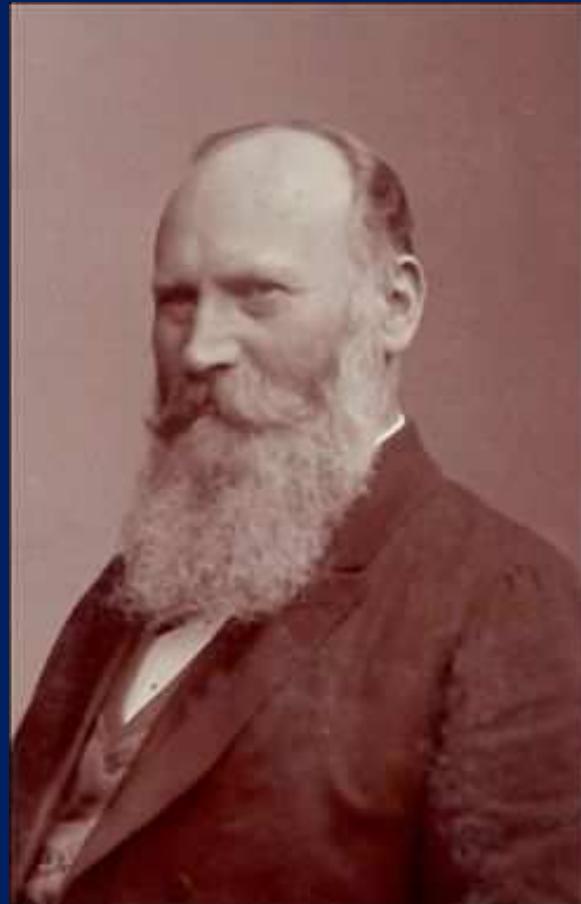
CARCINOMA CONDUCIDO POR VPH



Harald Zur Hausen (1936) VPI



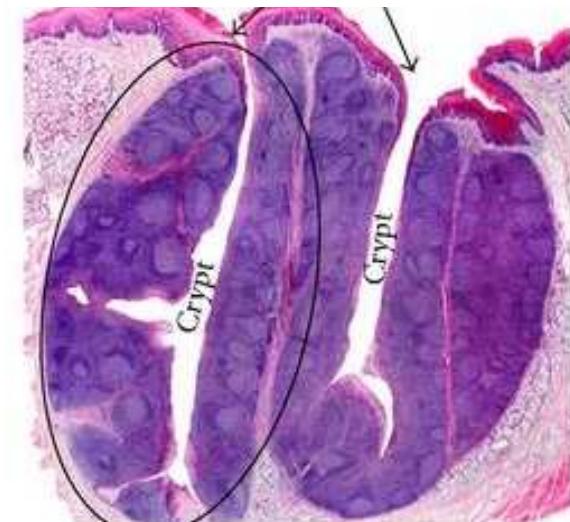
Anillo de Waldeyer



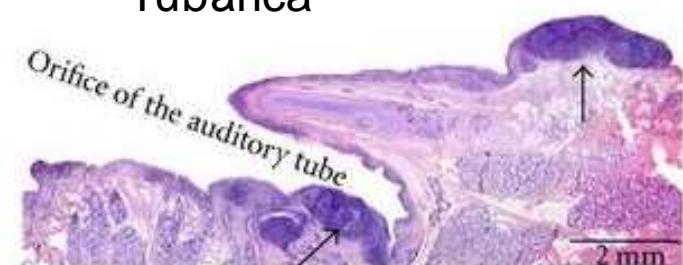
Nasofaríngea



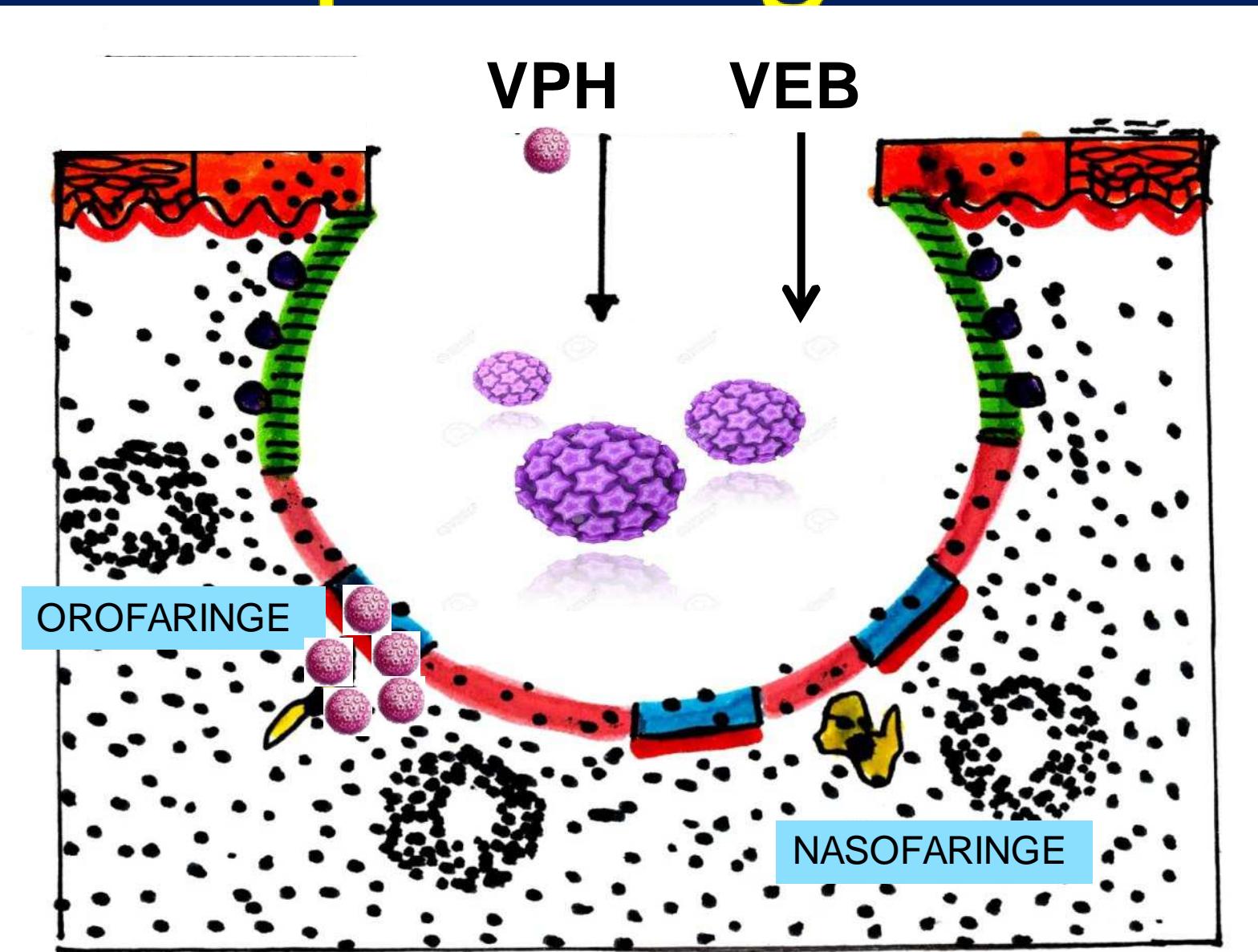
Palatina



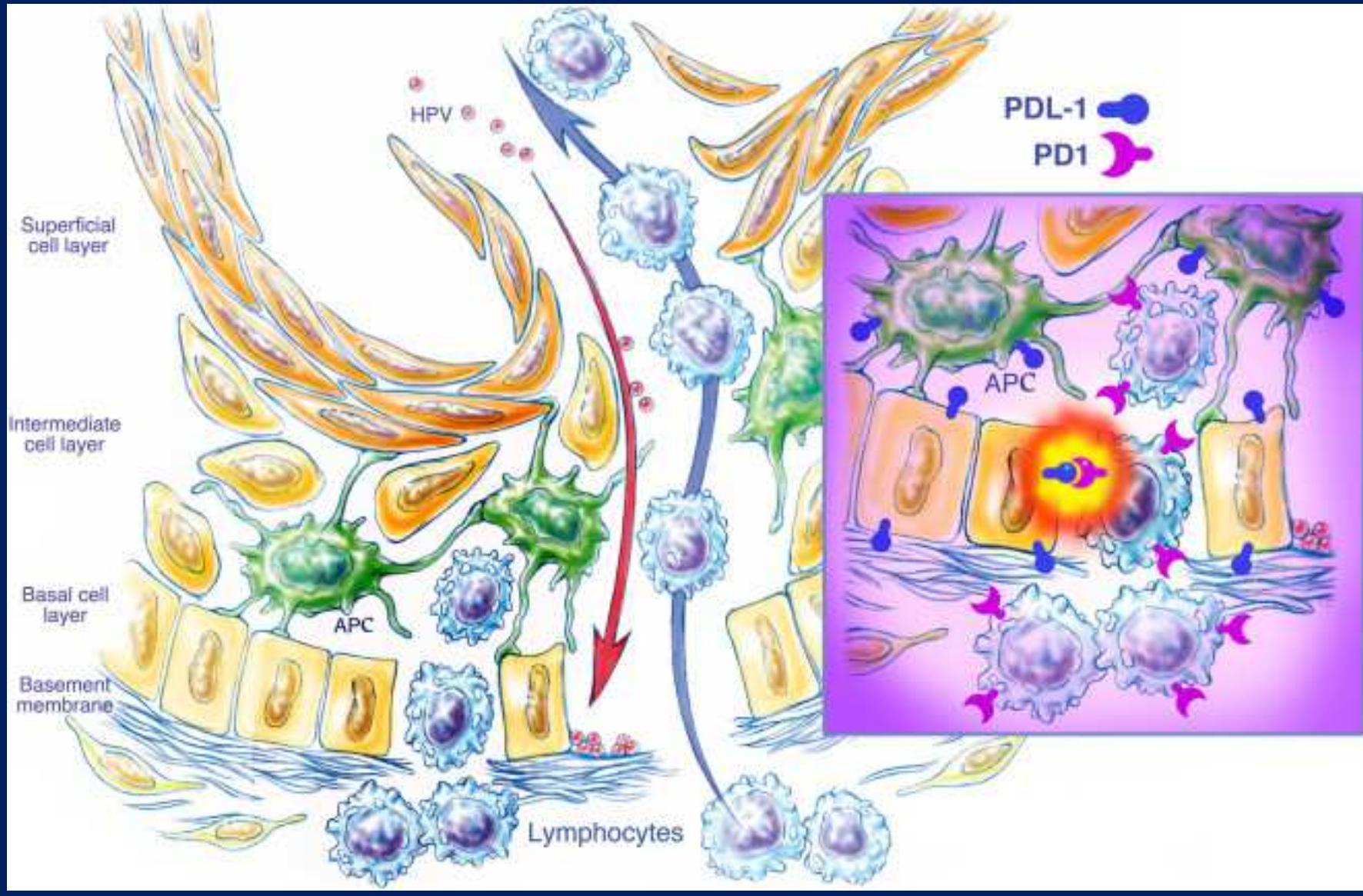
Tubárica



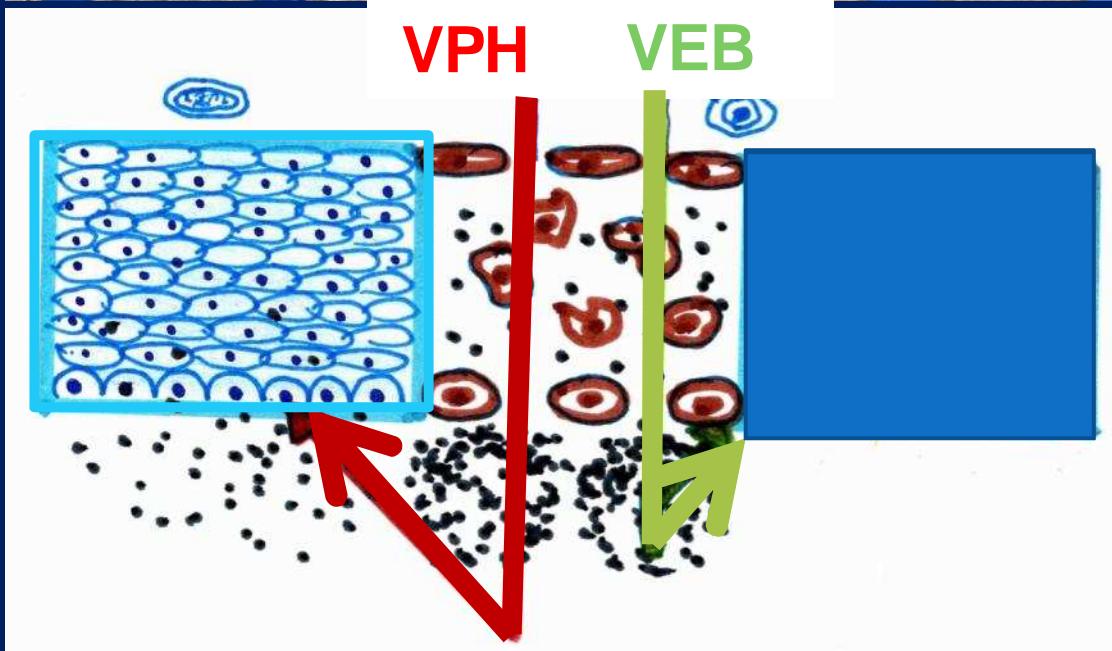
Cripta amigdalar



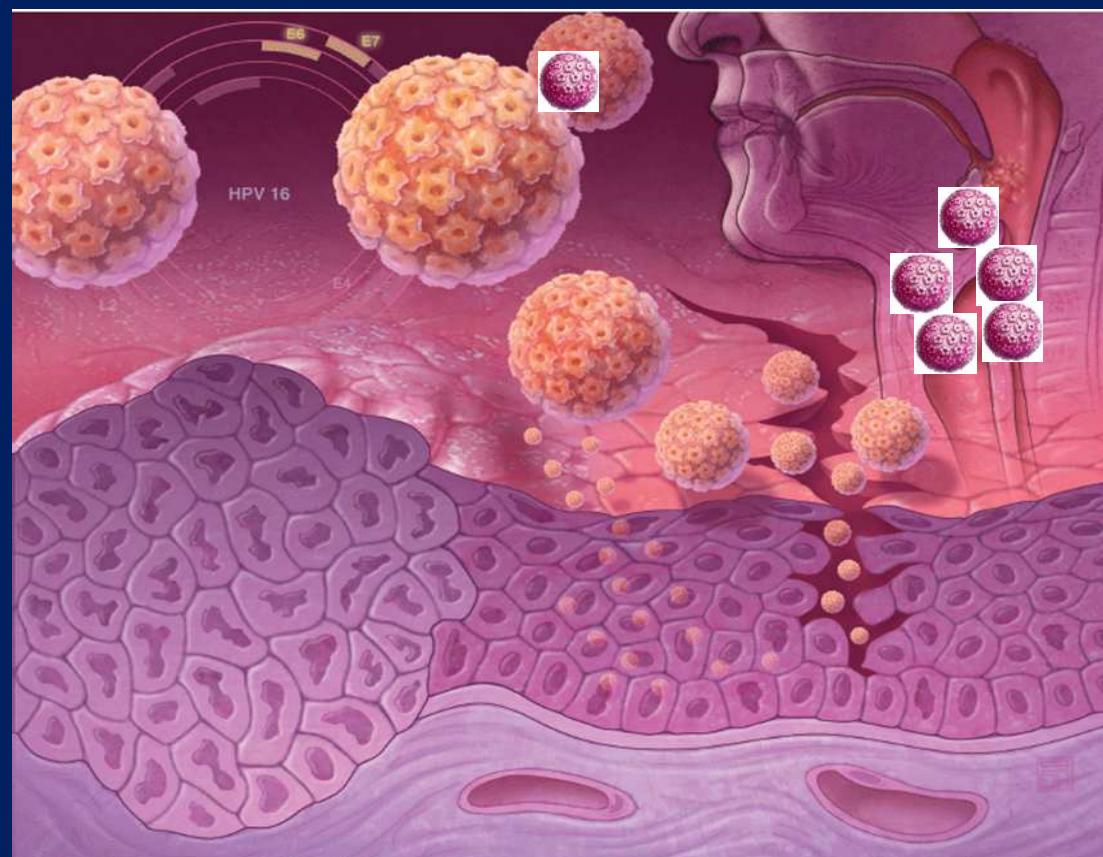
Cripta amigdalar



Cripta amigdalar

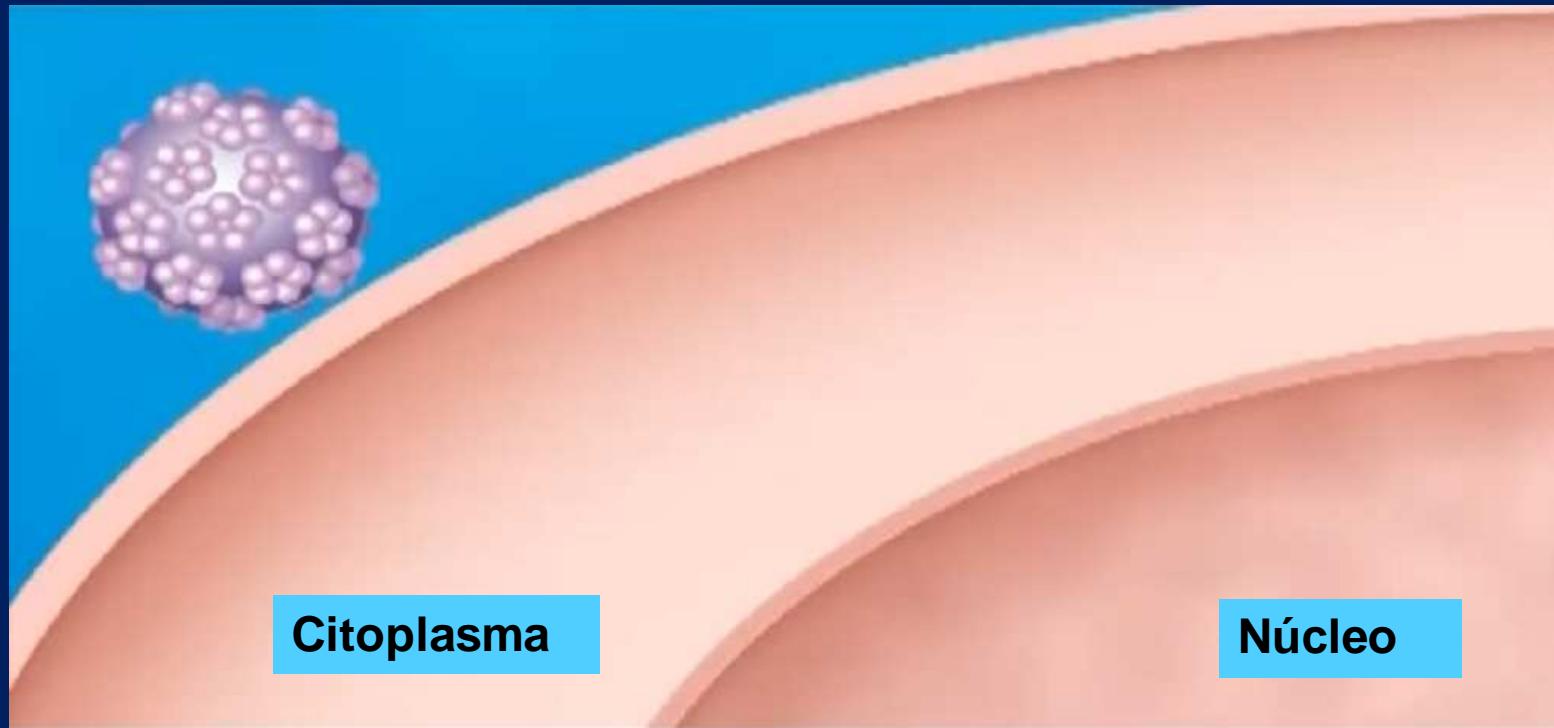


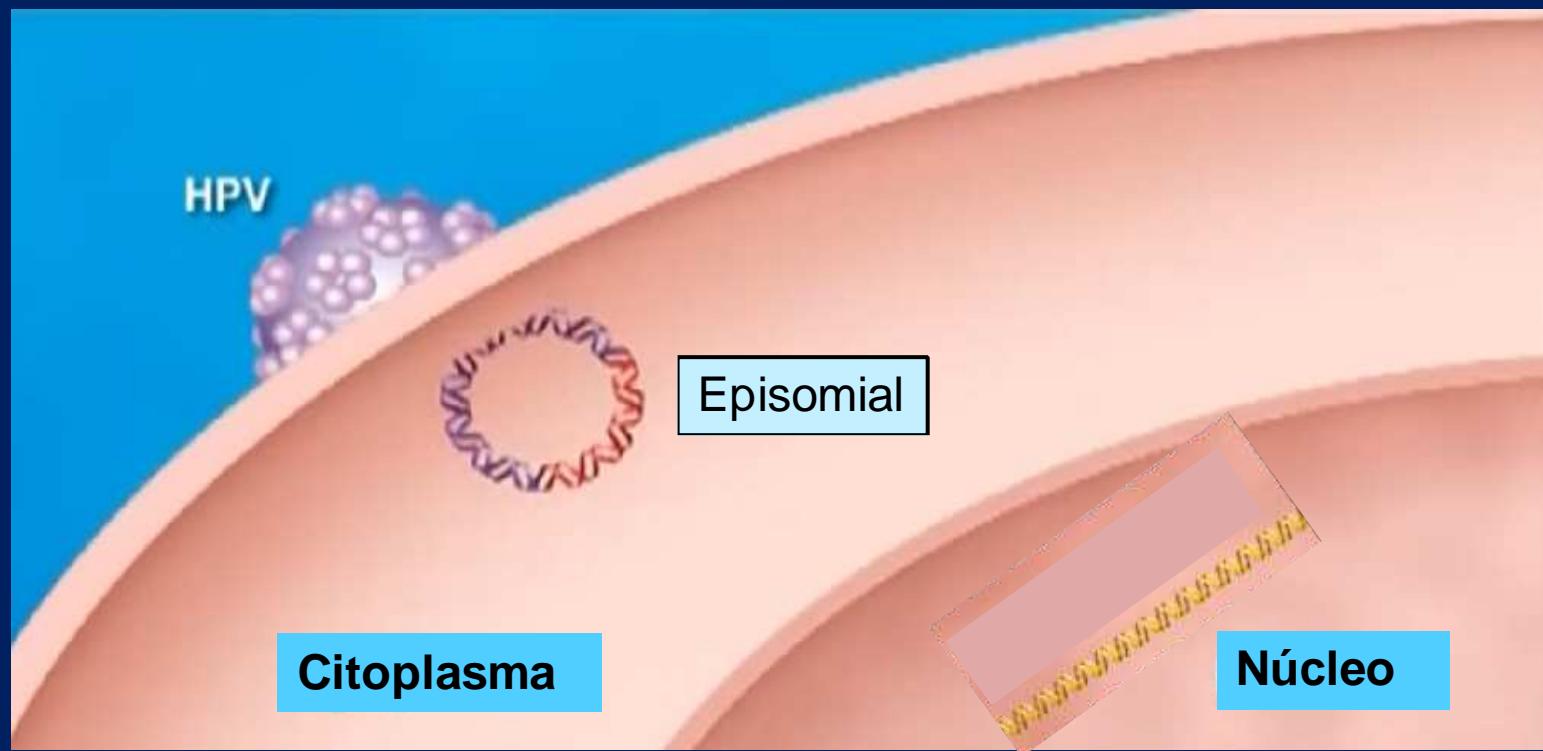
CARCINOMA OROFARÍNGEO POR VPH

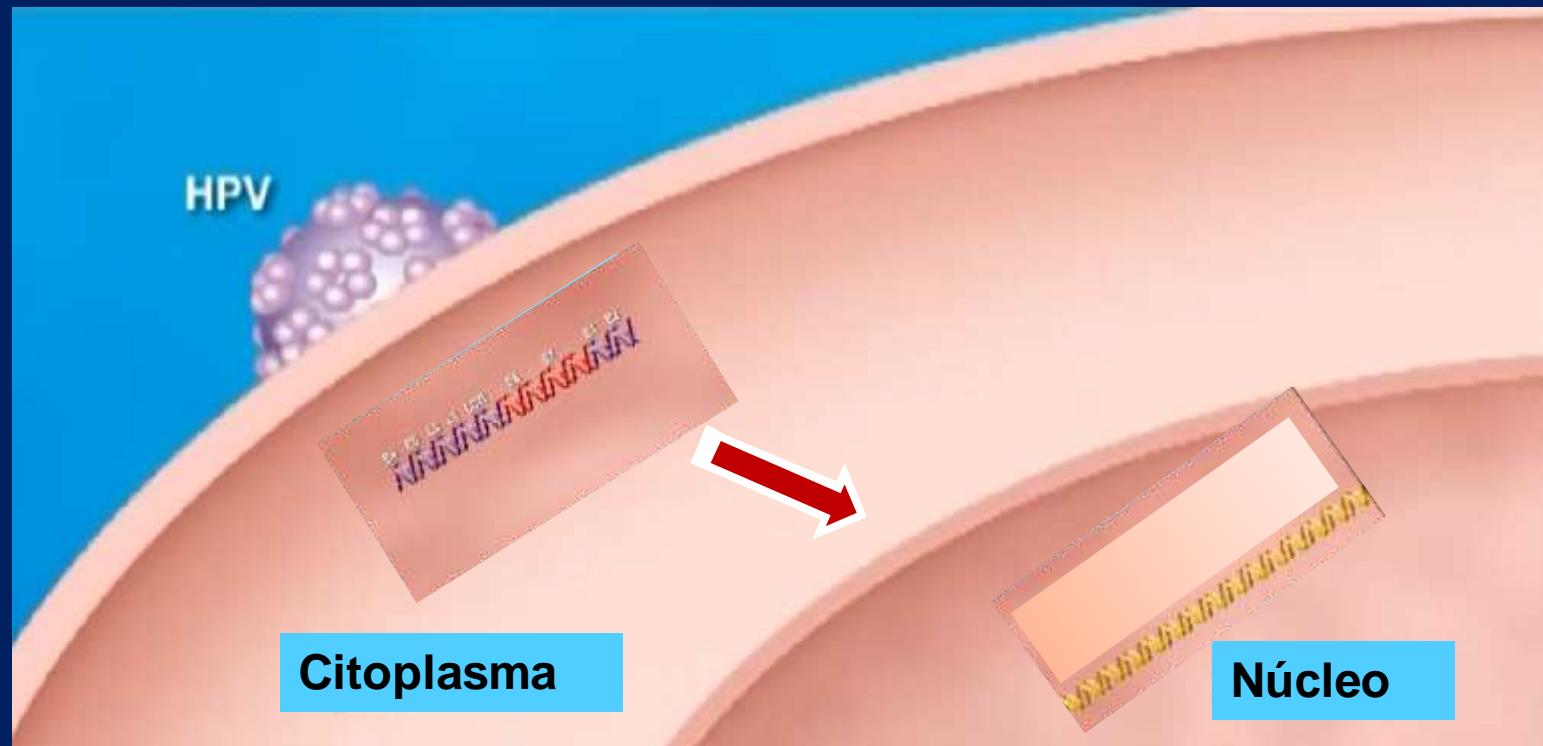


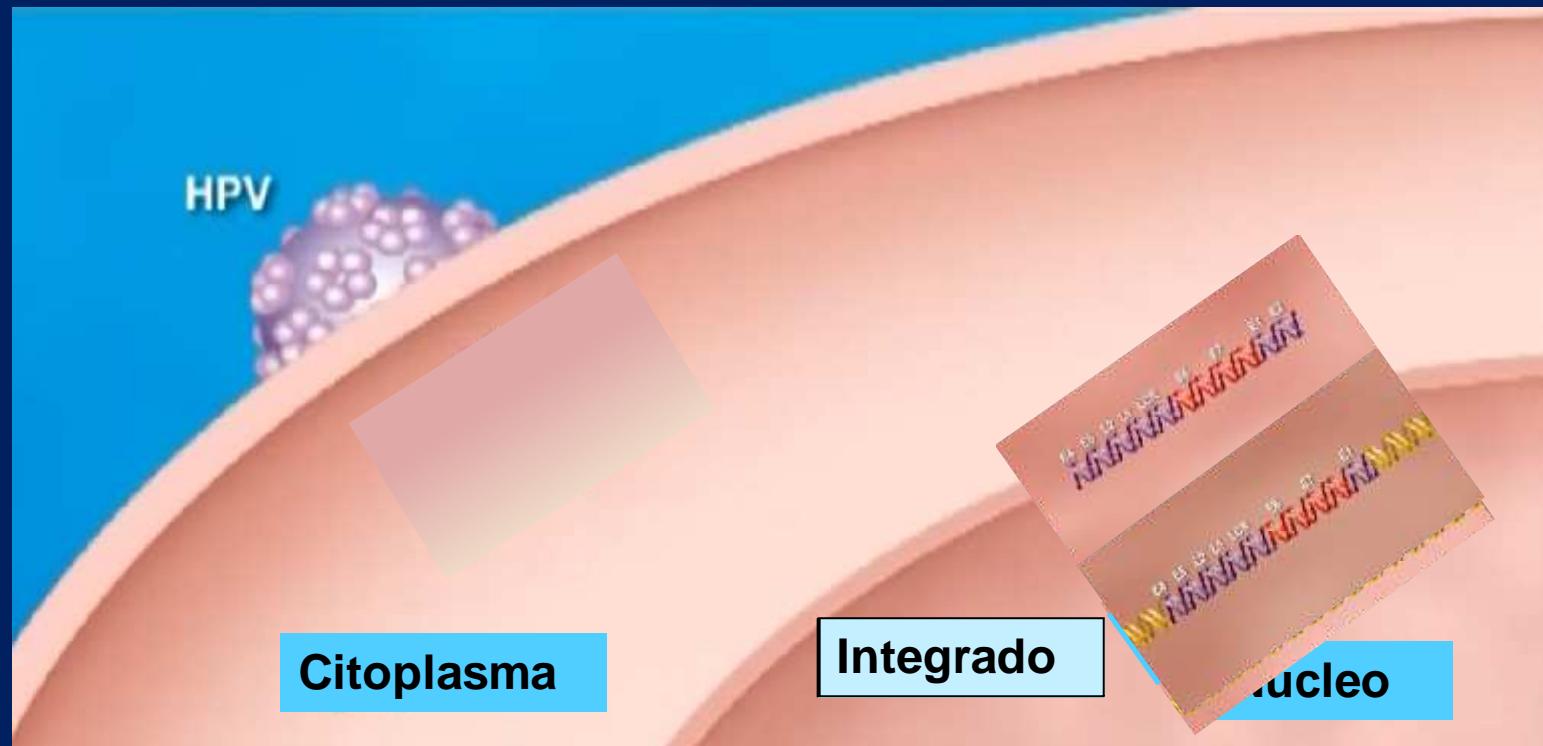
Mecanismos de replicación viral

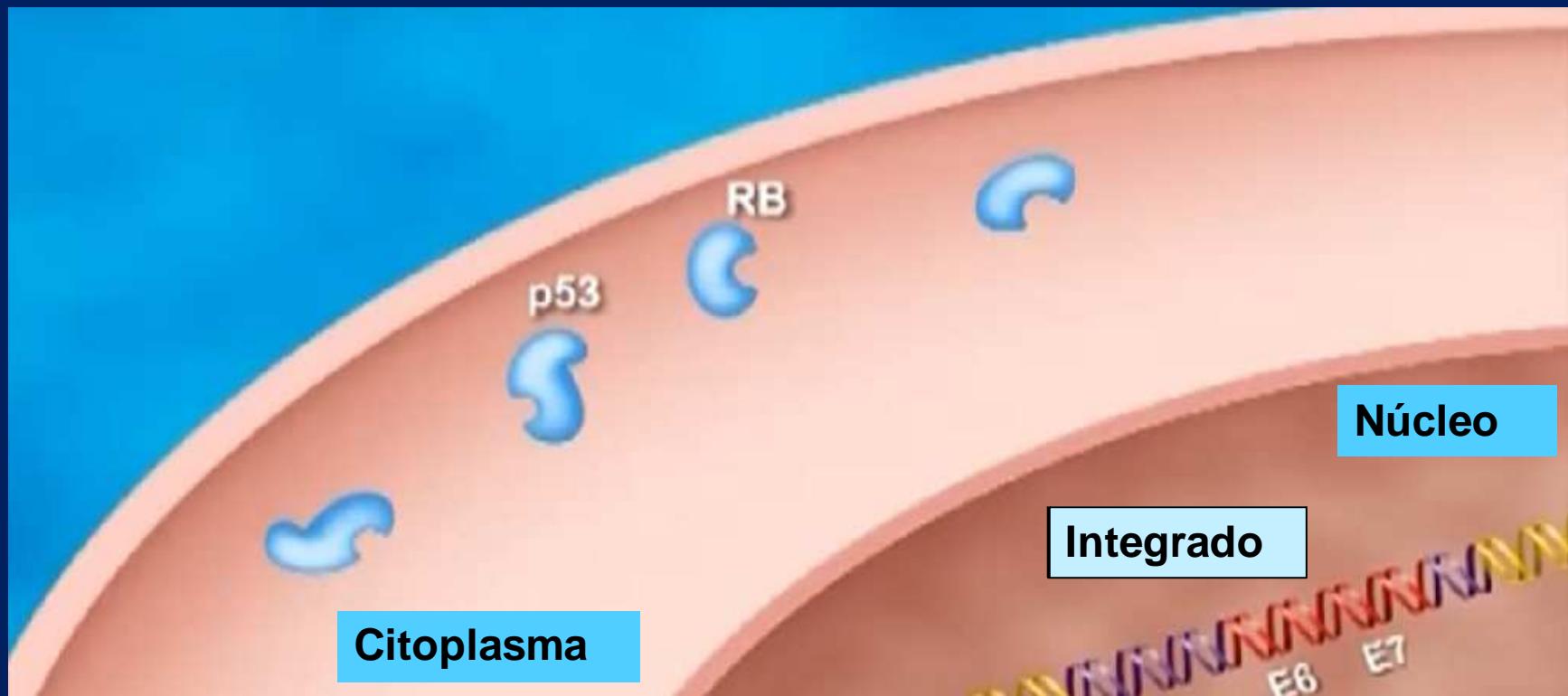
Carcinogénesis

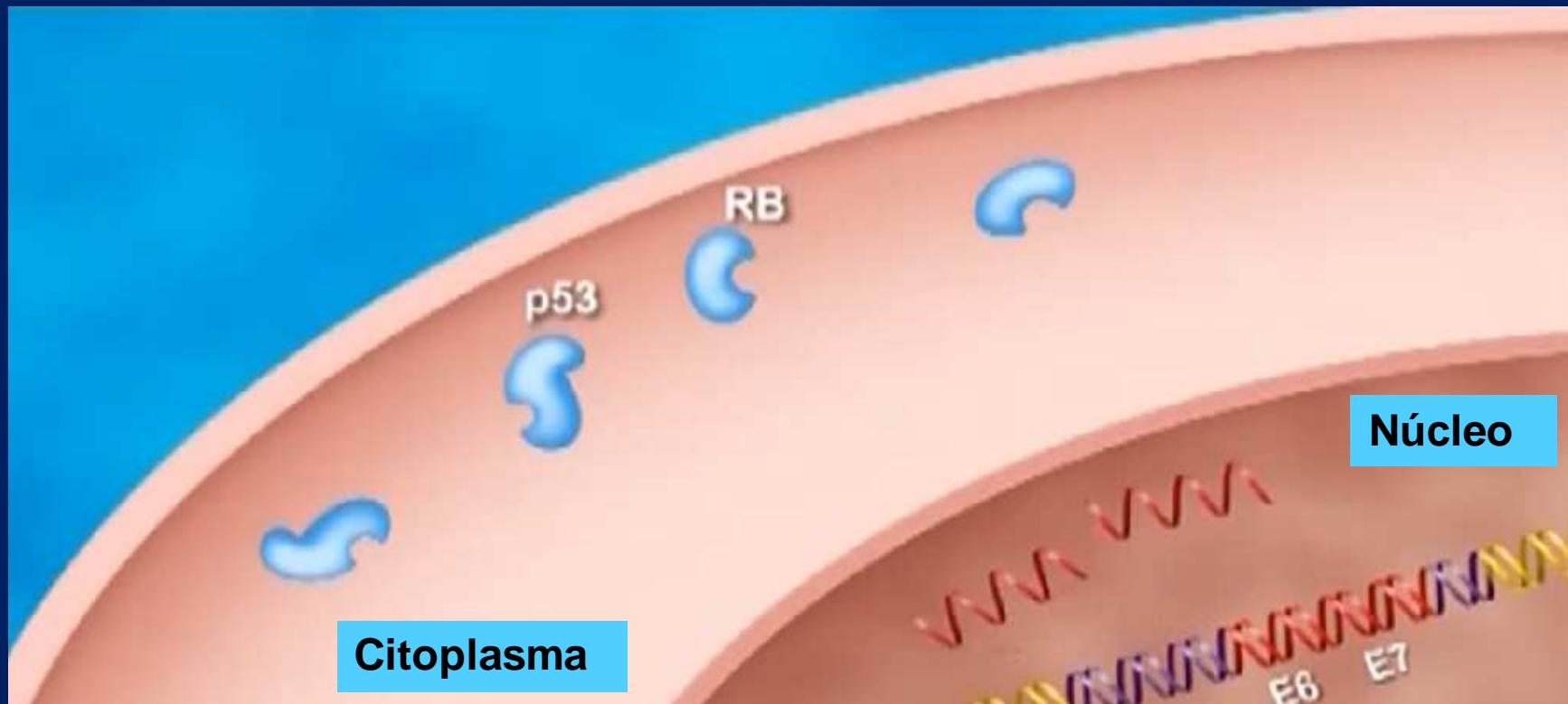


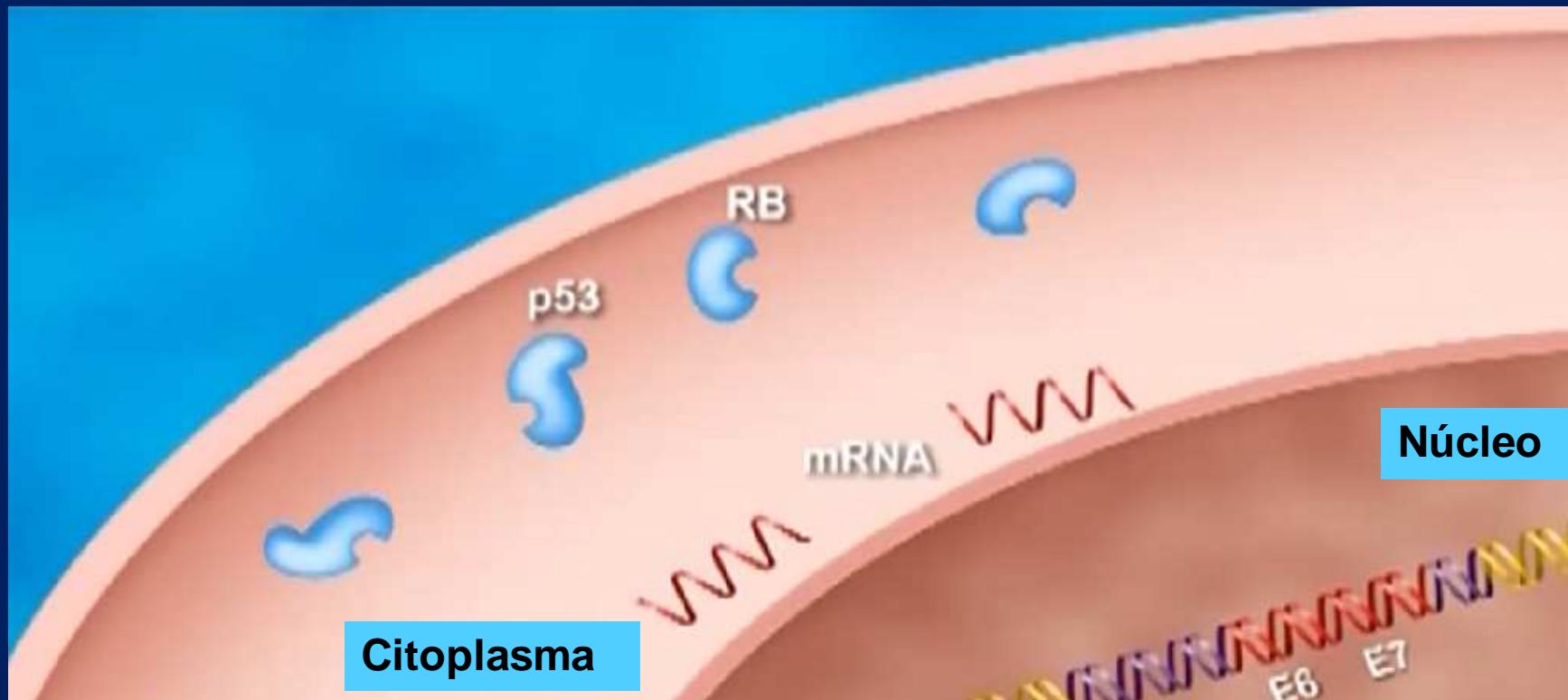


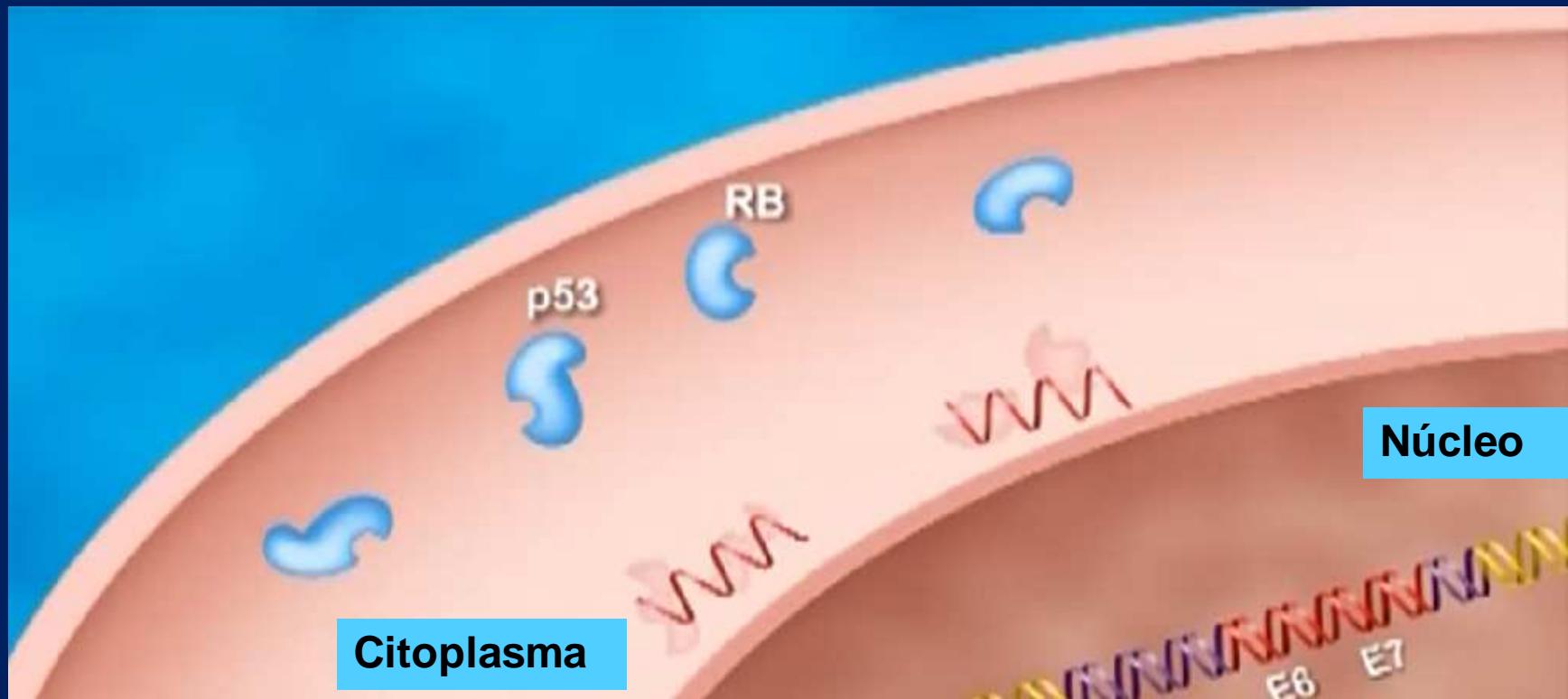


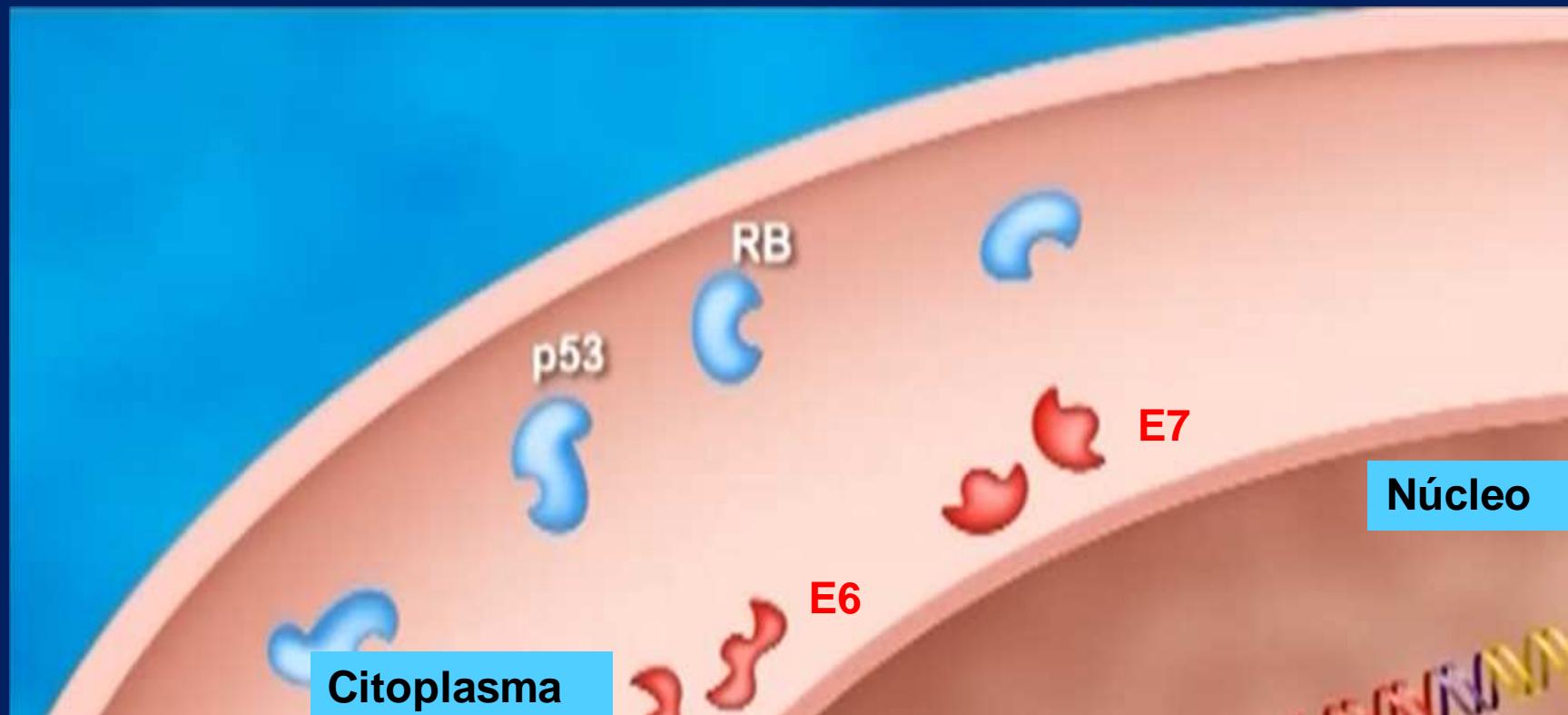




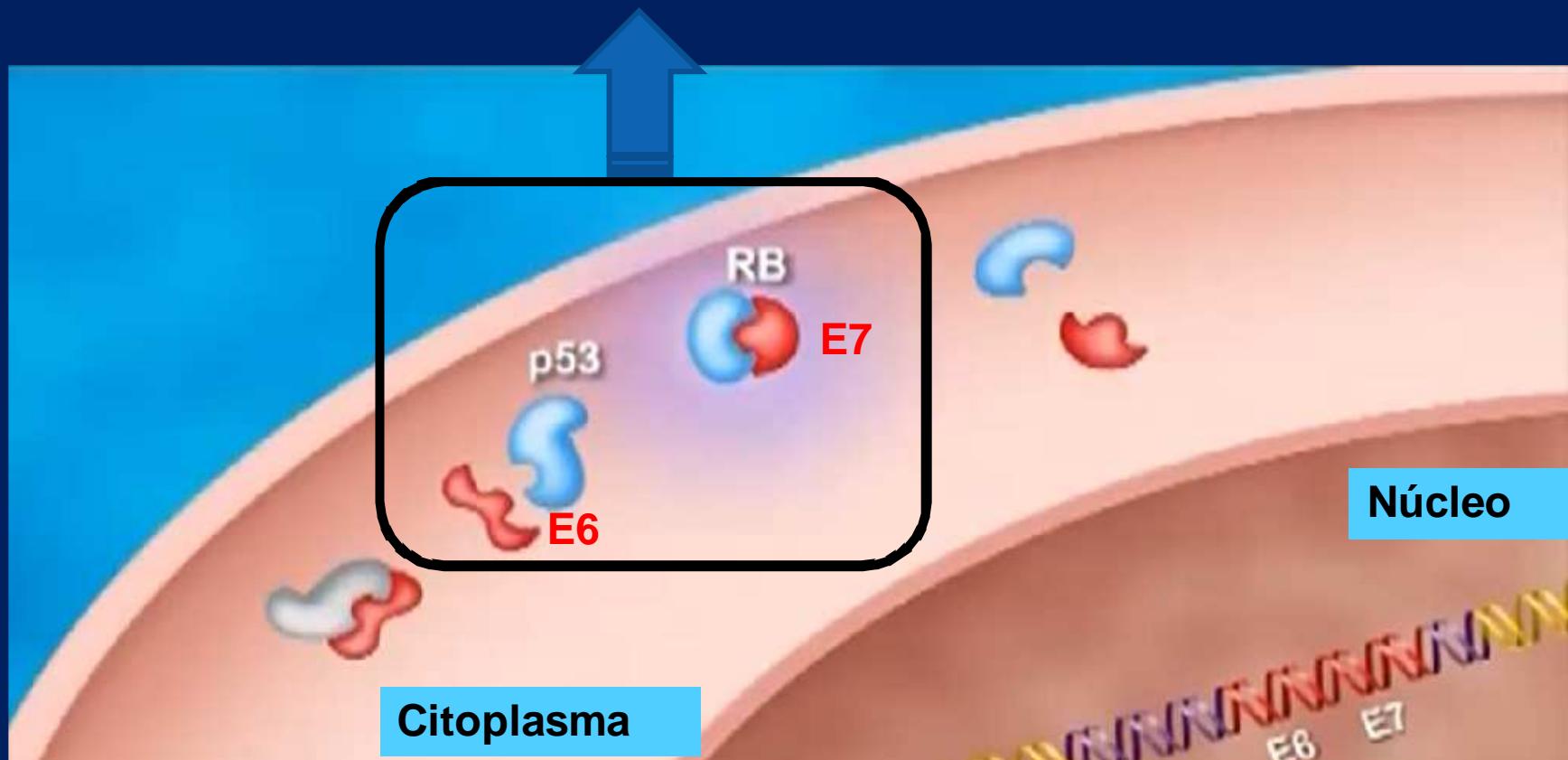






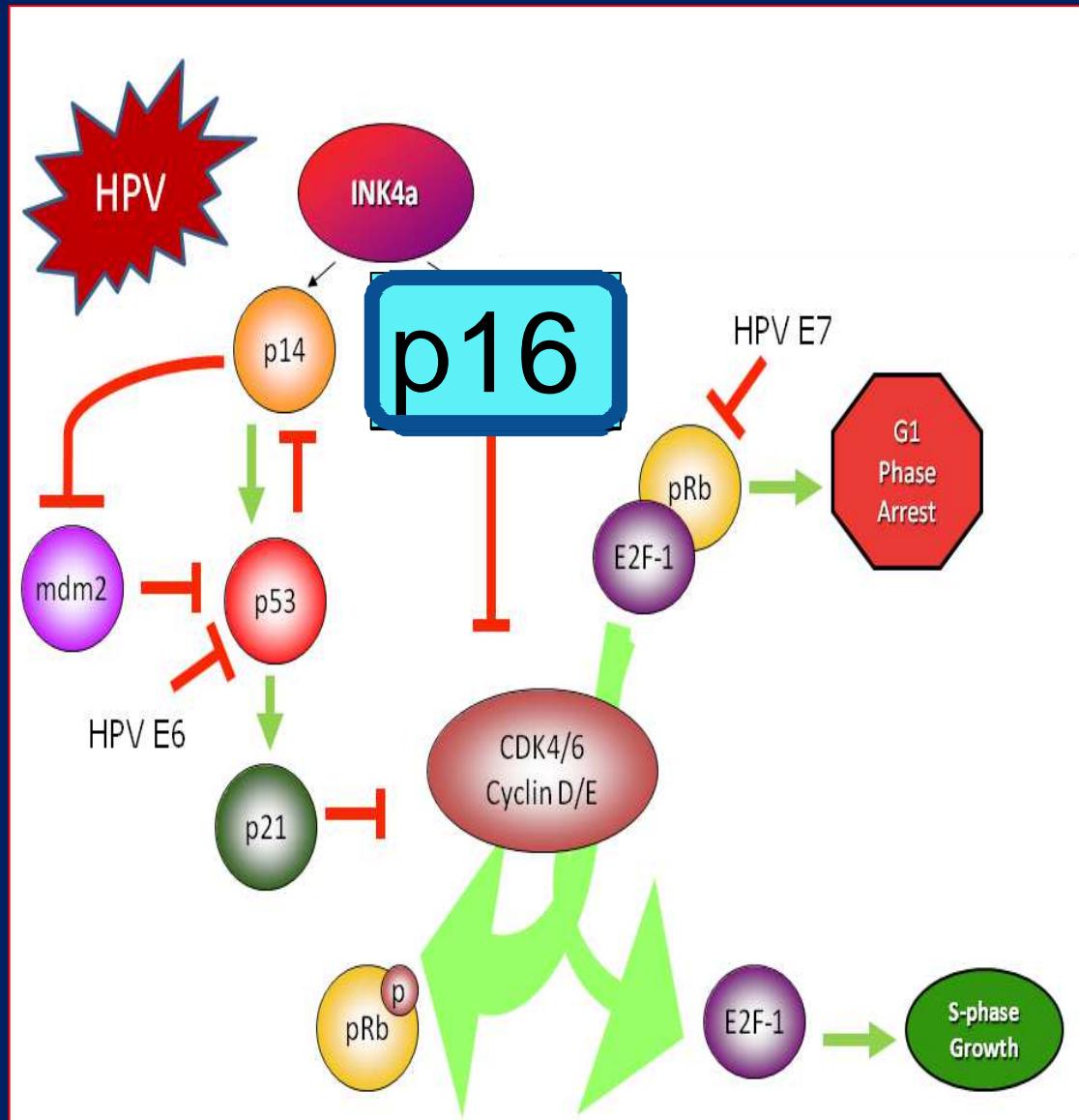


Interferencia en el
ciclo celular



Test inmunohistoquímico de Halec

- p16 ↑↑↑
- pRb ↓↓↓
- p53 —
- ciclina D1 ↓↓↓



Carcinomas VPH

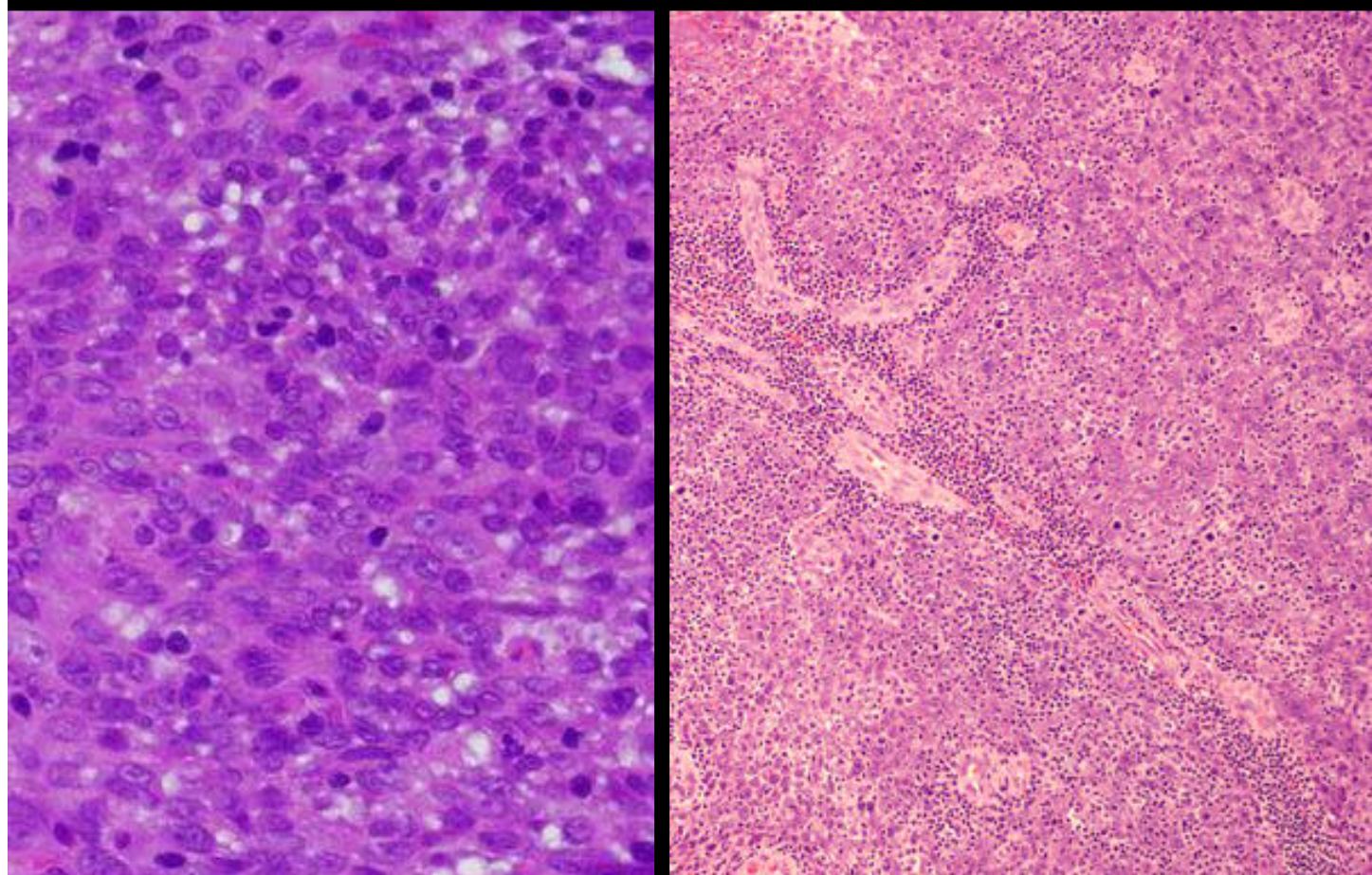
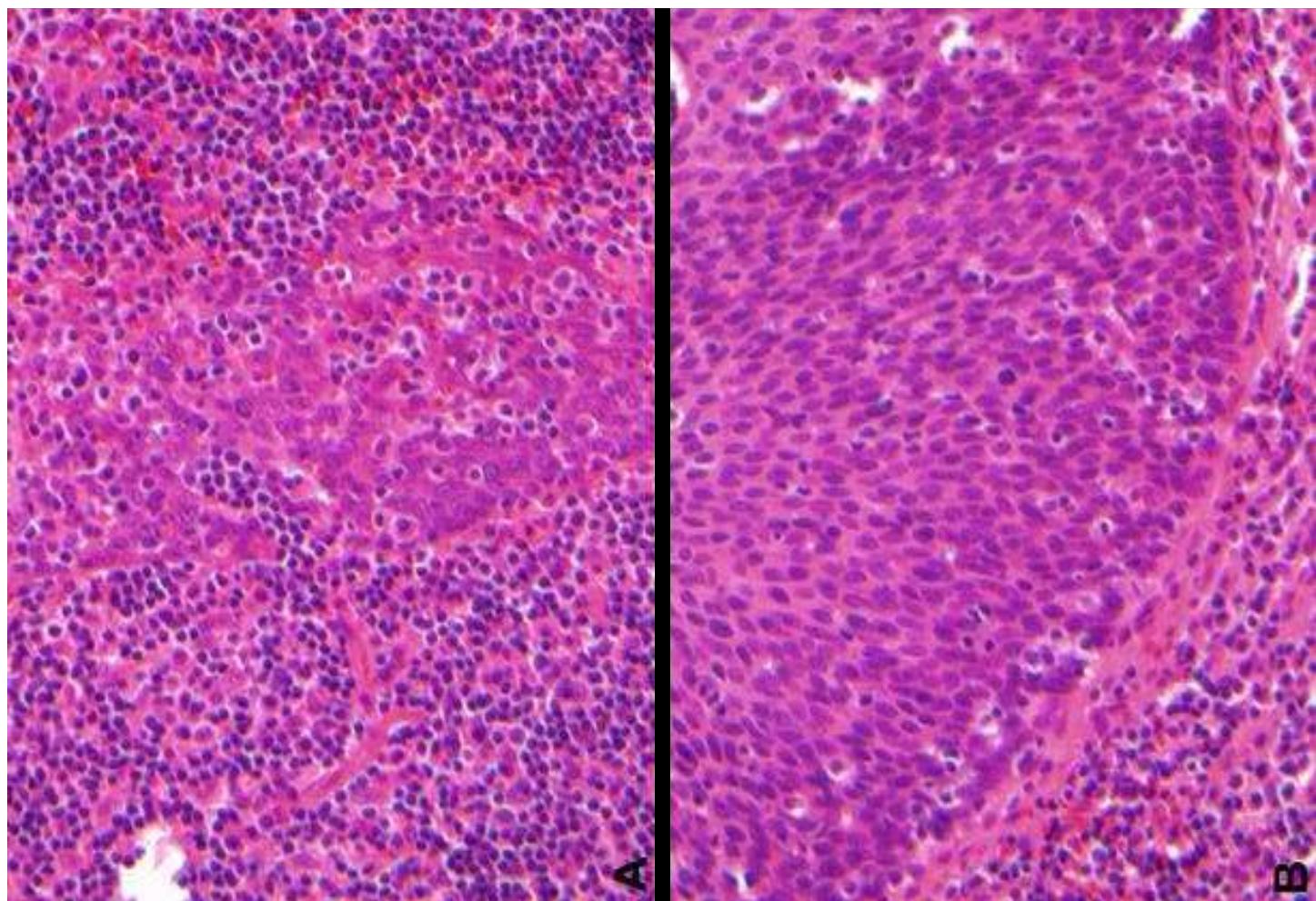
Generalidades

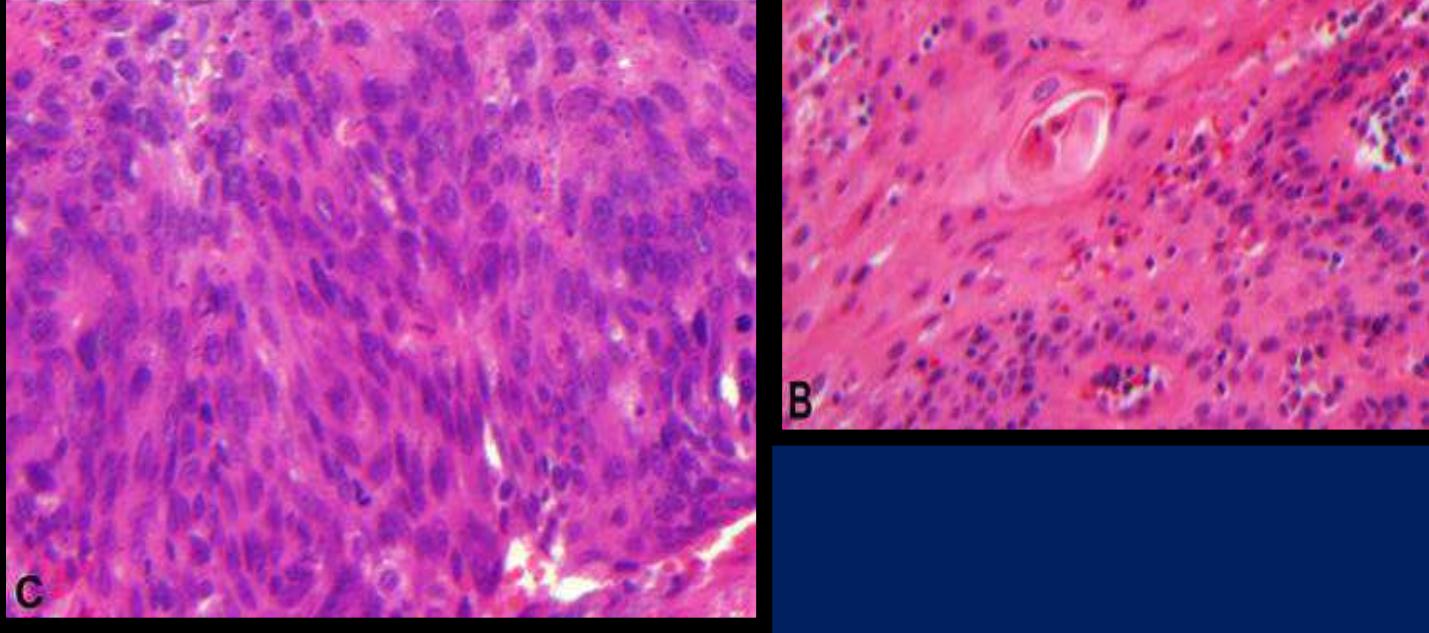
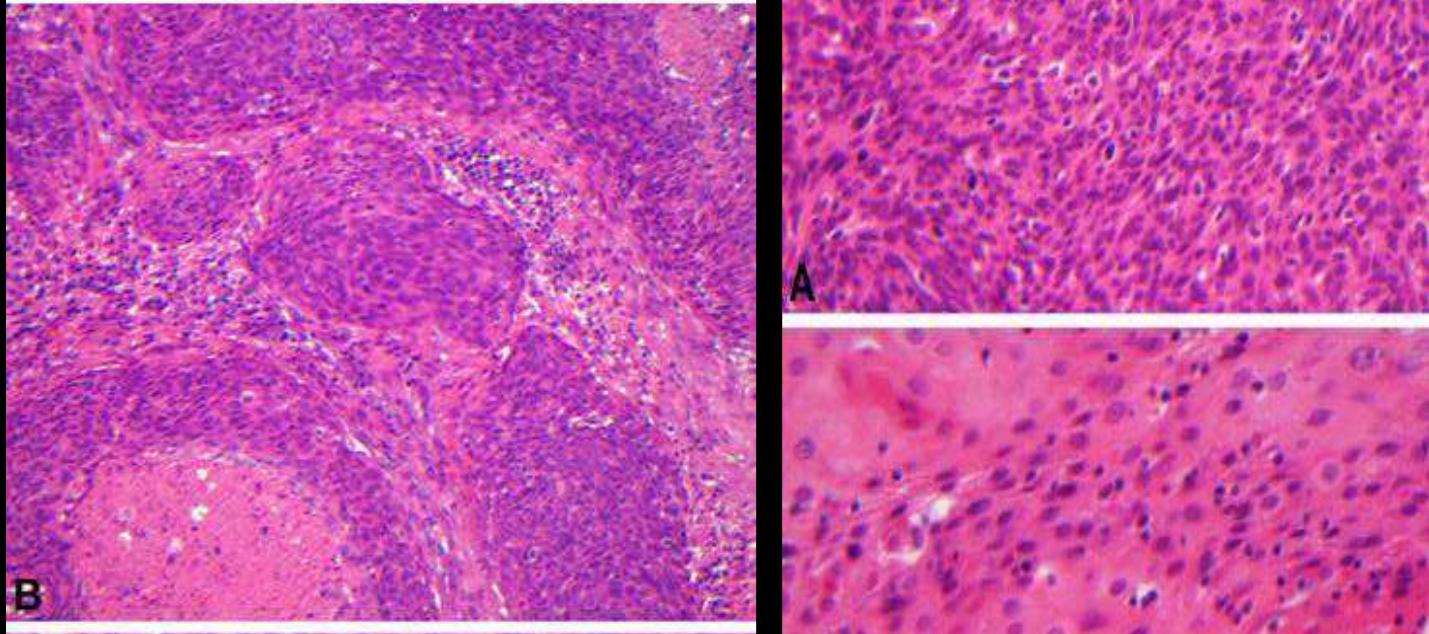
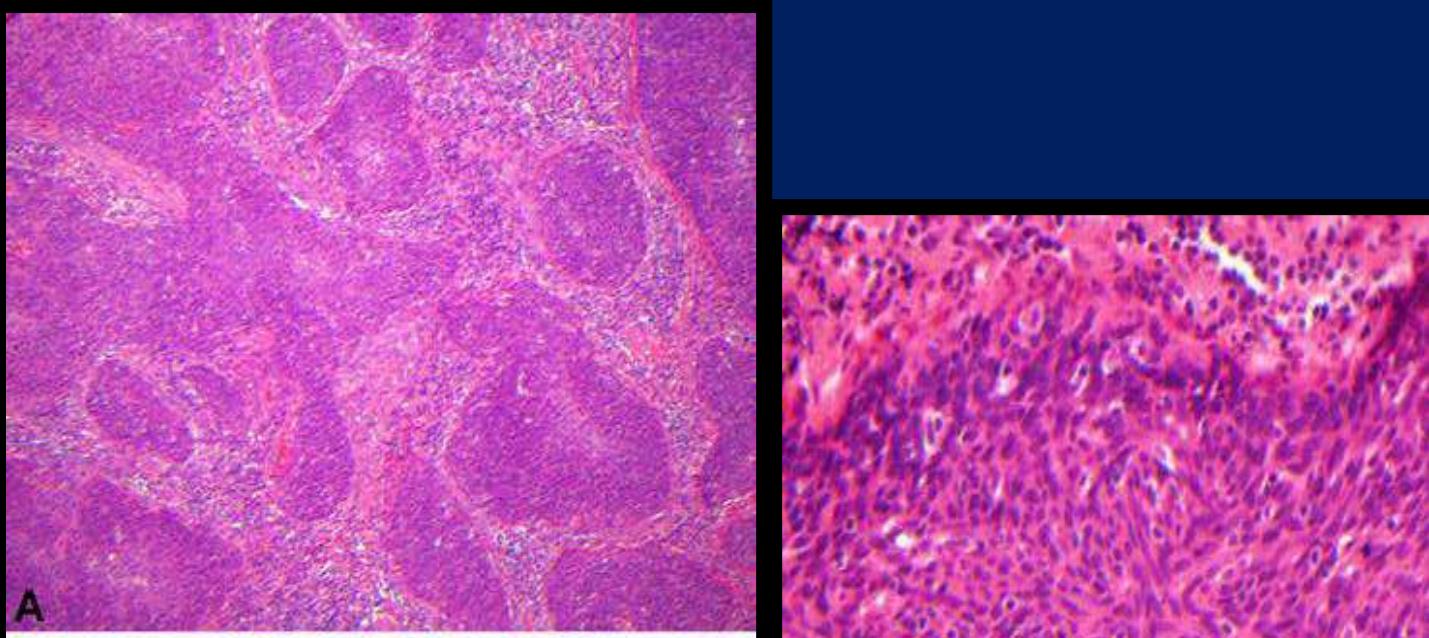
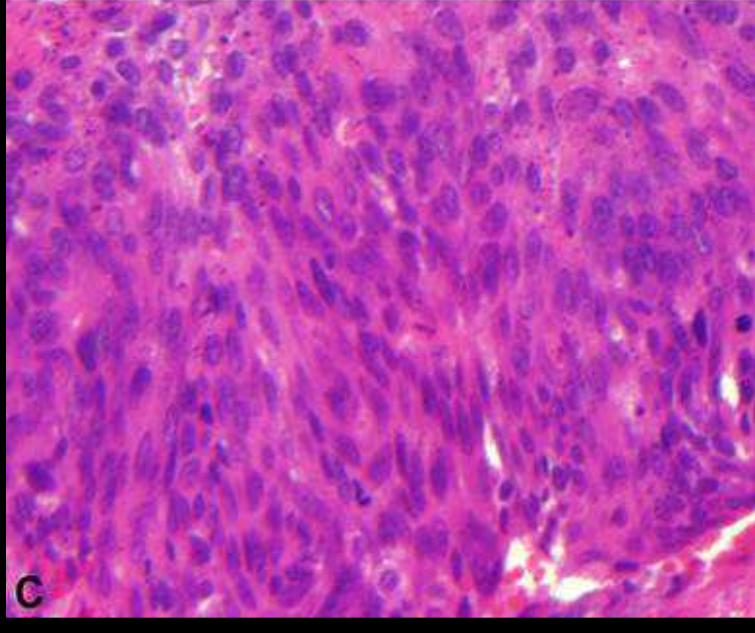
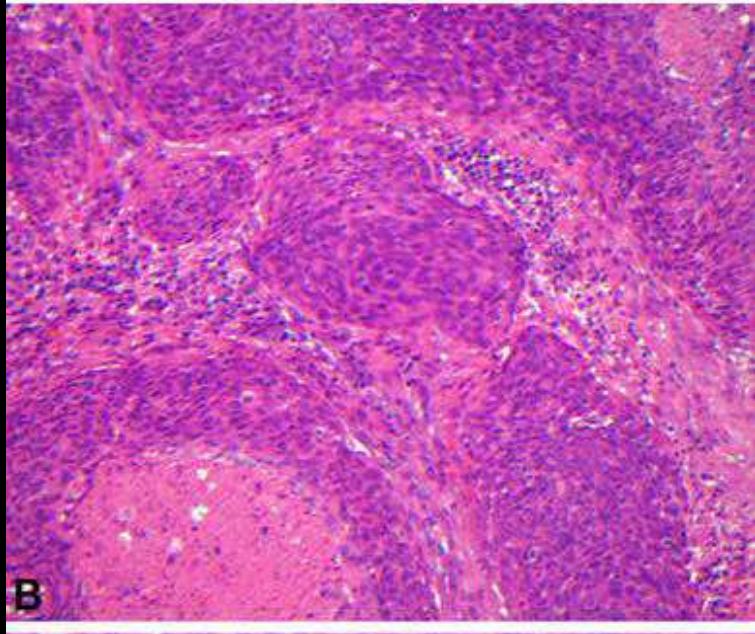
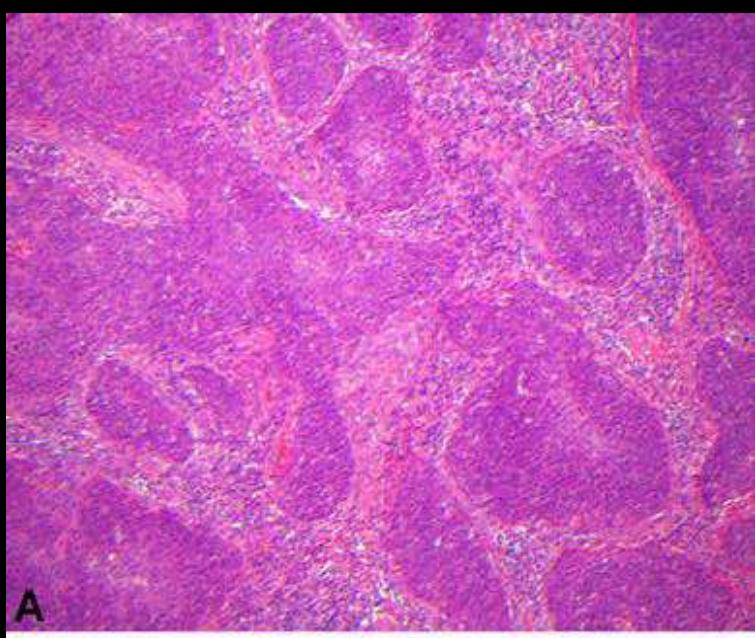
- Jóvenes (< 50 años). No fumadores. Hombres
- Frecuencia del 20%. Prácticas sexuales
- Epitelio críptico tonsilar no reticulado
- VPH-16 (75% casos)
- Metástasis quísticas
- Buen pronóstico
- Buena respuesta a quimio-radioterapia
- Casos asociados a EGFR

Carcinomas VPH

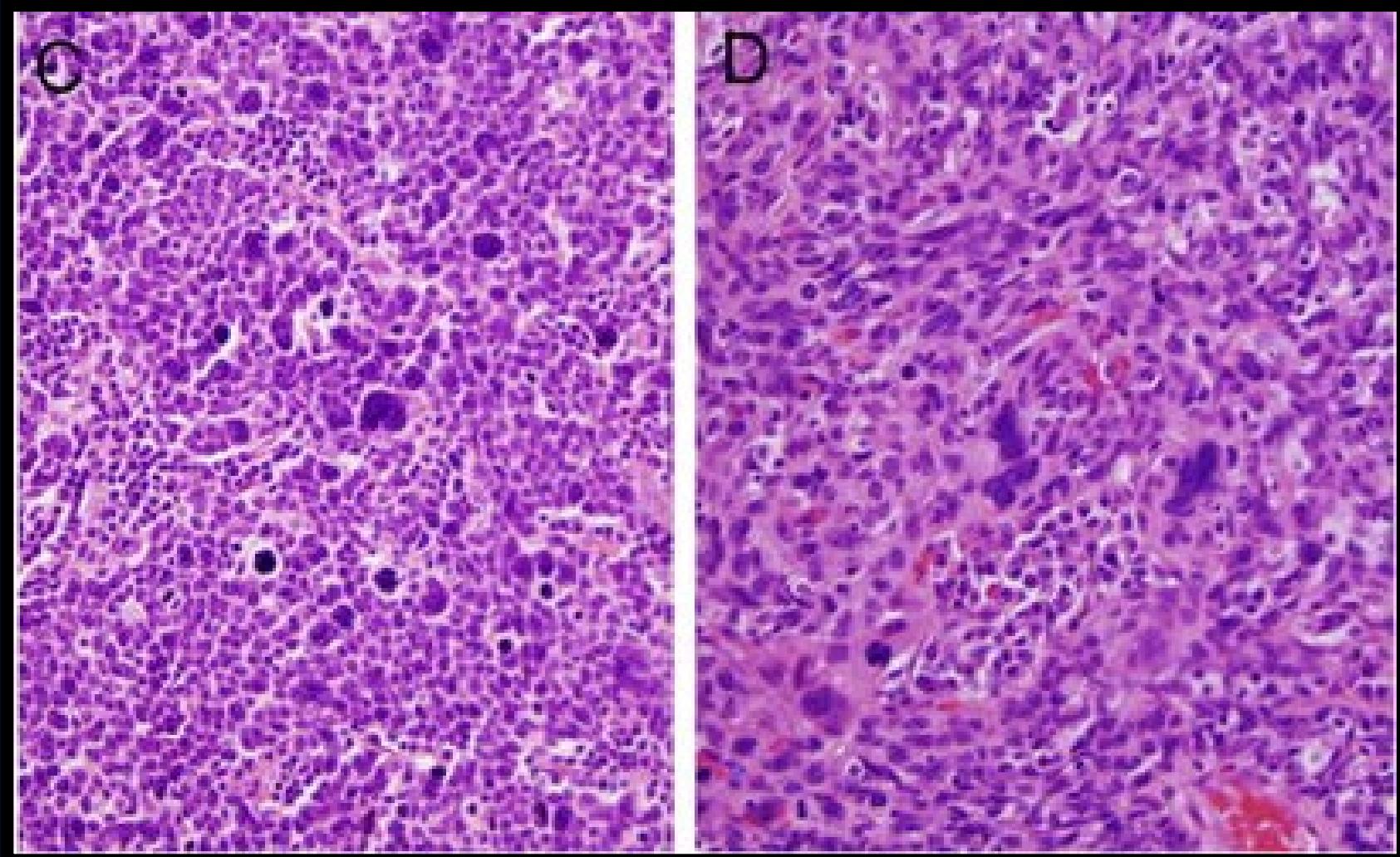
Histología

Considerado como una entidad clínicopatológica dentro de los carcinomas de cabeza y cuello





Anaplasia



Tipos histológicos carcinoma VPH

	TOTAL (%)	VPH +	VPH -
QUERATINIZANTES	10	4	96
NO QUERATINIZANTES	70	72	28
HÍBRIDO	16	64	36
VARIANTES			
BASALOIDE	2	100	0
PAPILAR	1	67	33
INCLASIFICABLE	1	50	50

CARCINOMAS FARÍNGEOS RELACIONADOS CON VIRUS

VEB

- Posterolateral de la nasofarínge (Rosenmuller)
- Lesiones preneoplásicas
- Gente mayor
- 60%
- Buen pronóstico
- Tipo linfoepitelial no queratinizante

VPH

- Epitelio críptico reticular tonsilar, palatinas y lengua
- No preneoplásicas
- Gente joven
- 40%
- Buen pronóstico
- Tipo linfoepitelial no queratinizante ó queratinización “paradójica”

Carcinomas VPH-AR

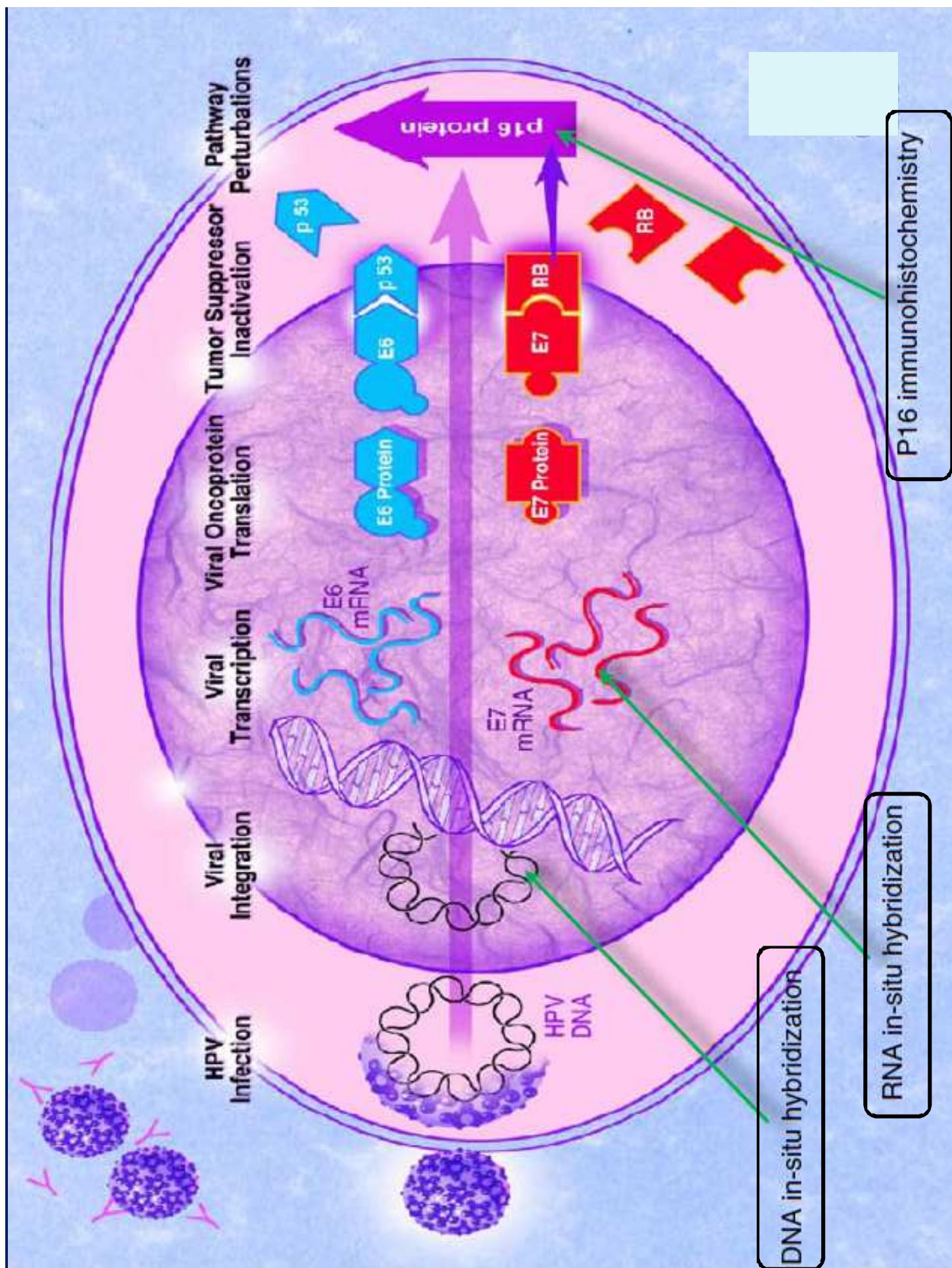
Métodos de detección

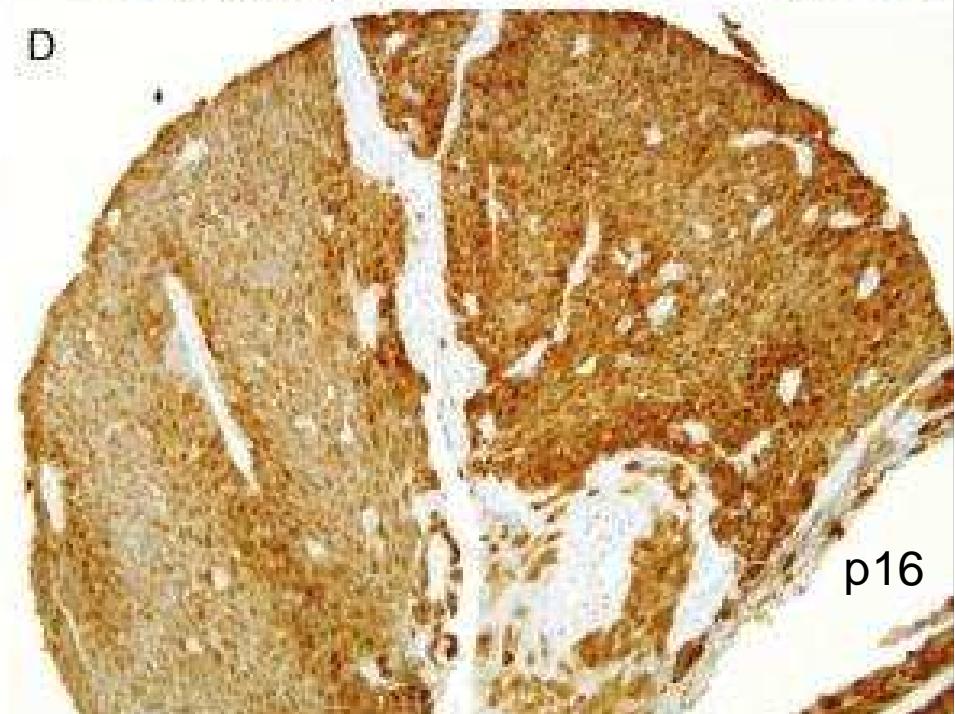
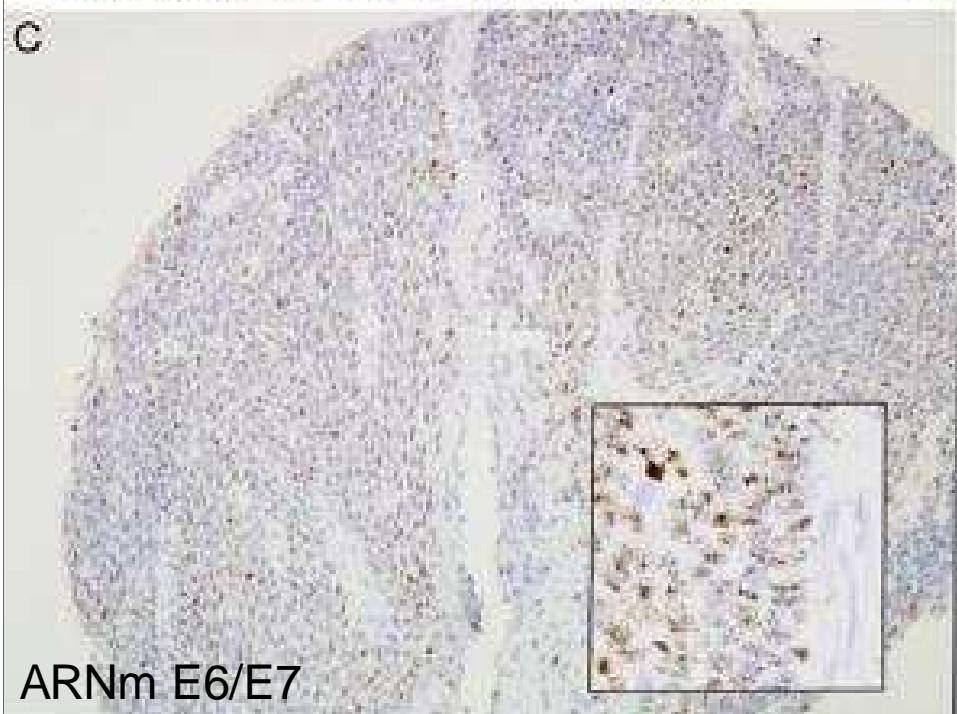
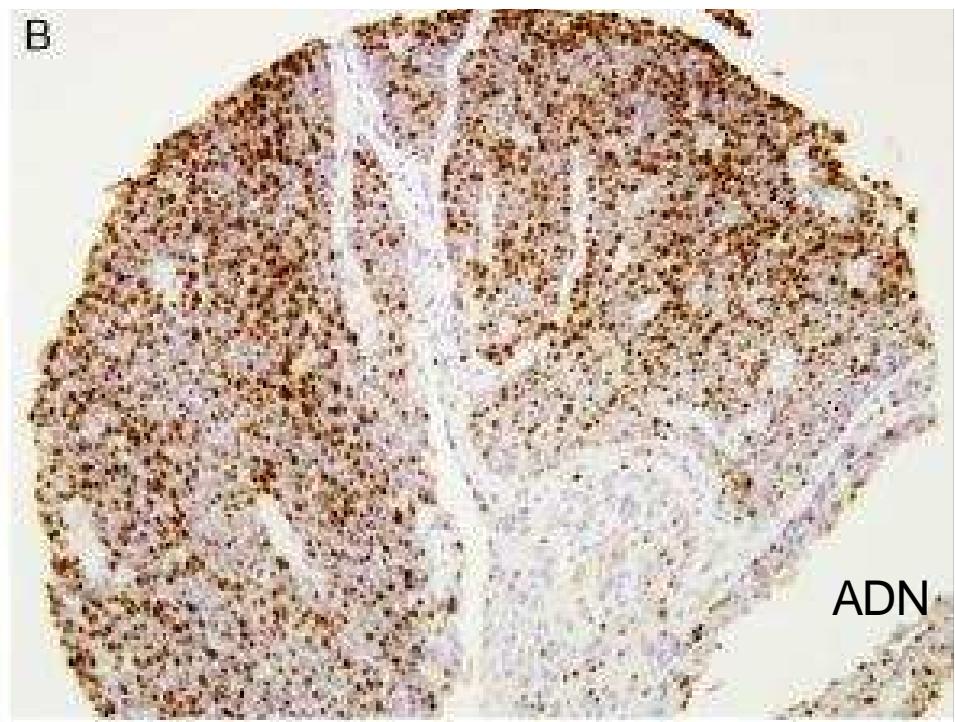
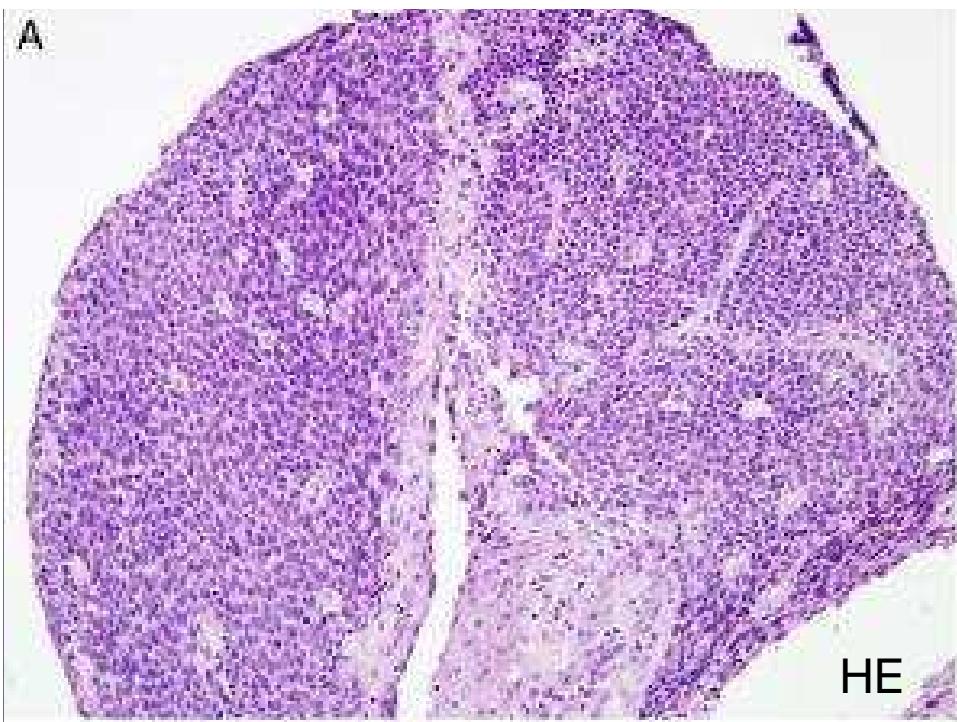
MÉTODOS

- TINCIÓN P16 INMUNOHITOQUÍMICA
- DETECCIÓN ADN HIBRIDACION IN SITU
- ARNm HIBRIDACIÓN IN SITU

Test detección VPH-AR

MÉTODOS	SENSIBILIDAD	ESPECIFICIDAD
P16-IHQ	96 %	75 %
ADN-HIS	76 %	94 %
ARN-E6/E7 HIS	96 %	94 %

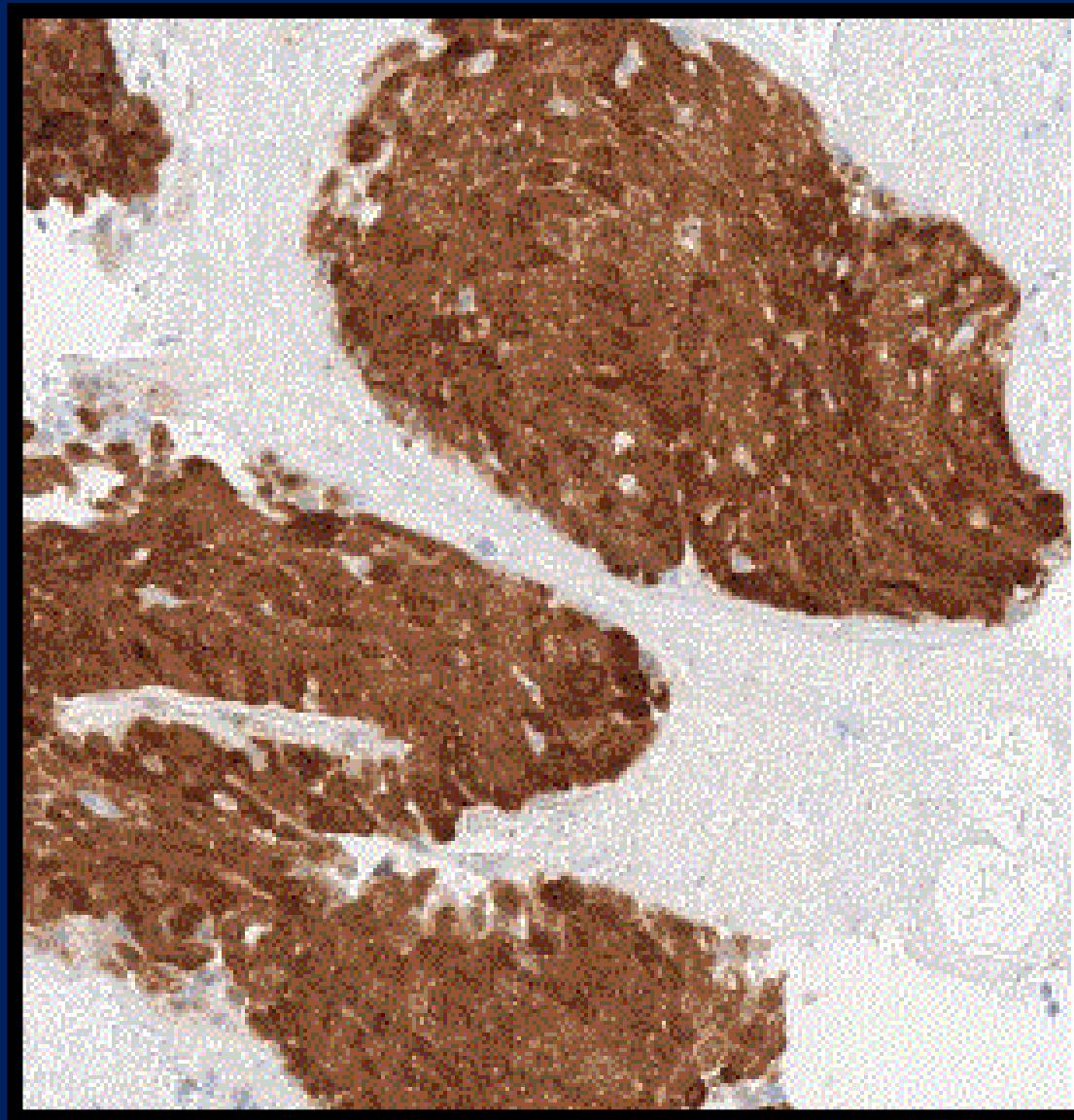




P16-IHQ

La tinción p16 IHQ es el mejor predictor de la presencia de VPH. Punto de corte $\geq 70\%$ con tinción citoplásrica y nuclear

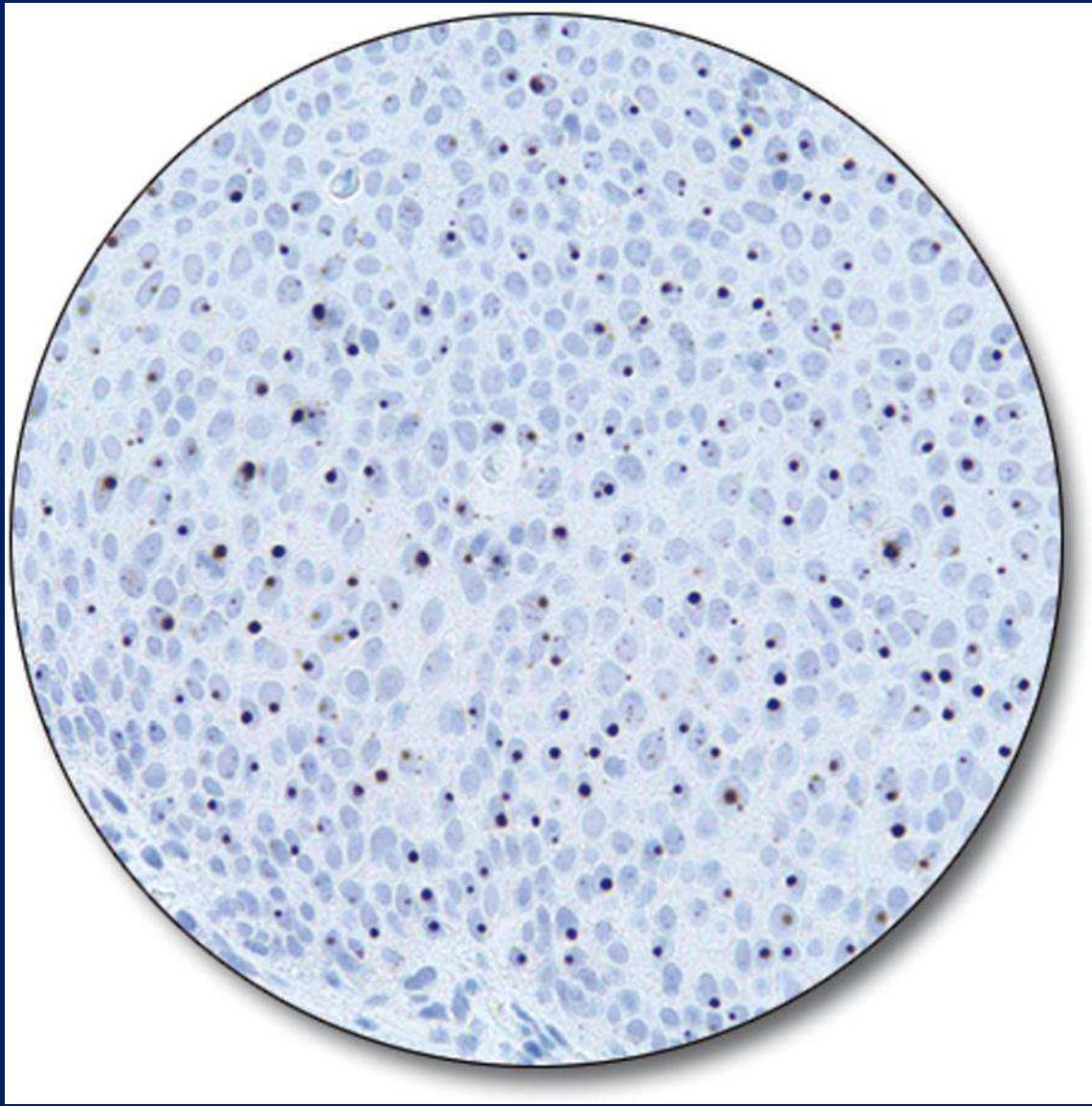
P16 VPH inmunohistoquímica



ADN Hibridación in situ

Es muy específica para la visualización directa del virus dentro del núcleo de la célula tumoral

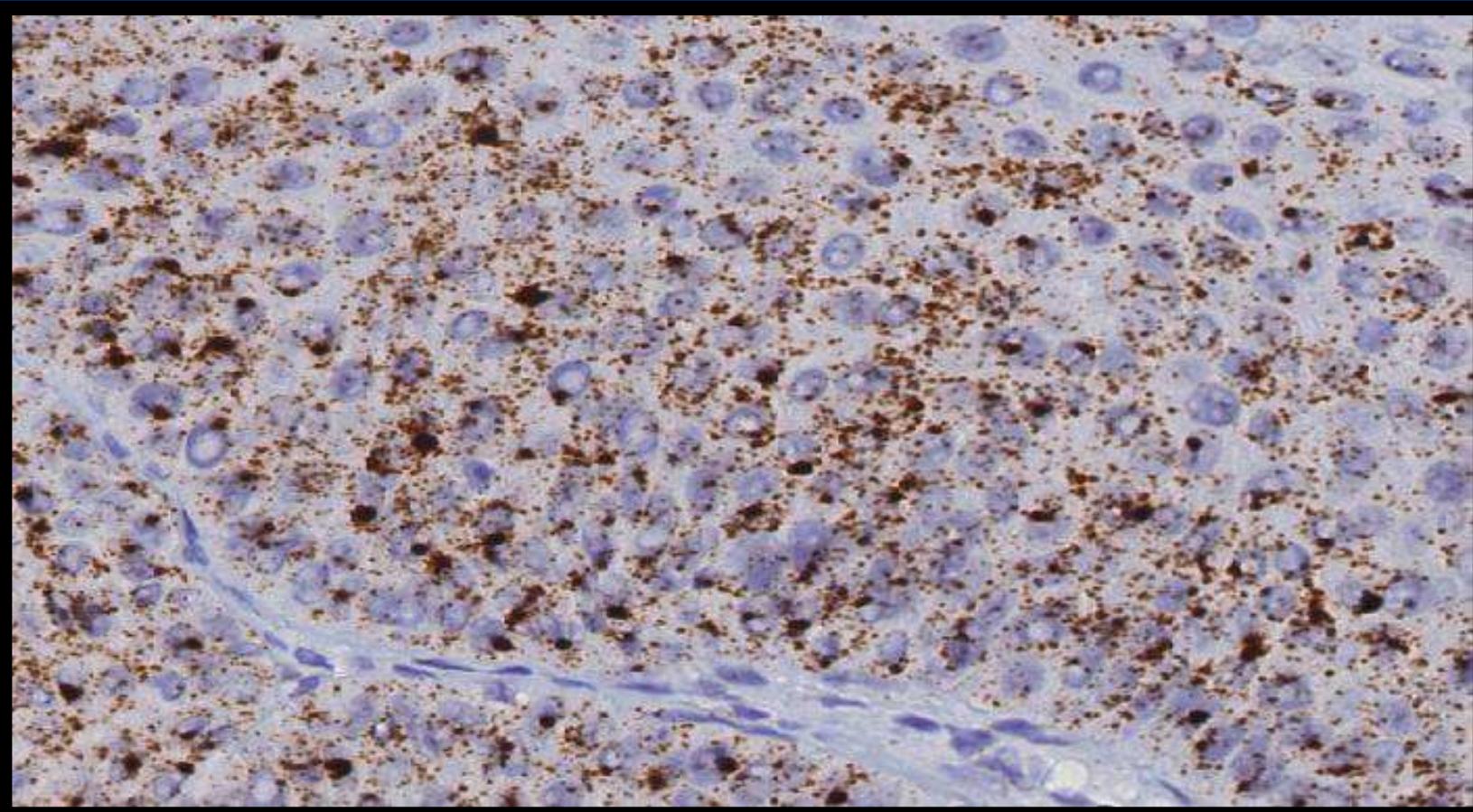
ADN VPH hibridacion in situ



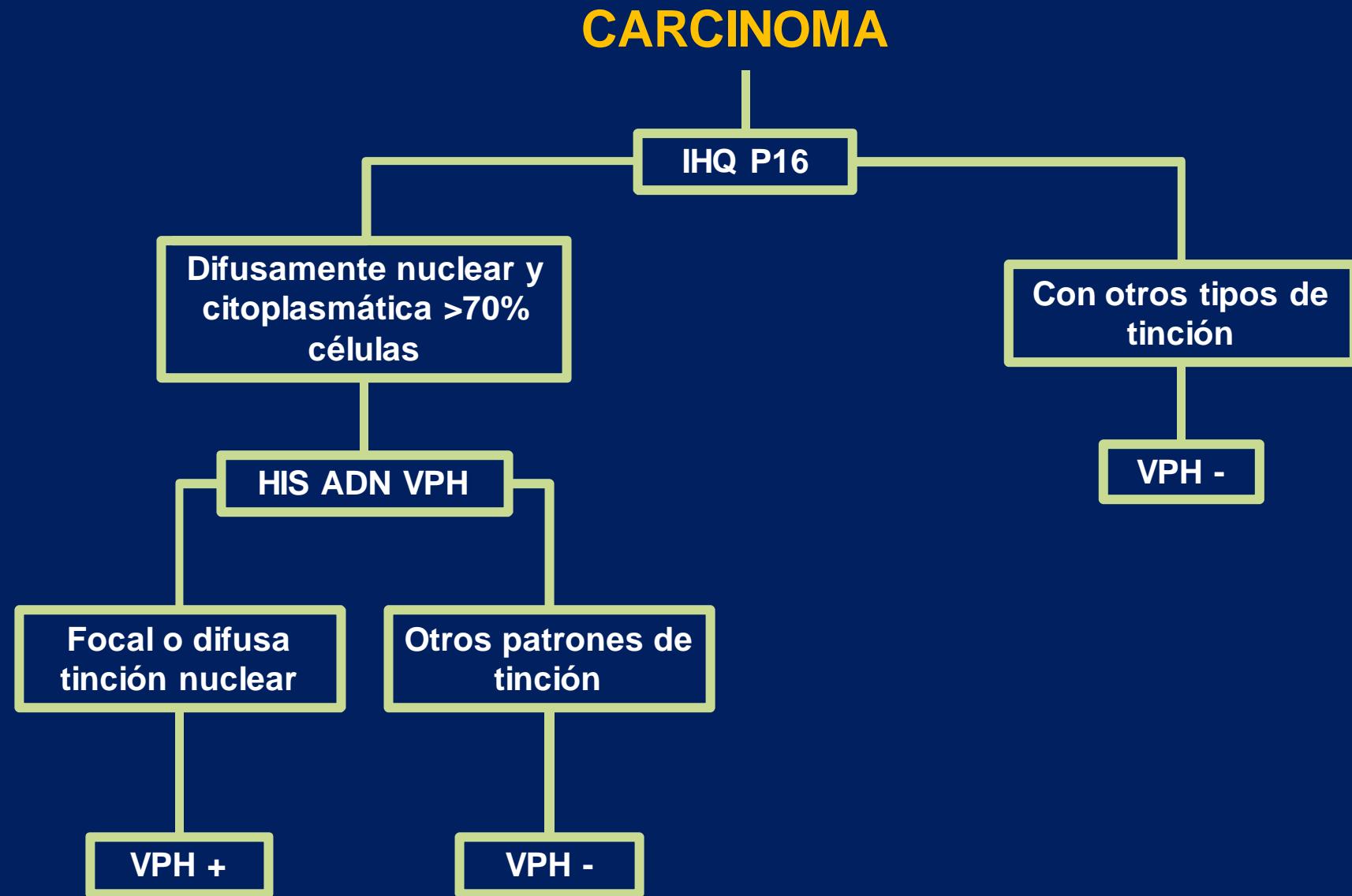
ARNm Hibridación in situ

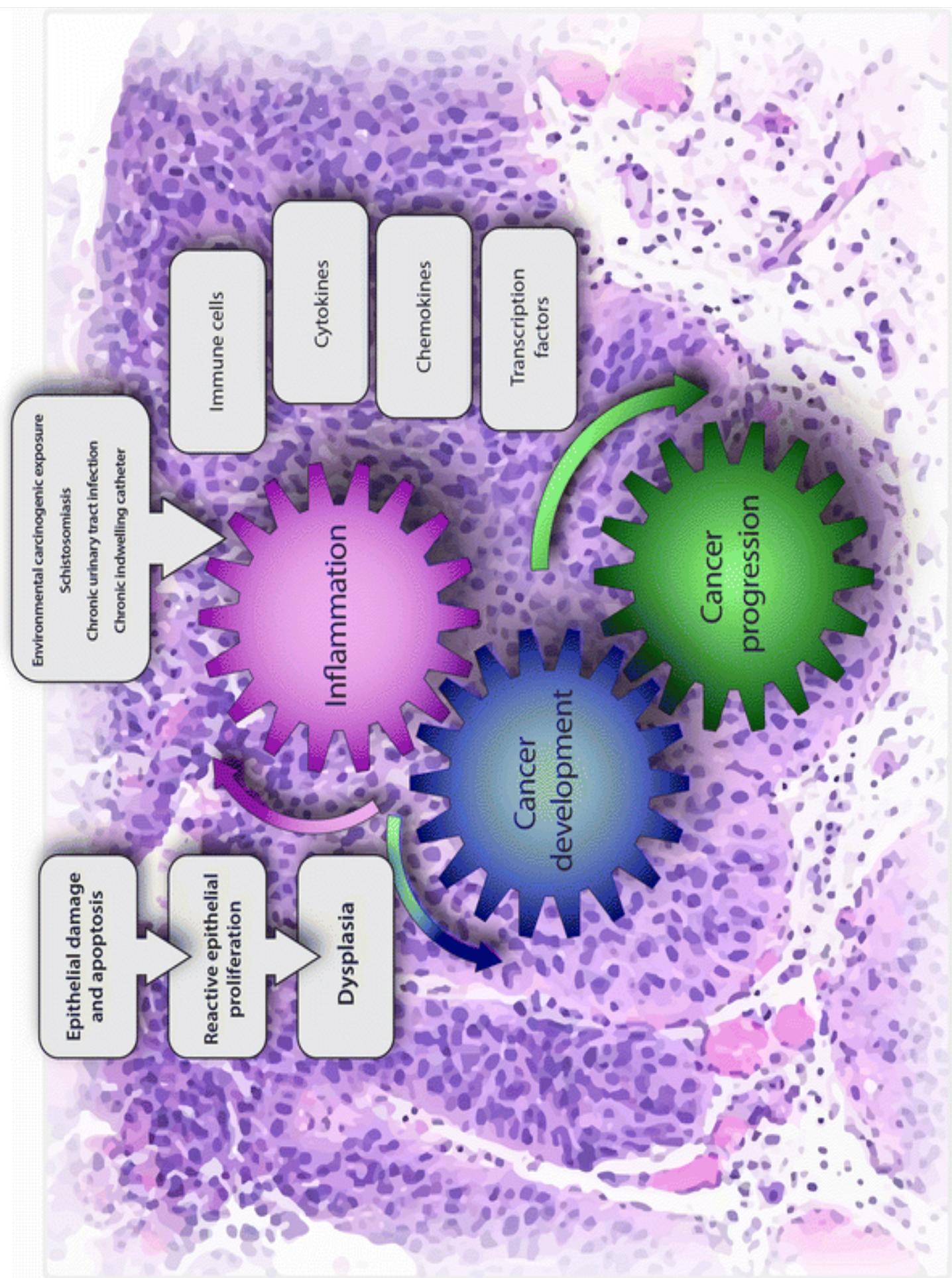
Es muy específica para la
visualización directa del
virus activo
transcripcionalmente

ARNm E6/E7 hibridacion in situ



ALGORITMO PARA DETERMINACIÓN DE VPH-AR



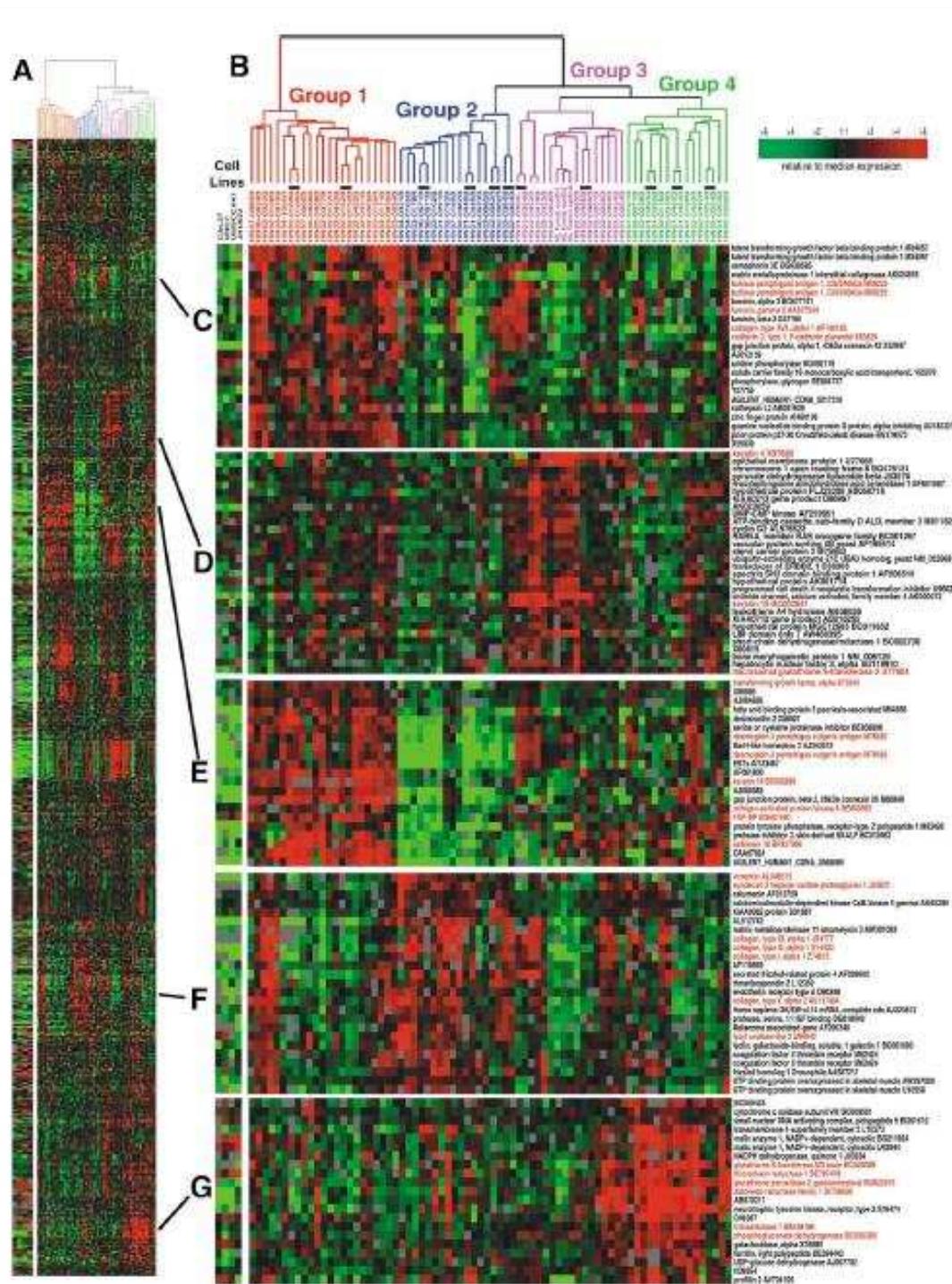


NUEVAS TAREAS EN PATOLOGÍA

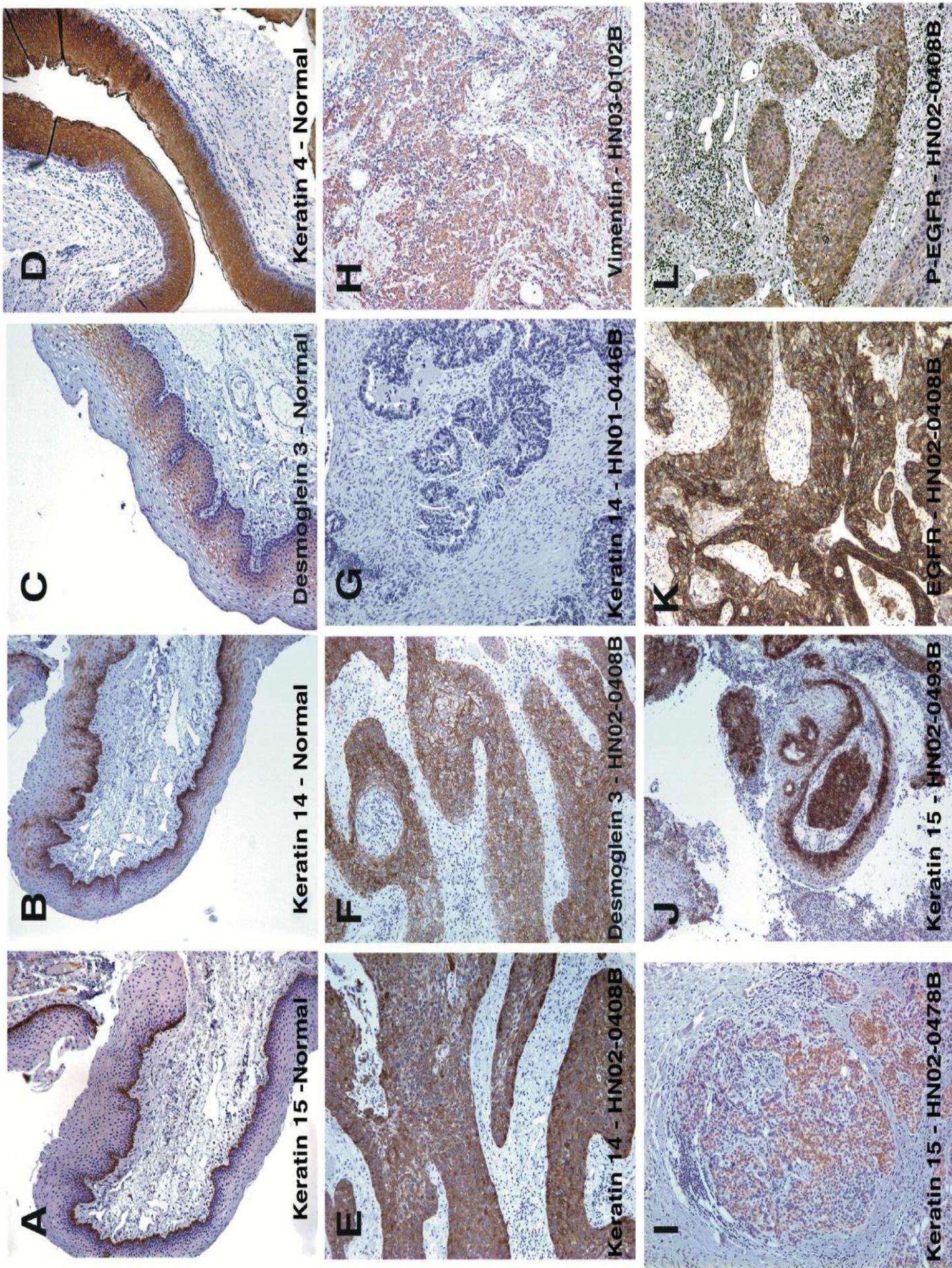
- LINFOCITOSIS INTRATUMORAL
- VIAS DE SEÑALIZACION PD-1:PD-L1
- FIRMAS MOLECULARES EGFR/VPH
- CLASIFICACIÓN MOLECULAR SEGÚN EXPRESIÓN GÉNICA

Cánceres de cabeza-cuello

Clasificación molecular
según
patrones de expresión génica



DENDOGRAMA



CLASIFICACION MOLECULAR

Libre enfer.

150 meses

Tipo 1. BASAL (CK14, EGFR, Desmogleína)

0 %

Tipo 2. MESENQUIMAL (VIM, Desmogleína)

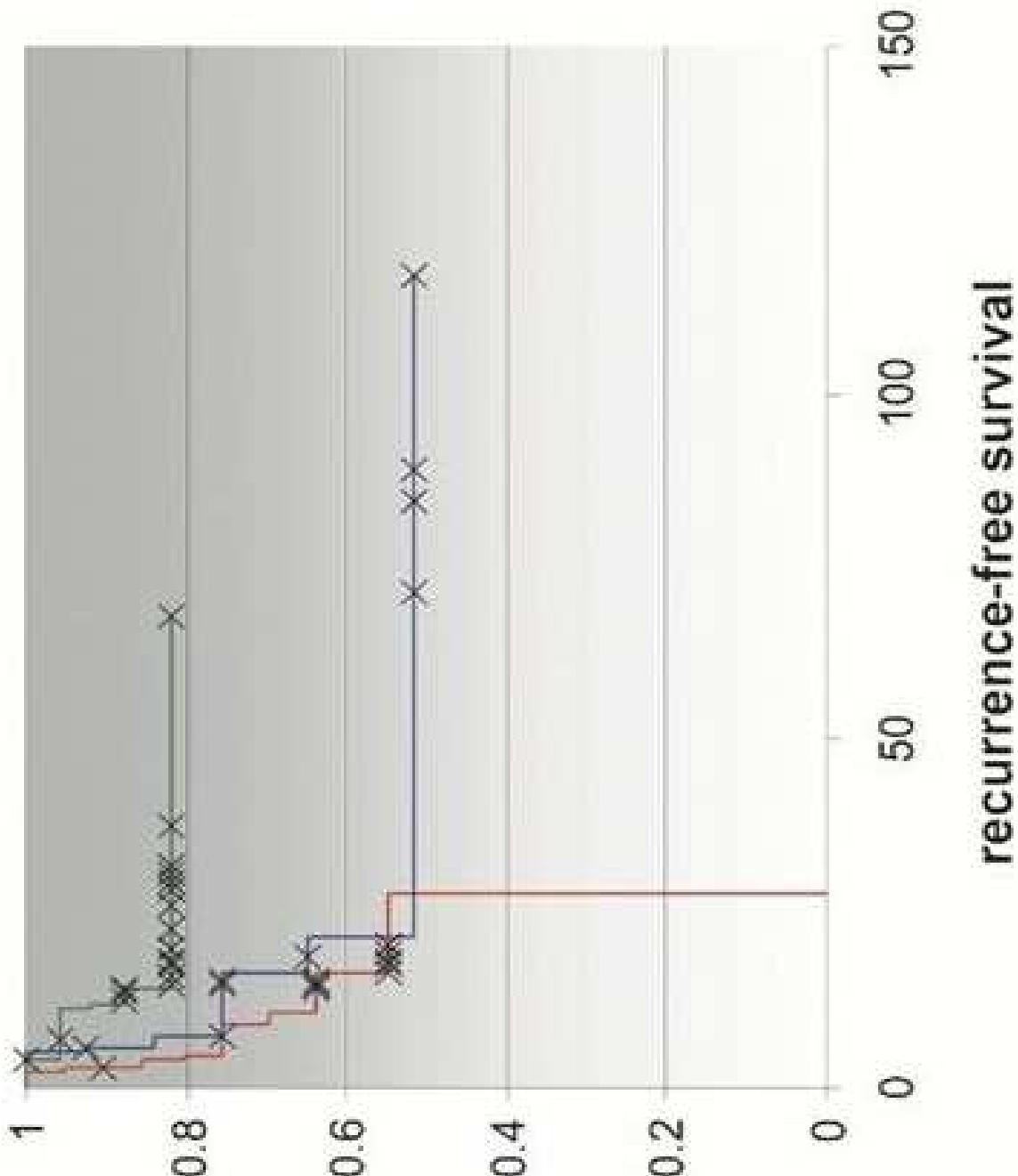
50 %

Tipo 3. ATIPICO (CK14, CK15)

85 %

Tipo 4. CLASICO (Enzimas antioxidantes)

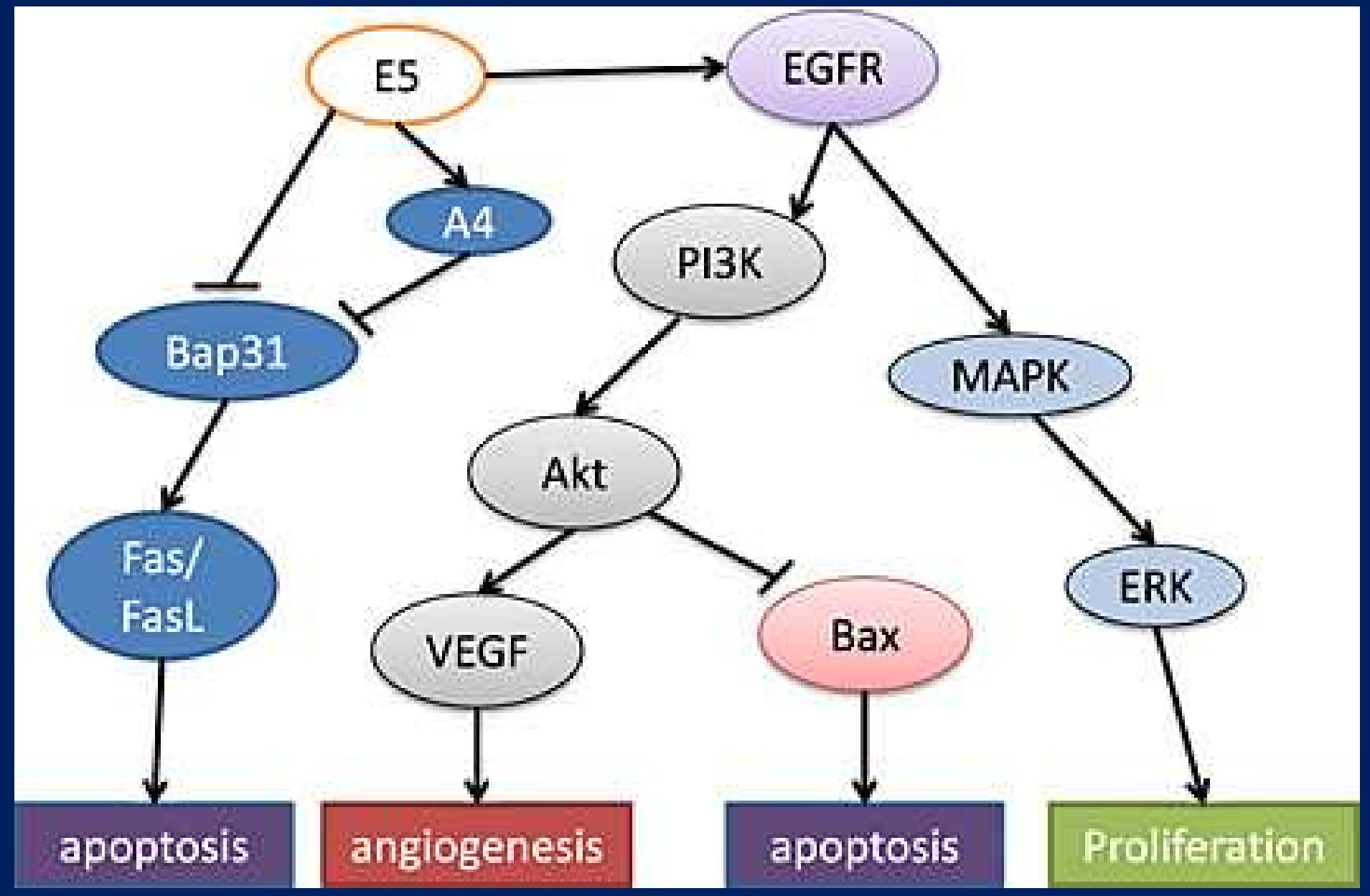
Probability of recurrence-free survival



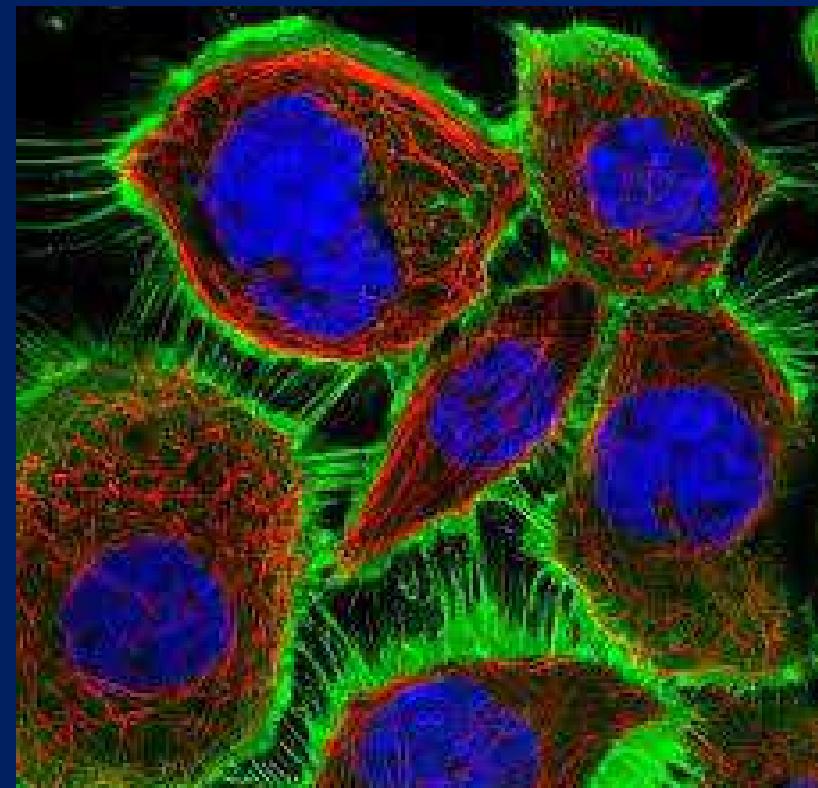
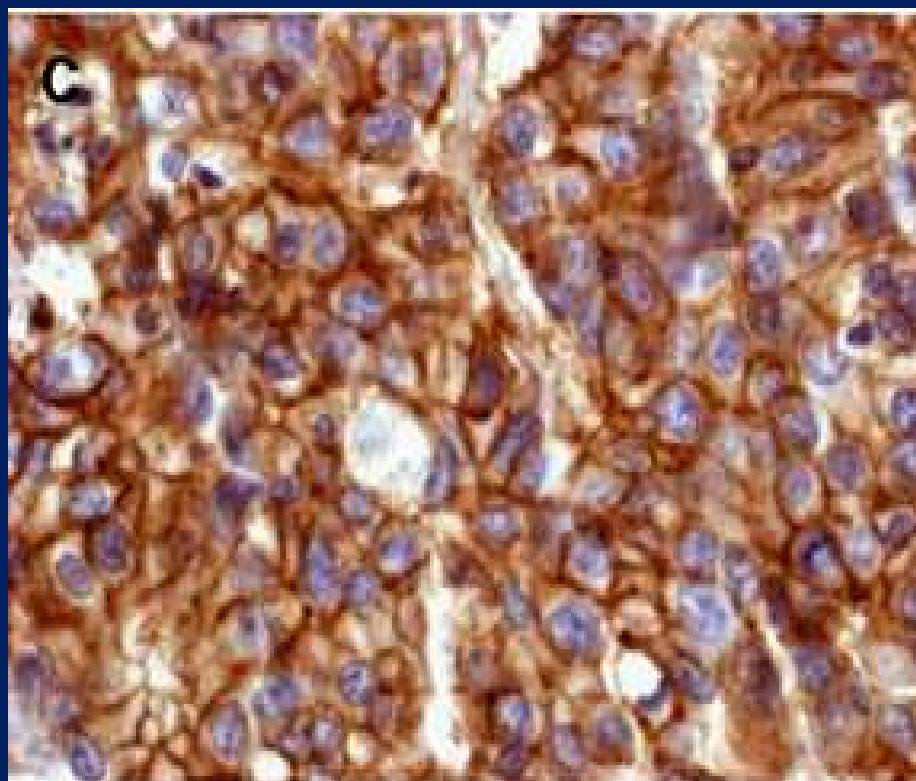
Cánceres de cabeza-cuello

Subclasiación molecular en
cánceres orofaríngeos VPH
según estado de EGFR

VPH E5-EGFR



EGFR



VPH / EGFR

TIPOS	FRECUENCIA	Superviv. 100 meses
Tipo 1 VPH+ / EGFR -	53 %	80%
Tipo 2 VPH - / EGFR -	34%	75%
Tipo 3 VPH - / EGFR+	13%	0% (cetuximab)

Cánceres de cabeza-cuello

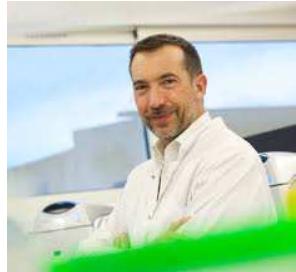
Los linfocitos intratumorales (LIT) predicen el comportamiento de los cánceres orofaríngeos

VPH+

Método semicuantitativo de contaje de LIT

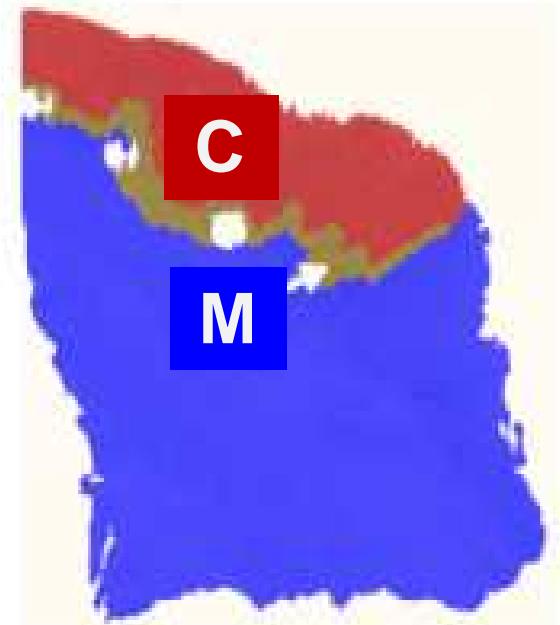
TINCION HE y 2,5X

ALTO	Difuso: presentes > 80% tumor/estroma
MODERADO	Parcheado: presentes > 20-80% tumor/estroma
BAJO	Débil/ausente < 20%



Score Inmunológico *“Inmunoscore”*

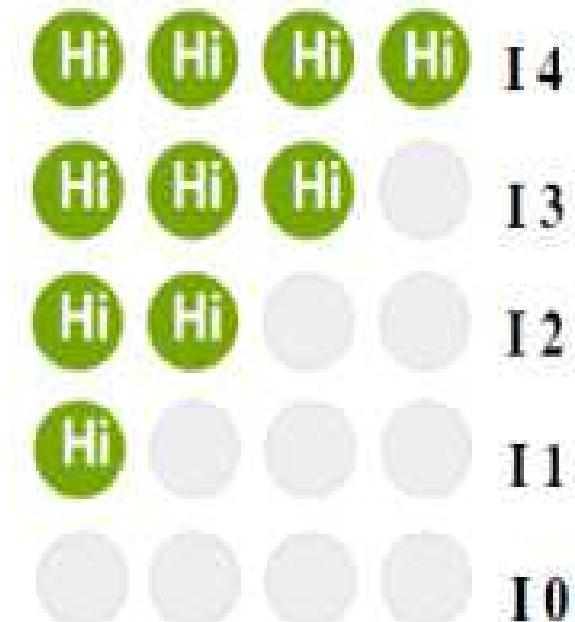
Regiones tumorales (CyM)



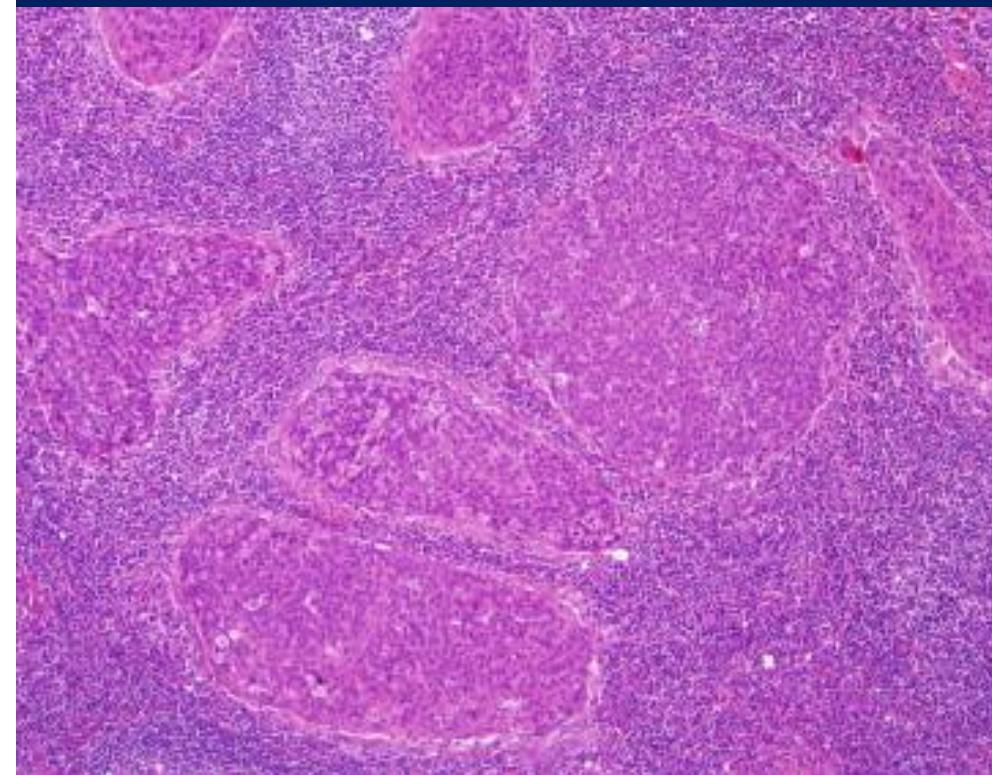
Inmunotinción



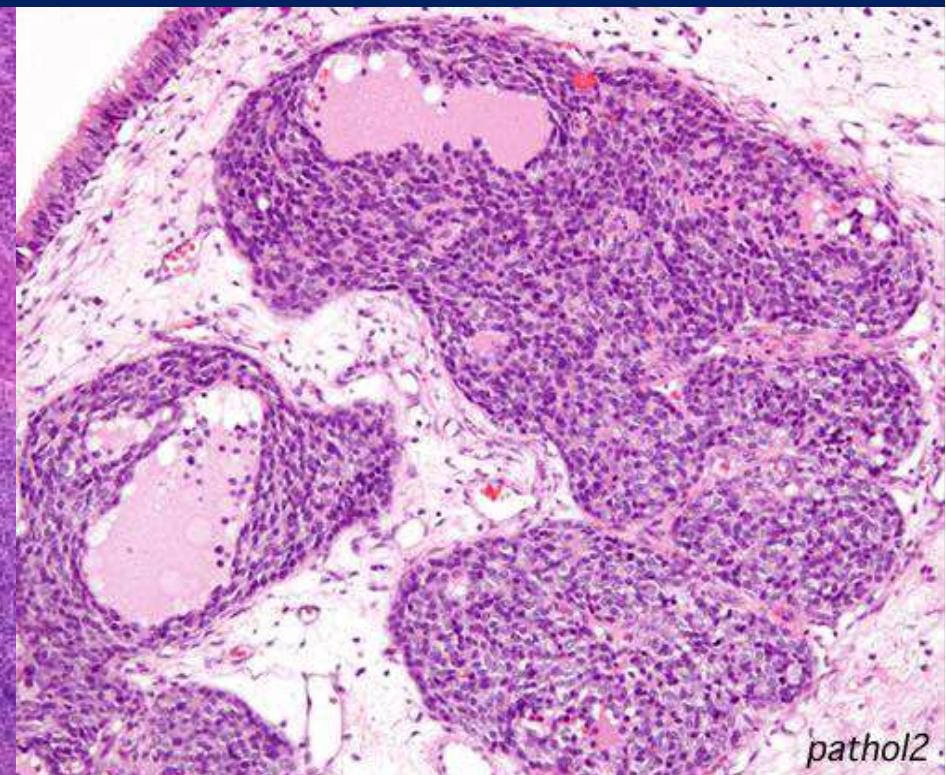
Inmunoscore (CyM)



LIT ALTO

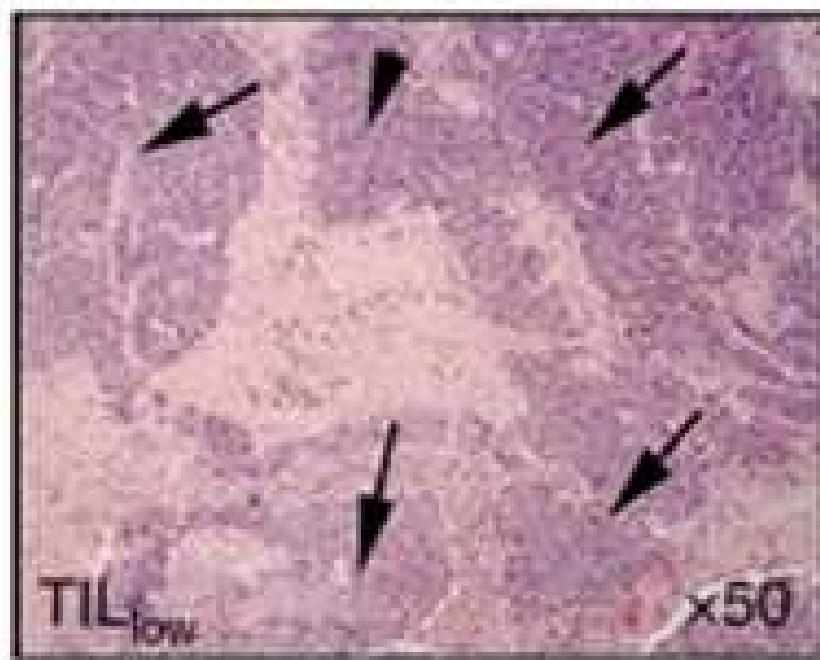
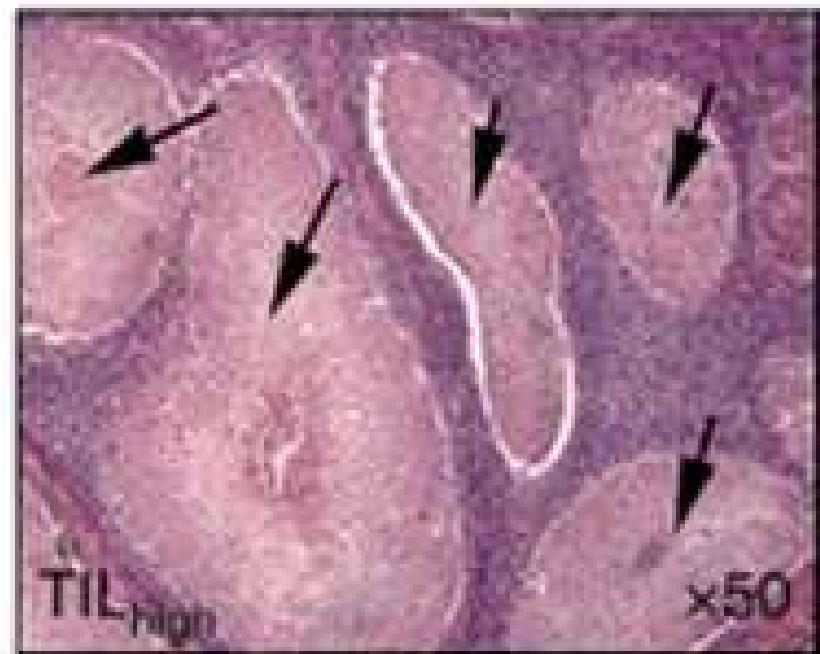
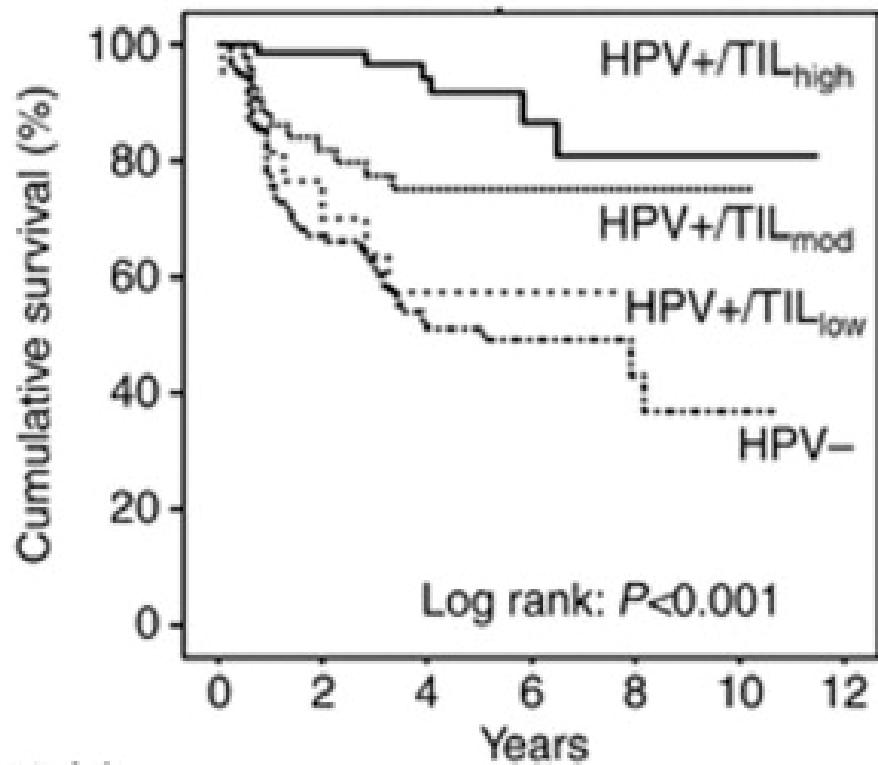


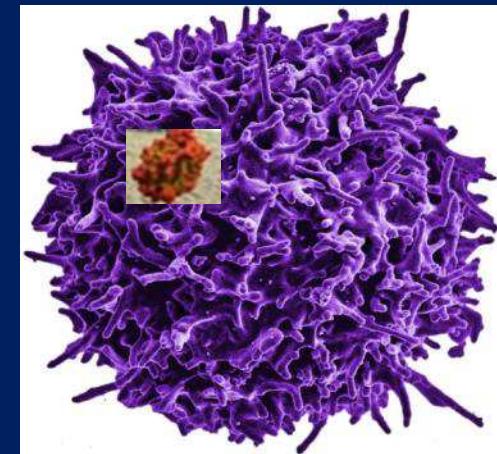
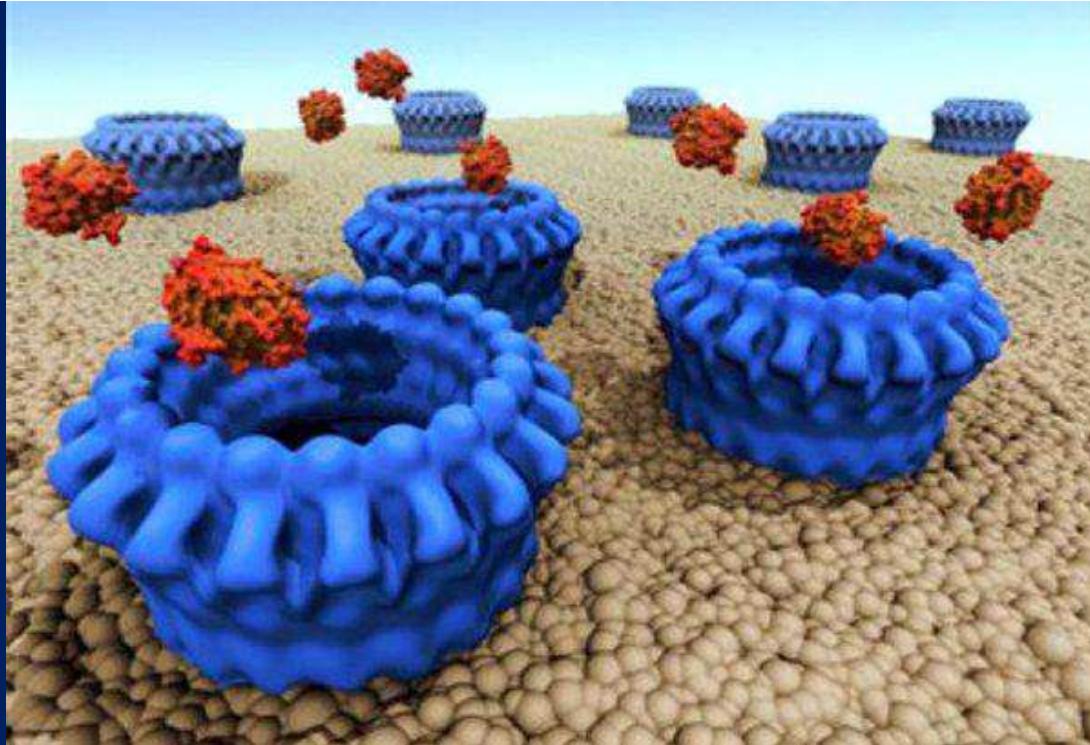
LIT BAJO



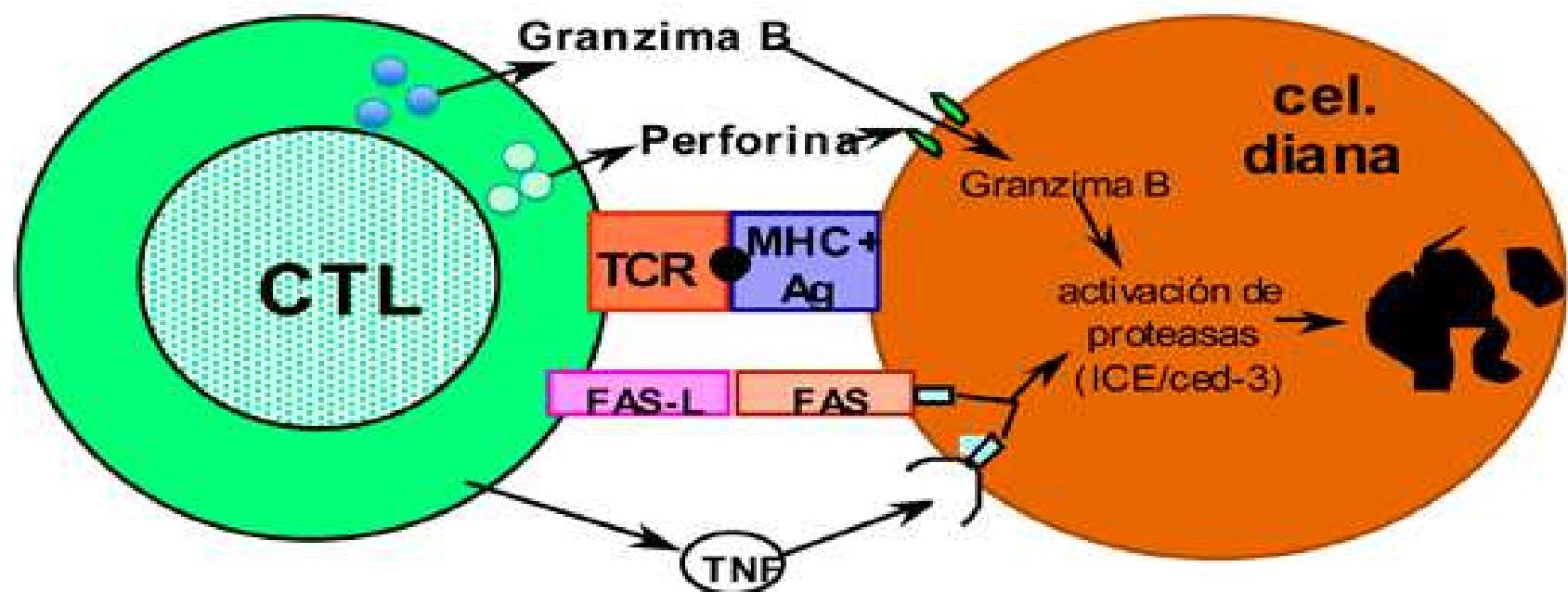
pathol2.

VPH / LIT





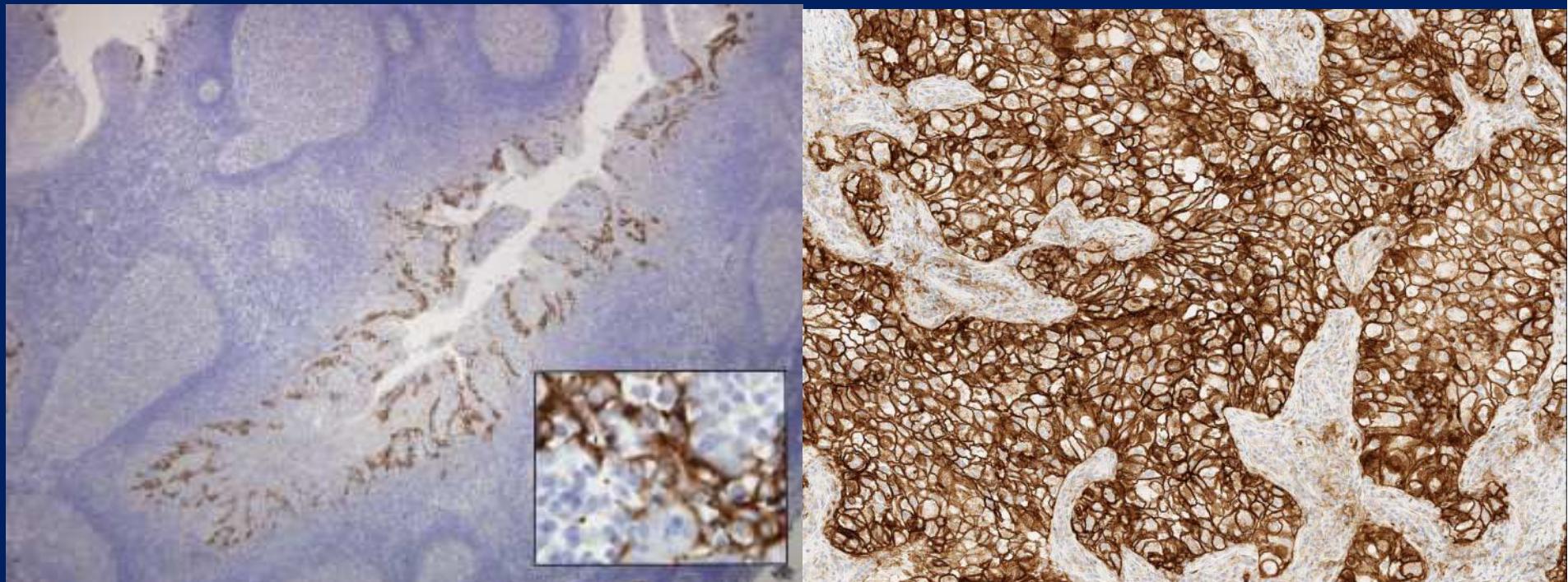
CD8 T



VPH / LIT

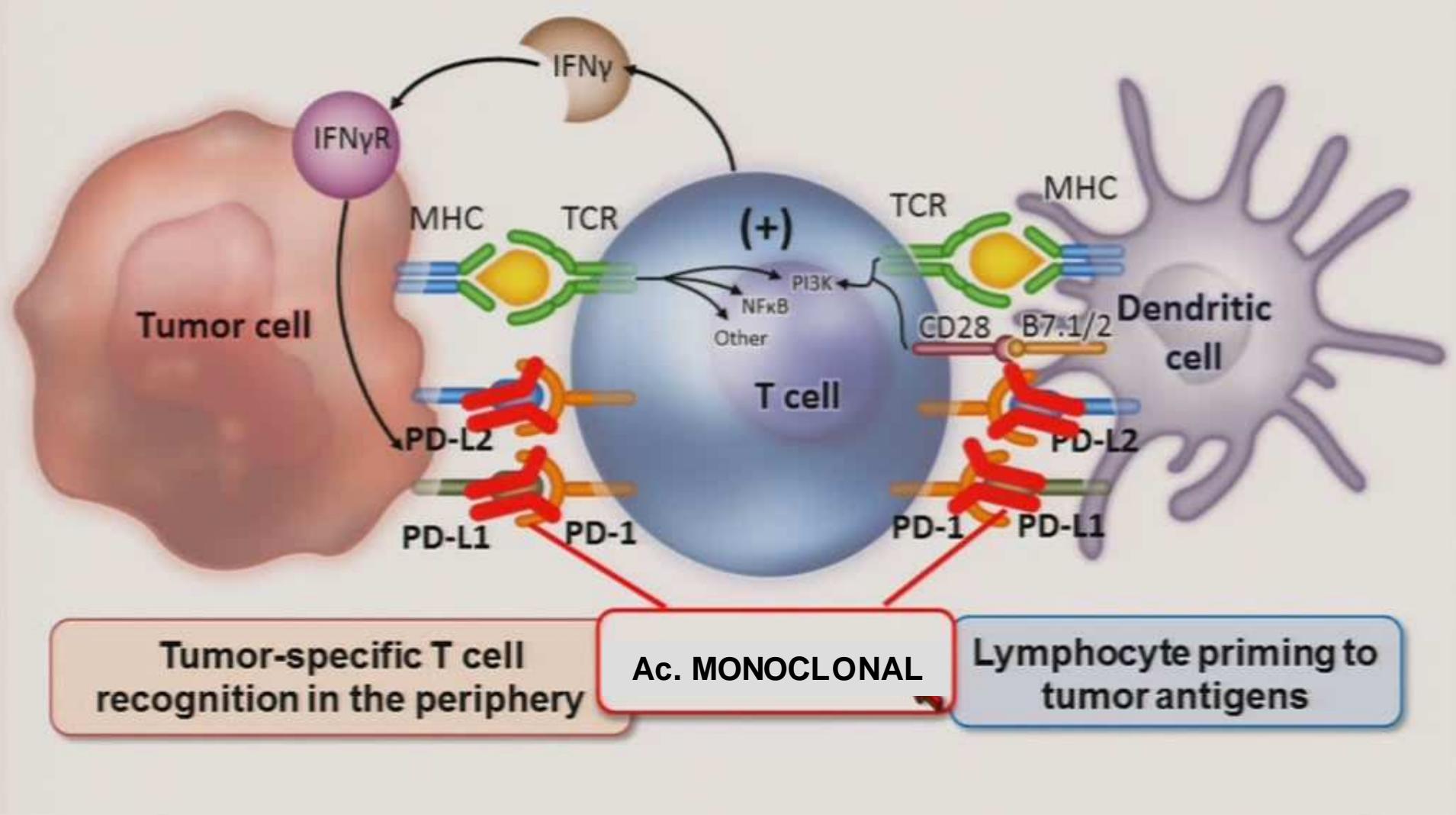
TIPOS	Superviv. 3 años
VPH+ / LIT ALTO	80%
VPH +/ LIT MODERADO	75%
VPH +/ LIT BAJO	55%

Vía señalización PD-1: PD-L1



PDL1 + > 5% de las células teñidas

Papel de la vía PD-1 en la supresión de la inmunidad antitumoral



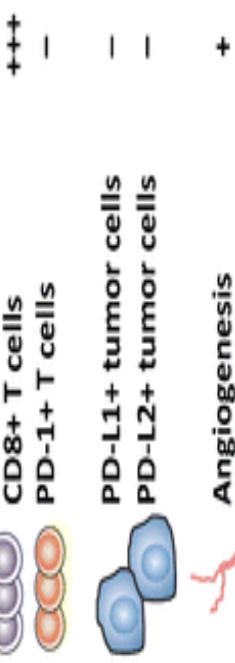
Clinical Relevance

Potential benefit of target and immune-based therapies

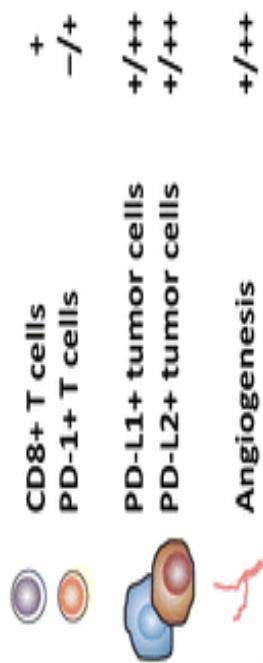
Prognosis

Immune and pathological features

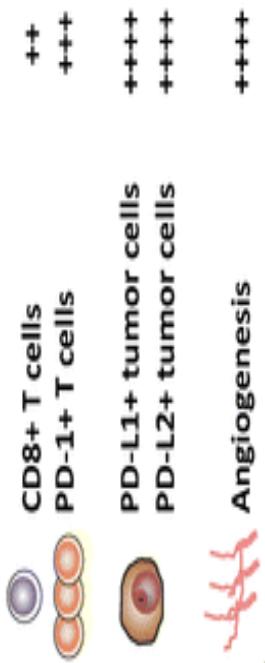
Low-grade neoplasia



Intermediate-grade neoplasia



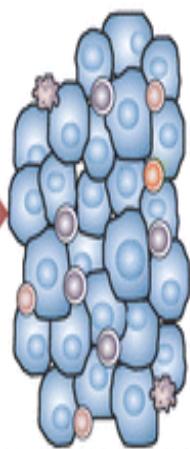
High-grade neoplasia



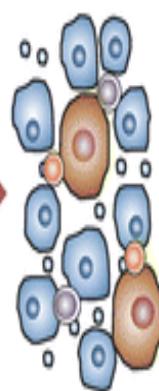
Tumor cell immunogenicity

Cancer natural history

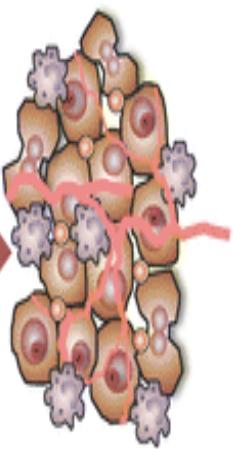
- Chronic viral/bacterial Infection
- Chemical Exposure
- Chronic Inflammation



Selection of less immunogenic antigens



Selection of more aggressive tumor cells





ONDAS GRAVITACIONALES