

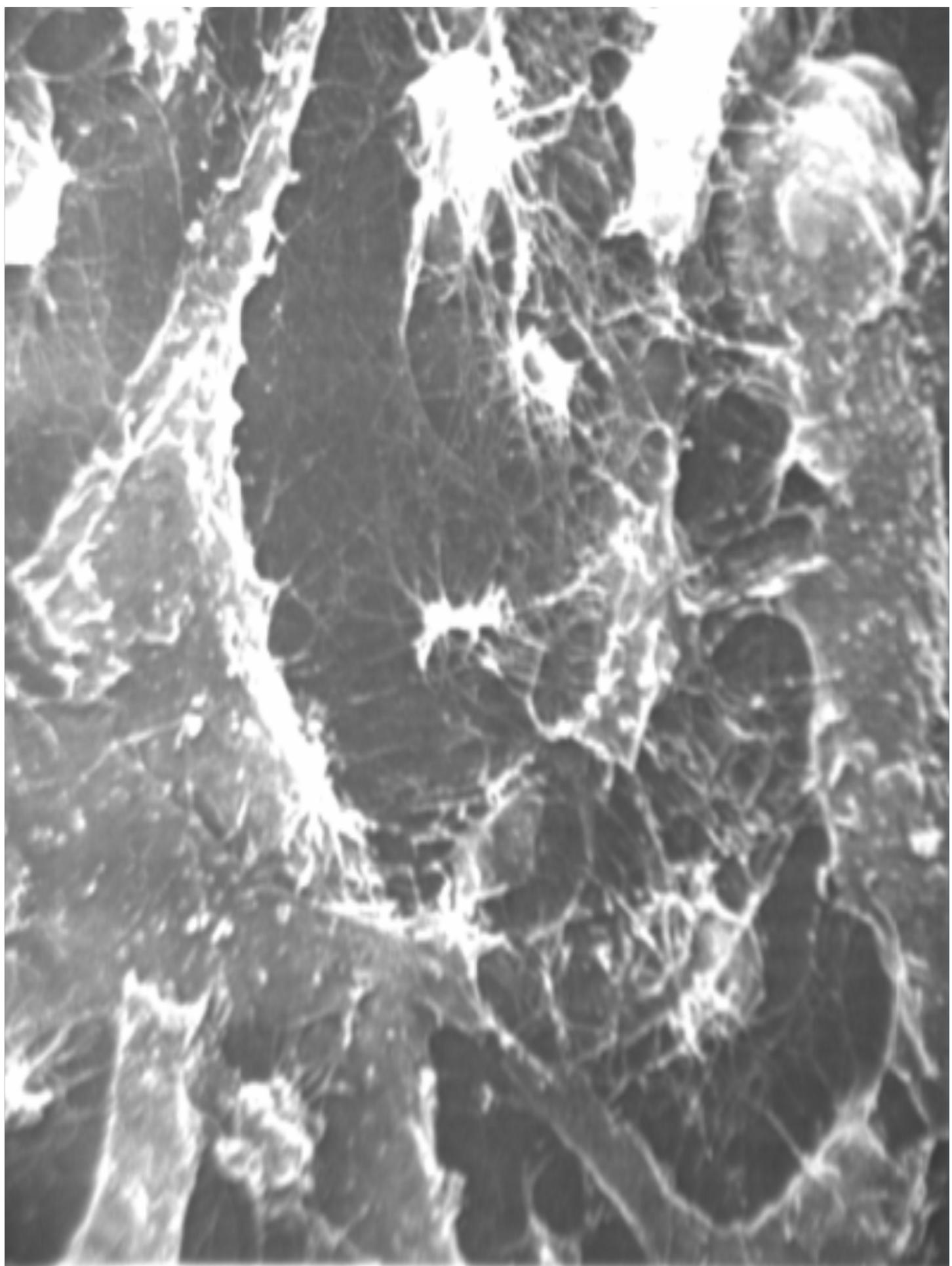
NOWE KONCEPCJE EKSPERYMENALNEJ FARMAKOTERAPII PRZECIWNOWOTWOROWEJ Z UDZIALEM DEZINTEGRYN

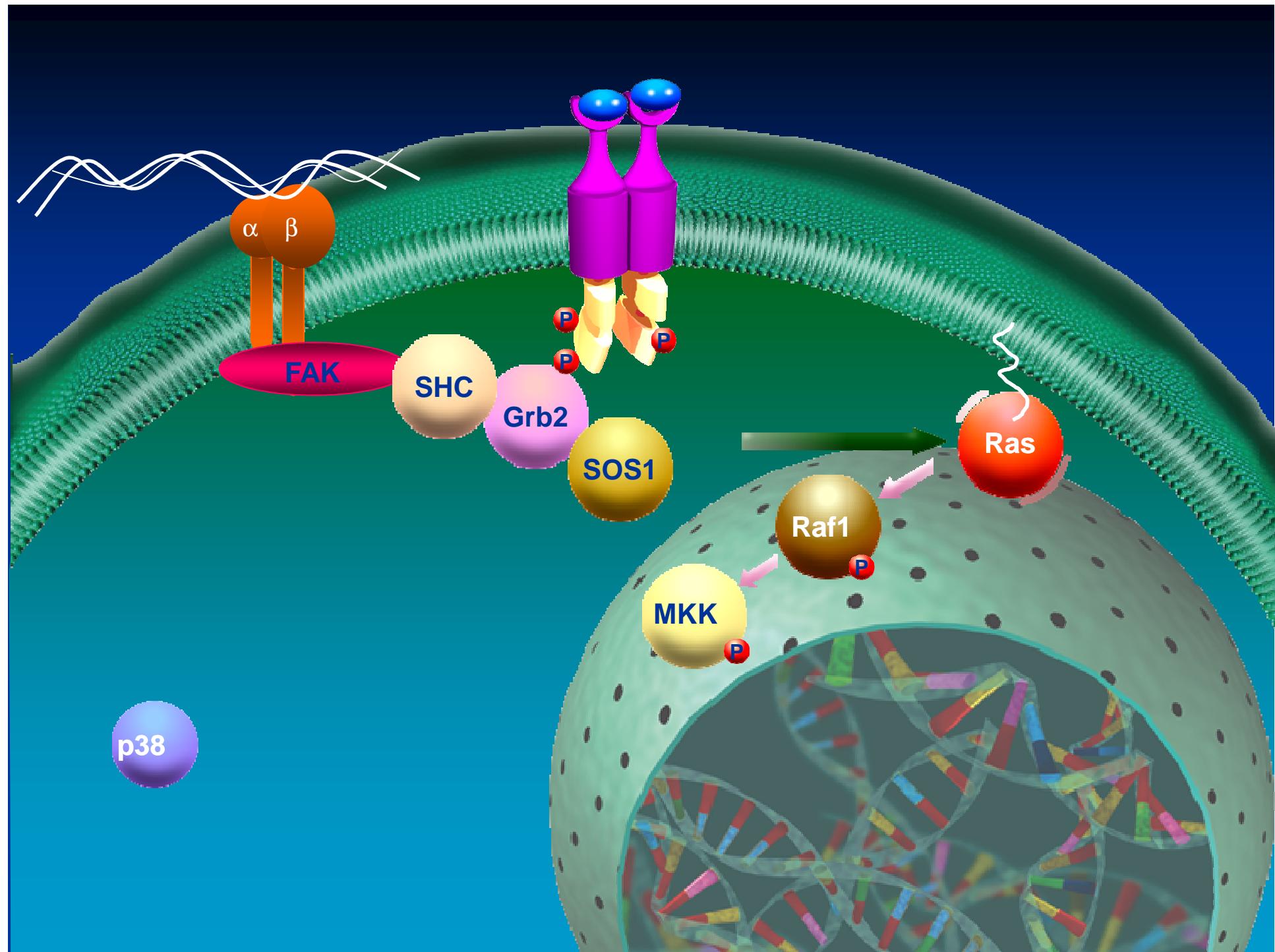
Jerzy Pałka

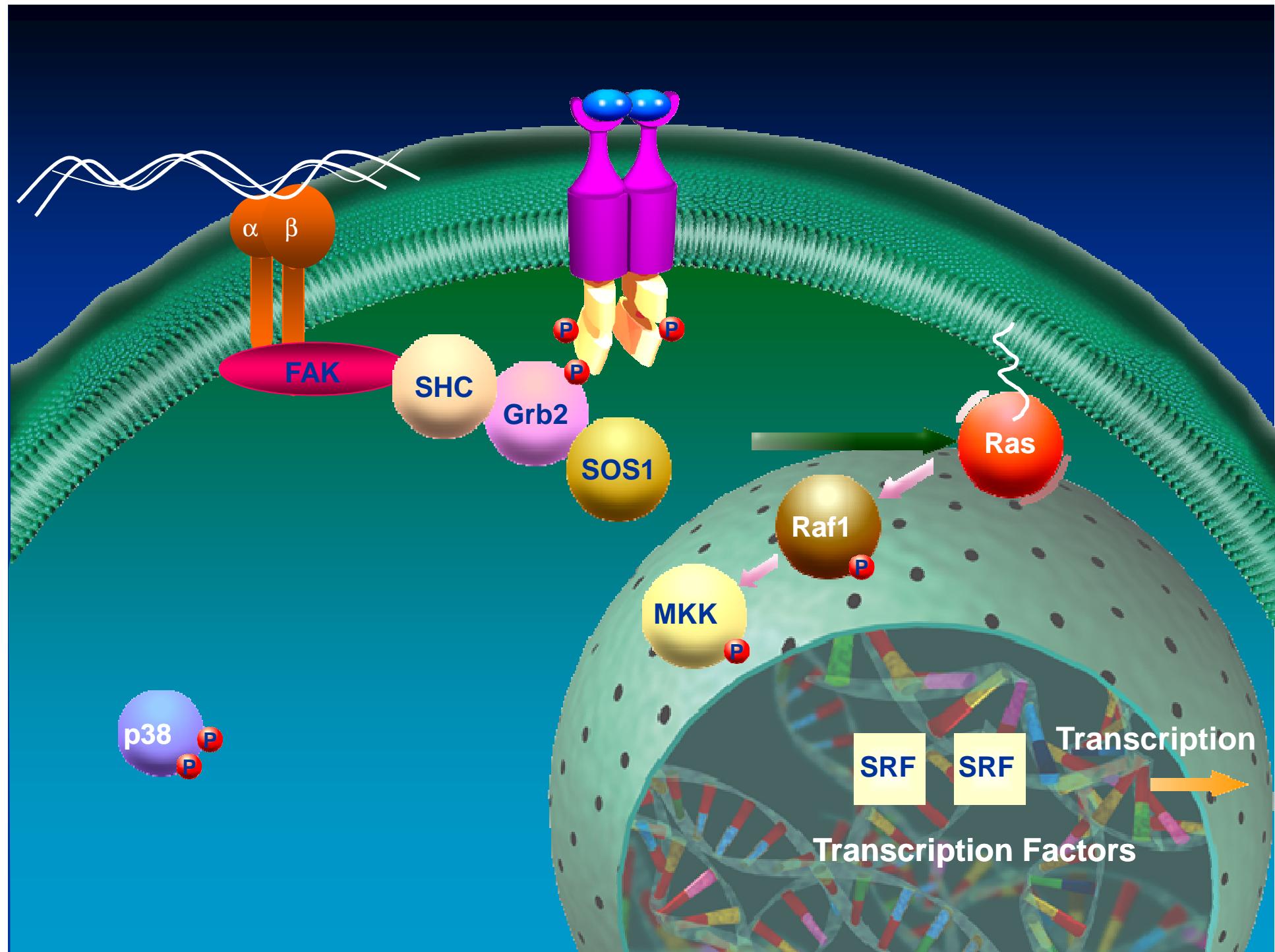
Zakład Chemii Leków, Uniwersytet Medyczny w Białymstoku

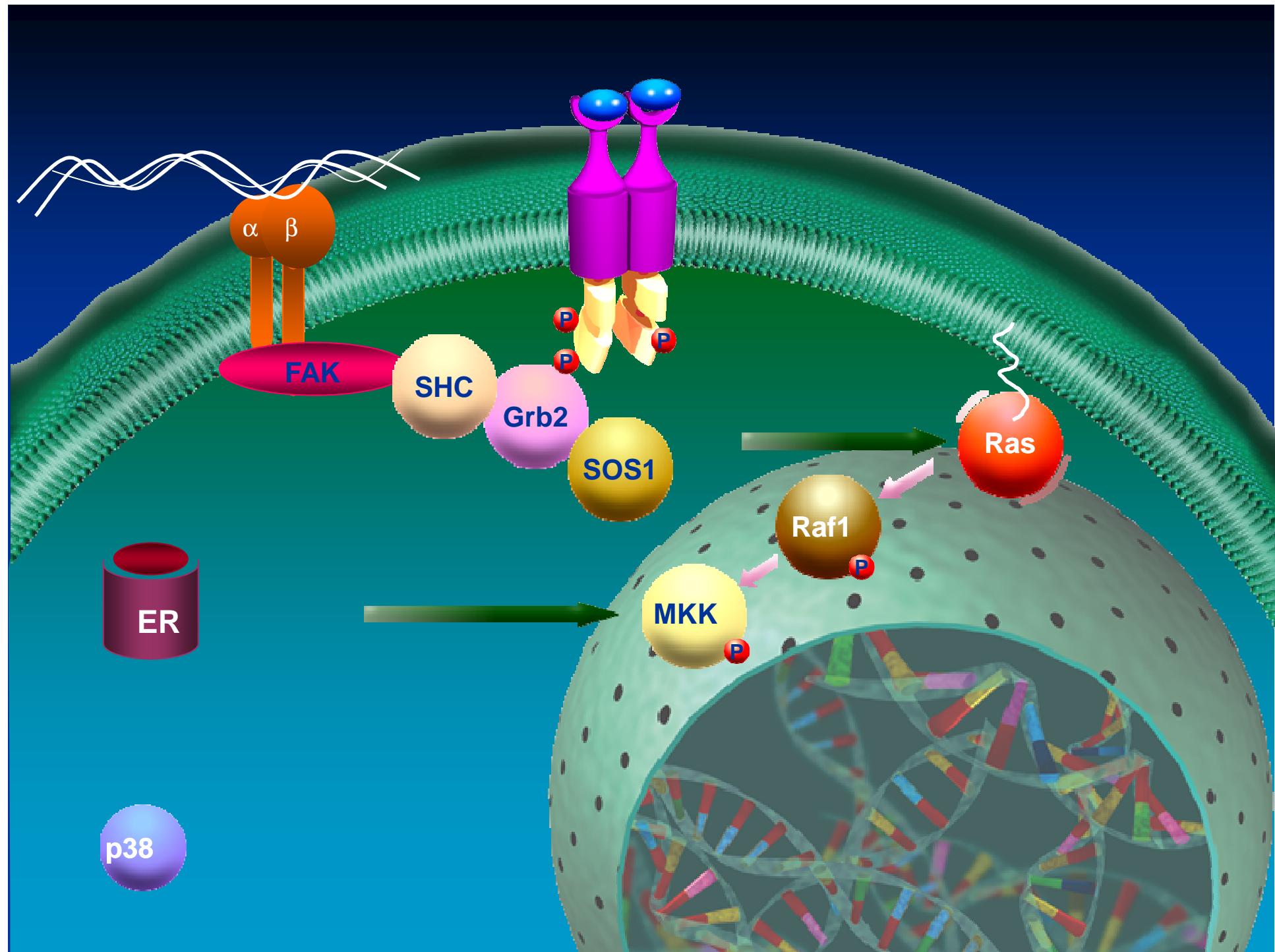
Sympozjum

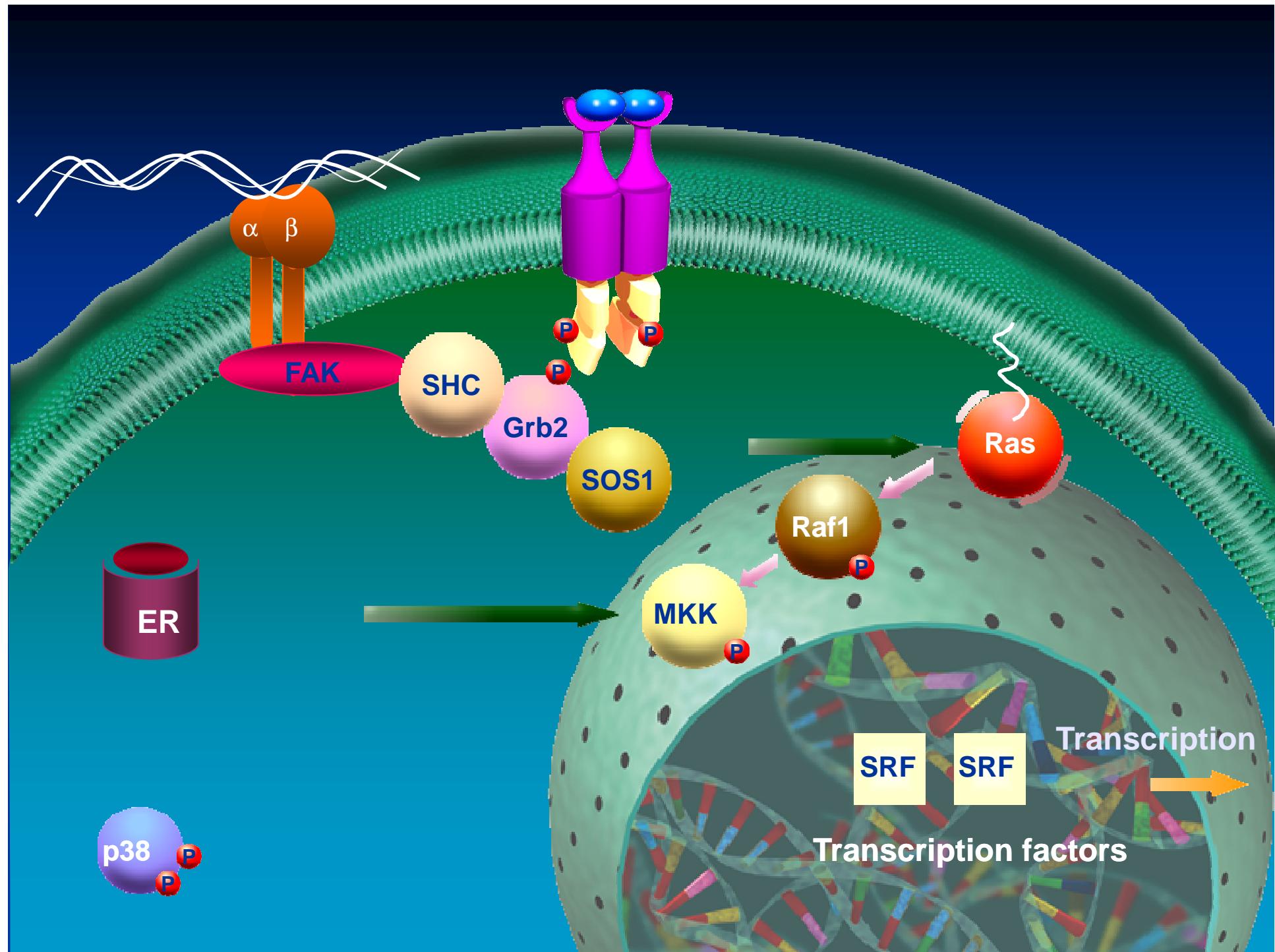
„Szkoła Chemii Medycznej”, Wrocław, 2013

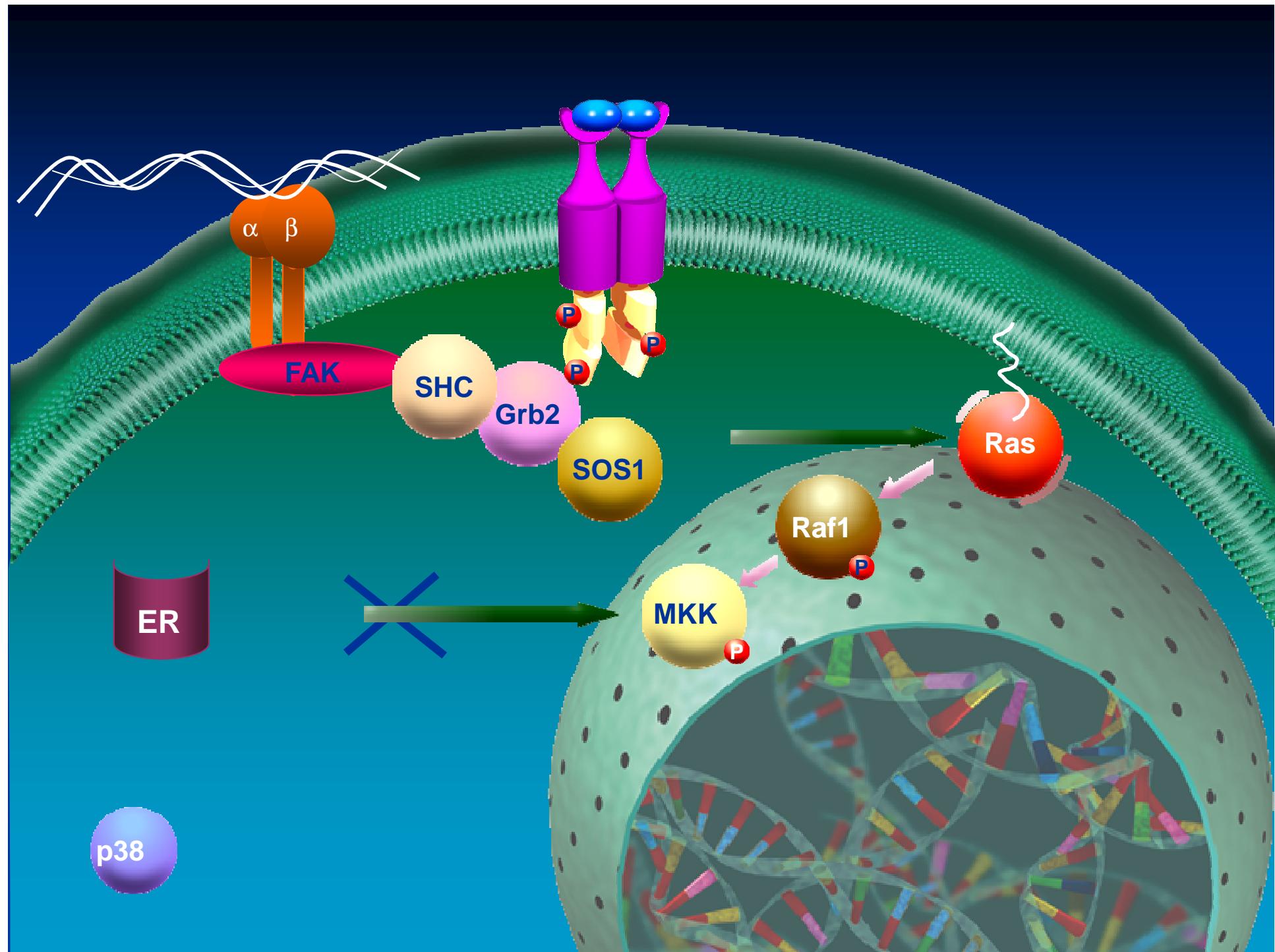






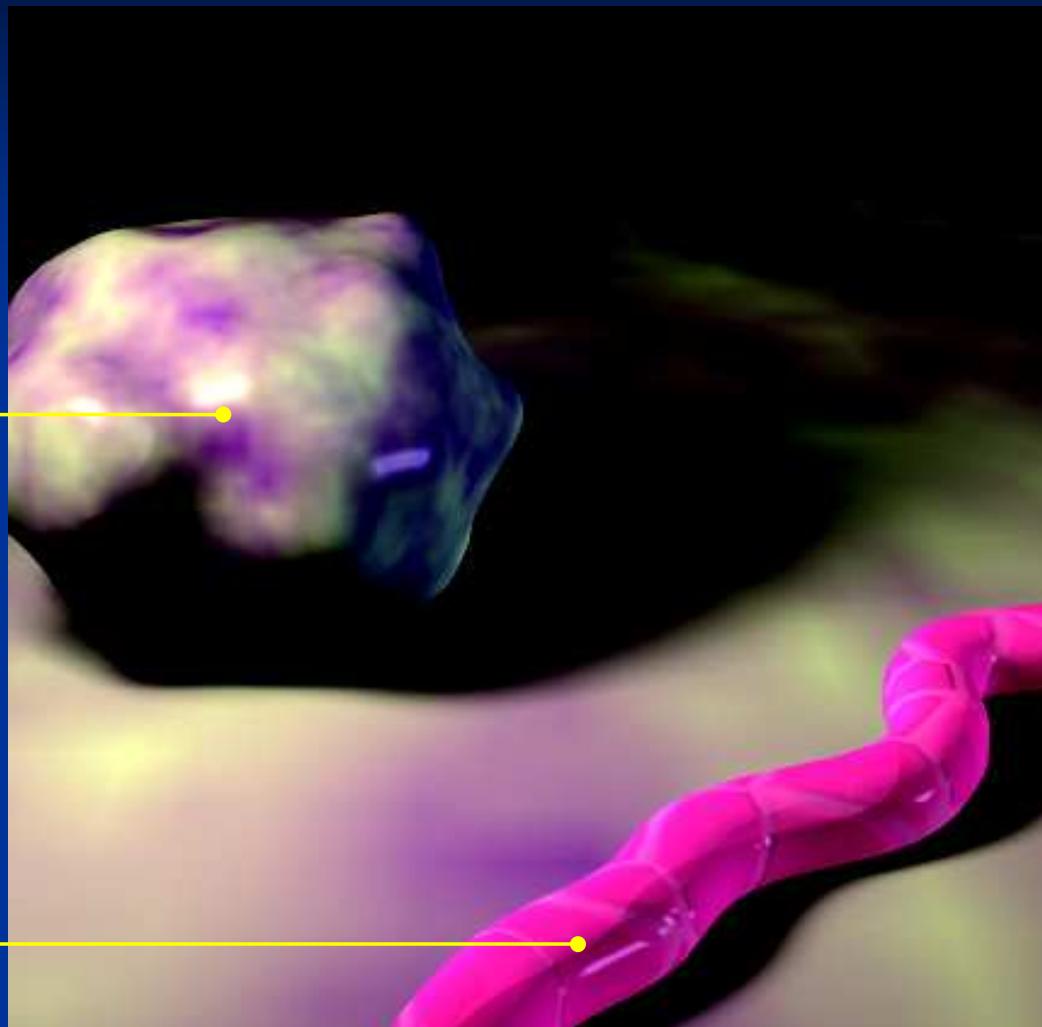






VEGF in Angiogenesis





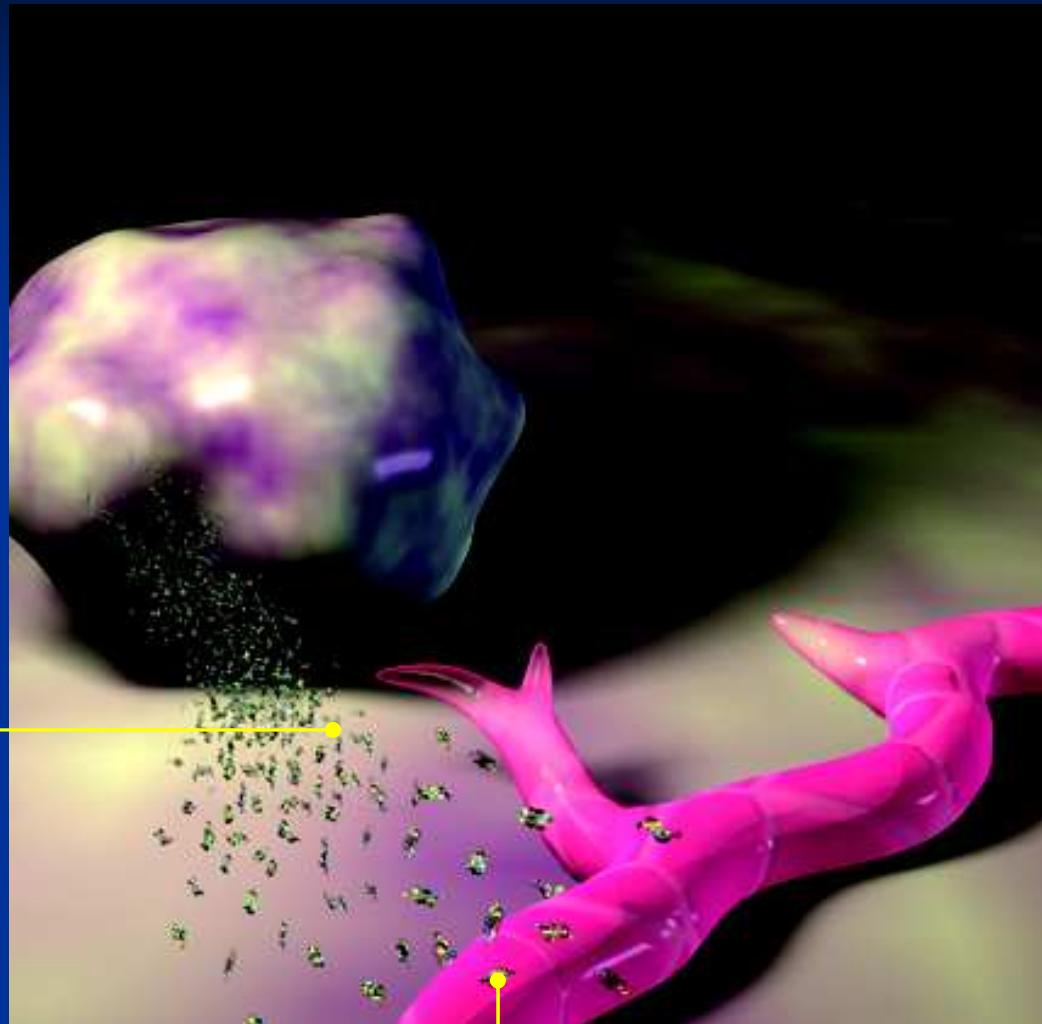
Tumour

Vessel

VEGF

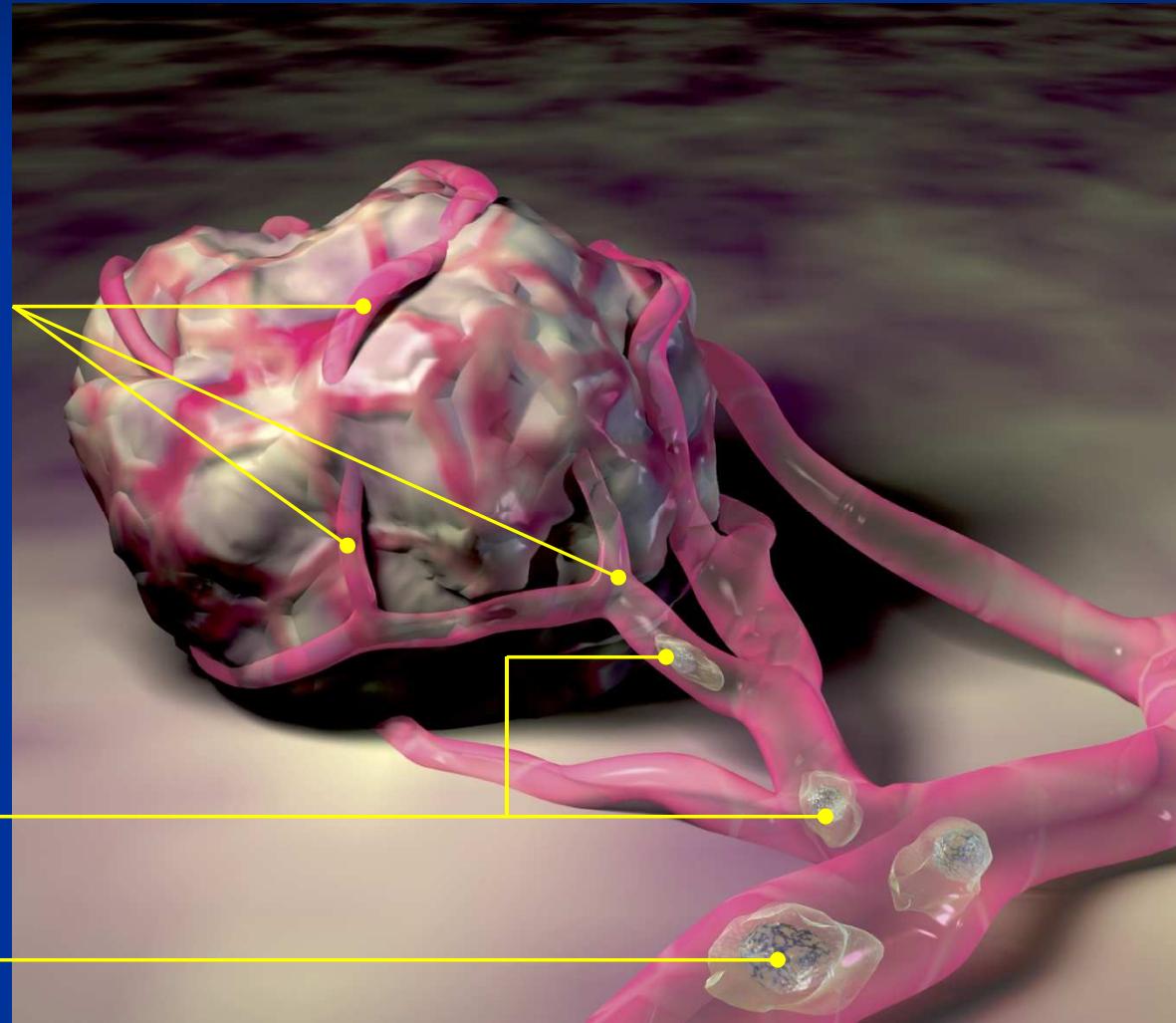


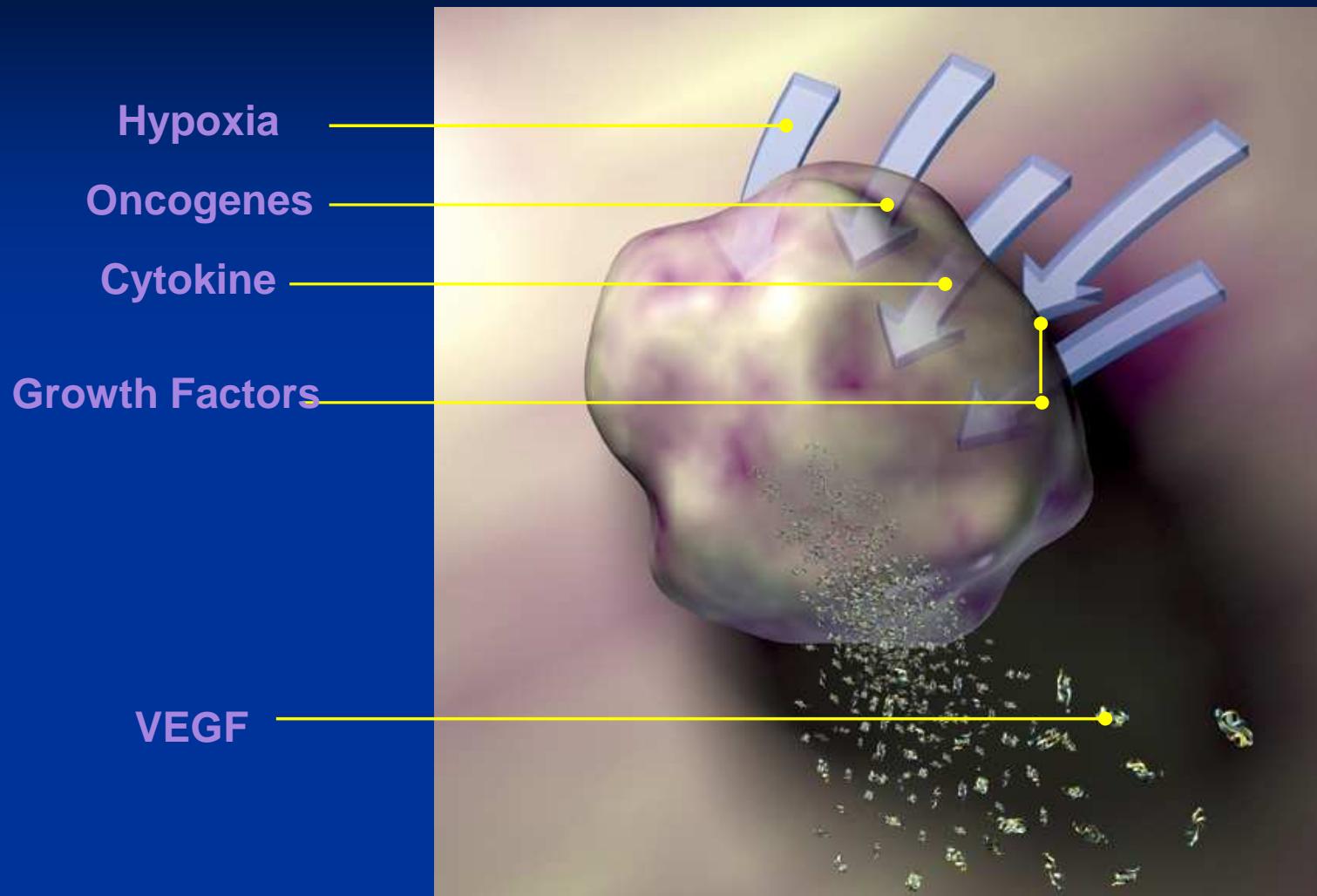
Angiogenesis



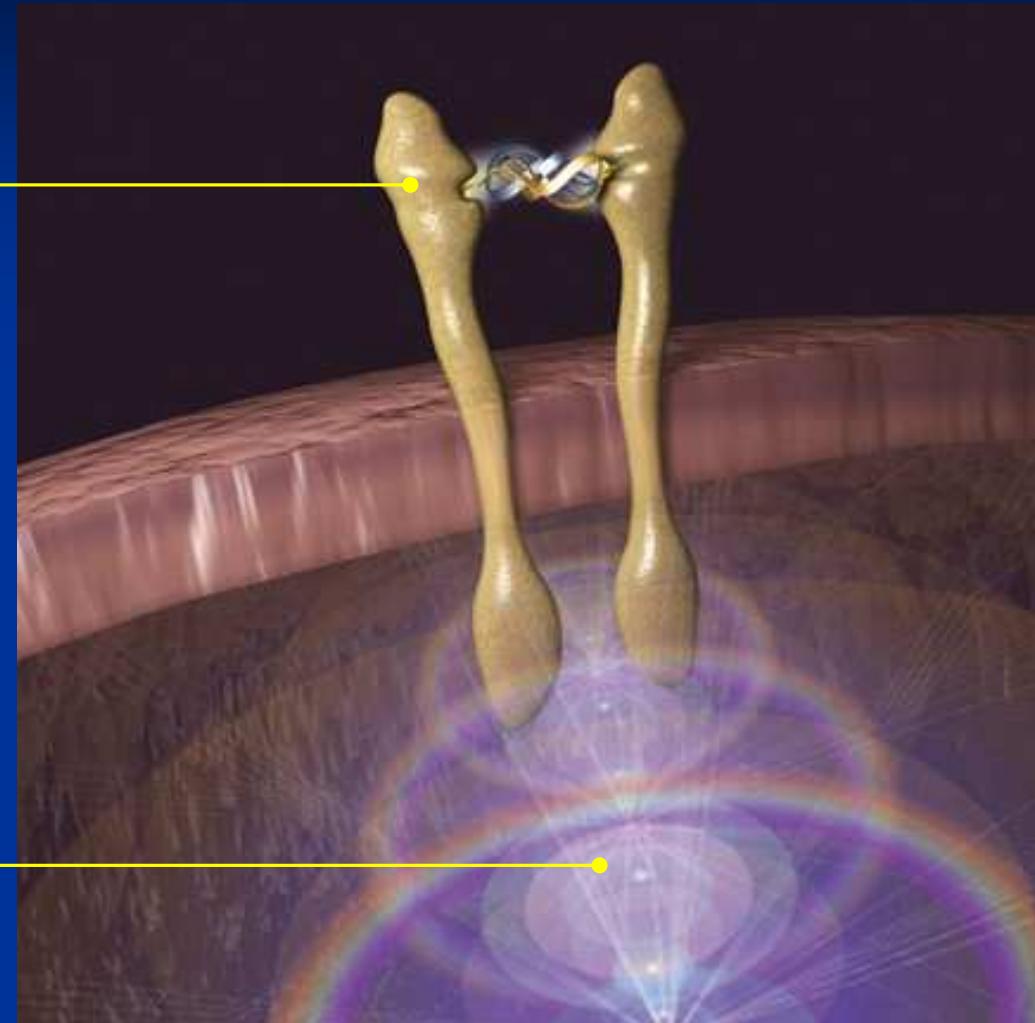
Vascularization

Tumor cell





Receptor VEGF

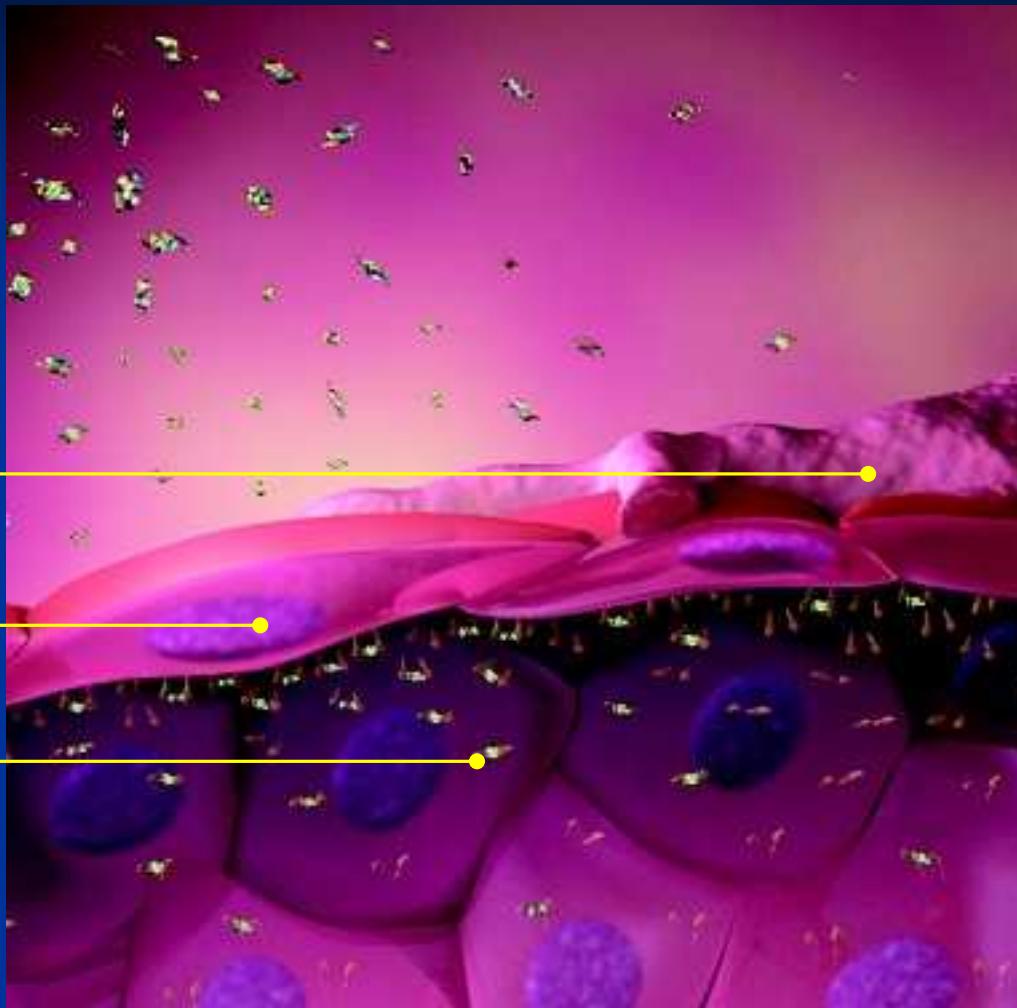


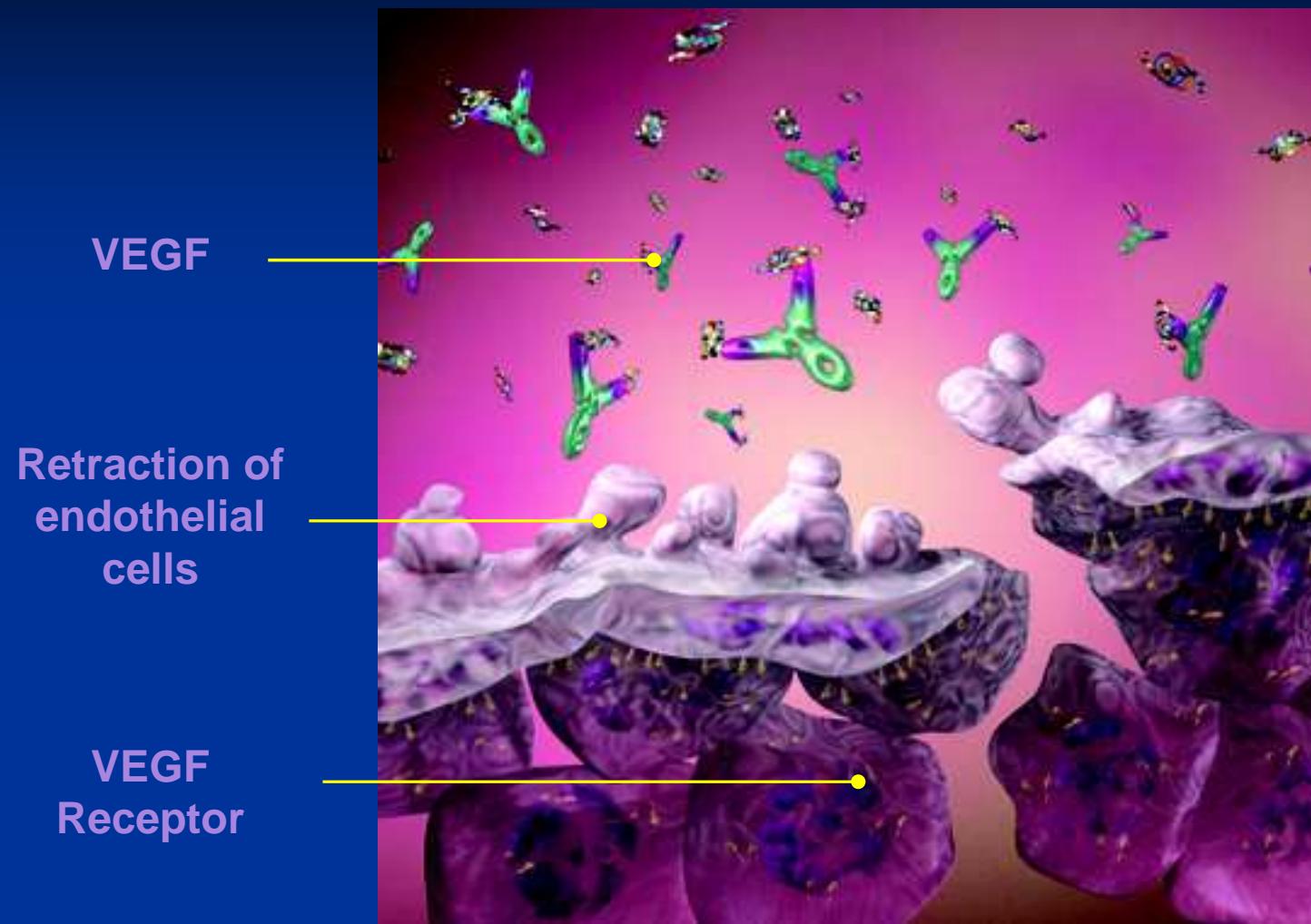
**Signaling
cascade**

Periocyte

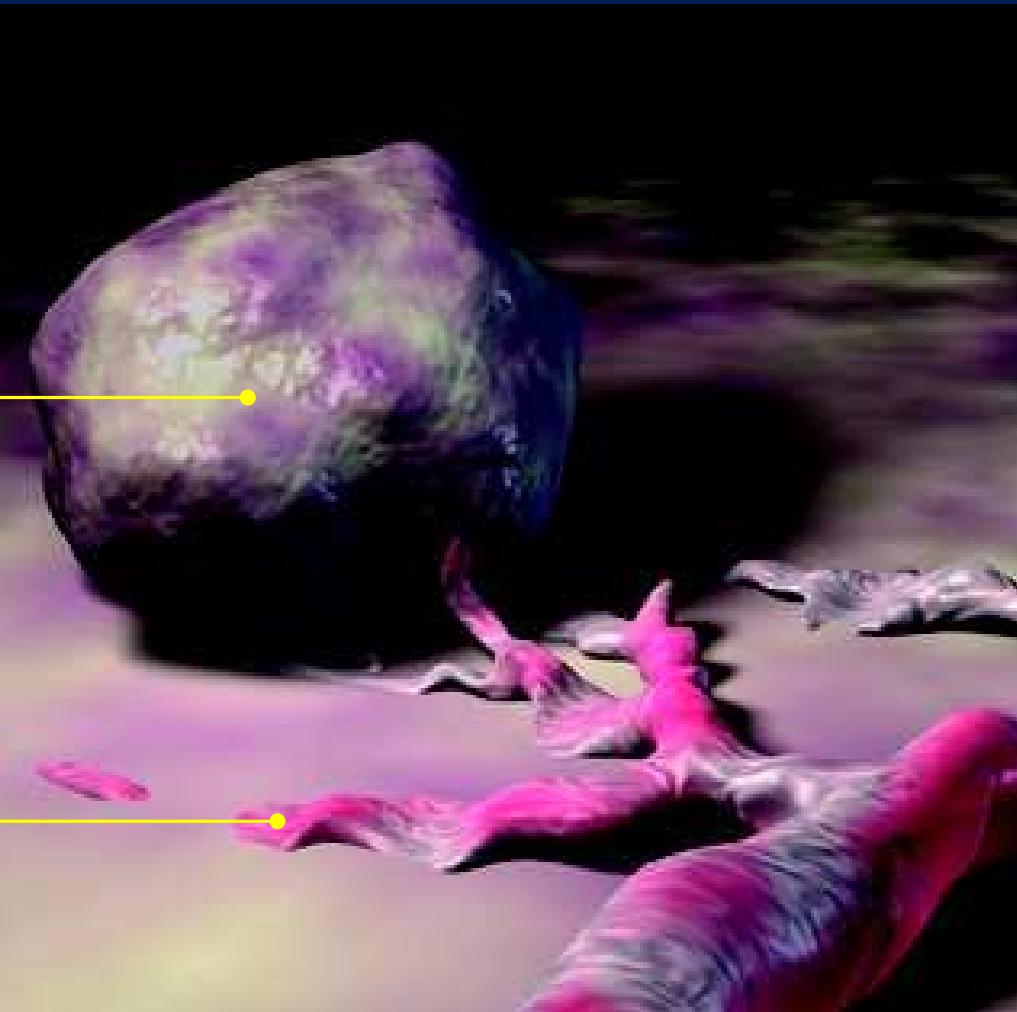
**Vascular
Endothelial cell**

**VEGF
Receptor**





Tumor cells
death



Regression of
vessels

EGF-r

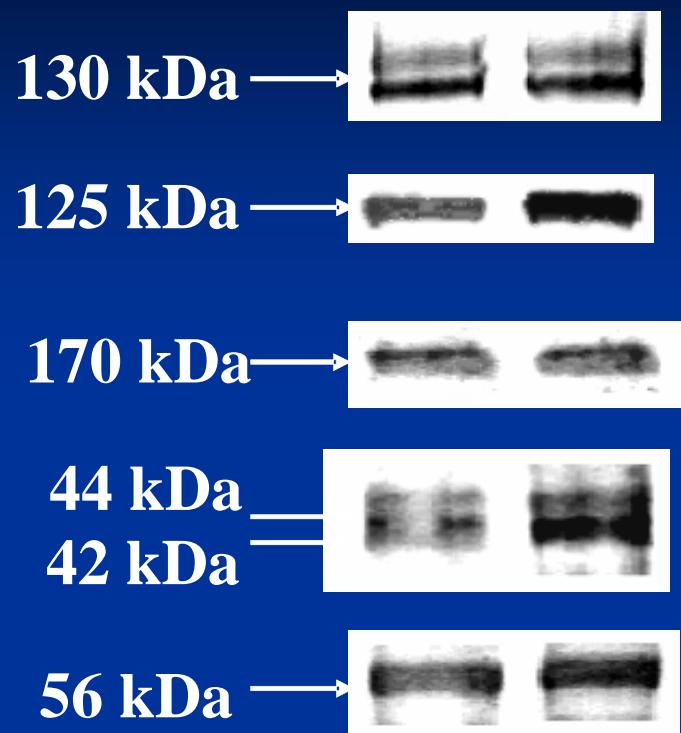
New drugs

- Anti-VEGF: AVASTIN
- Anti-VRGFR: VANTALANIB, SU 11248,
BAY 439006
- Anti-EGFR: ERBITUX, IRESSA
- Anti-HER1: TARCEVA
- Anti-HER2: HERCEPTIN (trastuzumab)
- Tyrosine kinase inhibitor of EGFR: PTK 787

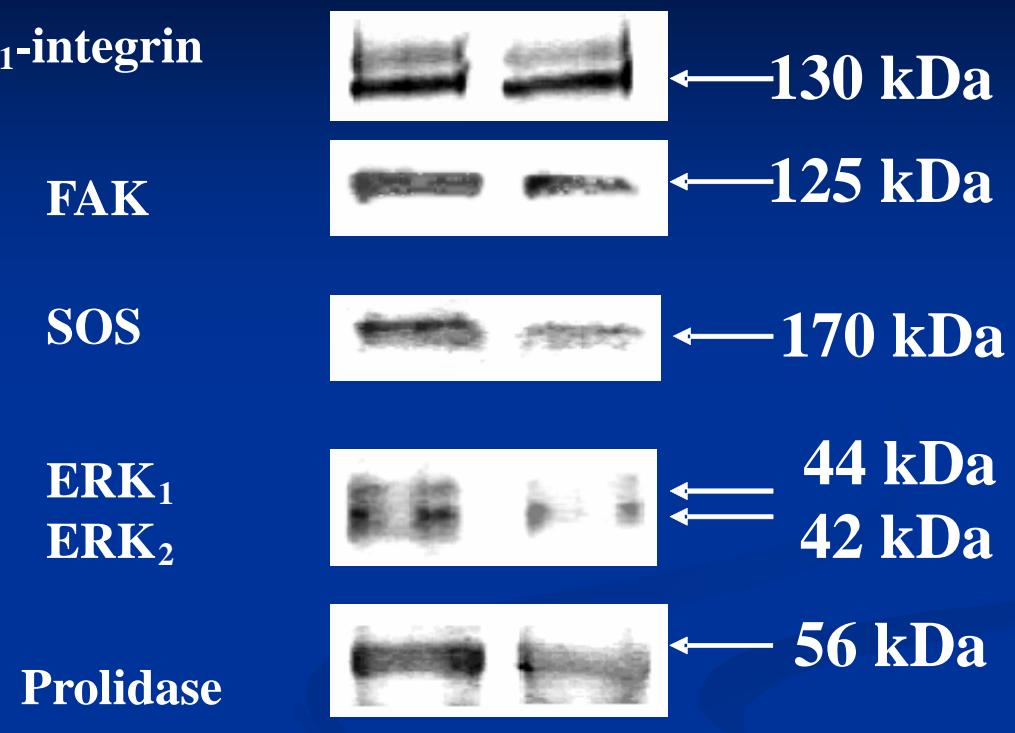
NOVEL AGENTS IN CLINICAL TRIALS

- INTEGRIN RECEPTOR BLOCKERS: Vitaxin; EMD 121974
- BLOCKERS OF SIGNALING PATHWAYS:
 - Kinase Src inhibitors: Herbamycin A
 - Kinase C inhibitors: Bryostatine, Staurosporine, Edelfosine –
 - Calcium signaling blockers: Carboxyamidotriazol (CAI)
 - Ras blockers: 778123, BMS-214662, SCH-66336
- INHIBITORS OF MDR
 - PSC-833 – analog of cyclosporine
 - Incel (Biridocar)
 - GF-120918
- INHIBITORS OF METALLOPROTEINASES
 - Marimastat – inhibitor of MMPs
 - BAY 12-9566 – inhibitor MMP-2 i MMP-9
 - Neovastat – inhibitors of MMPs from shark cartilage

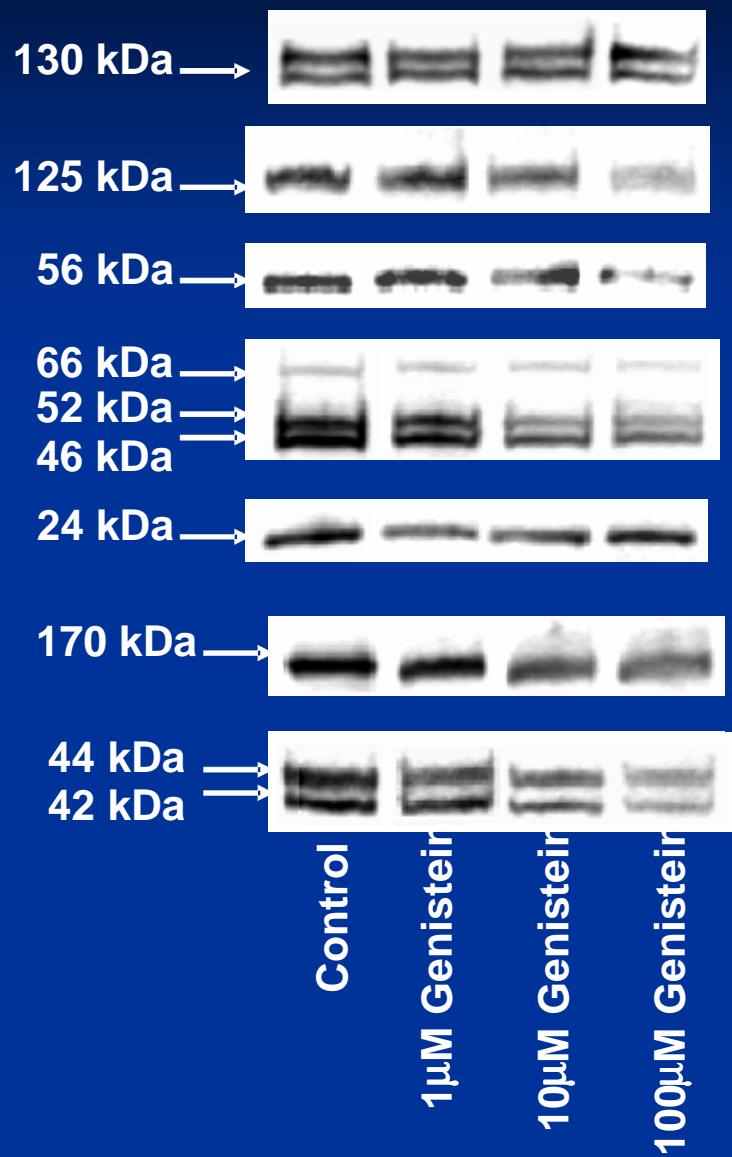
THROMBIN



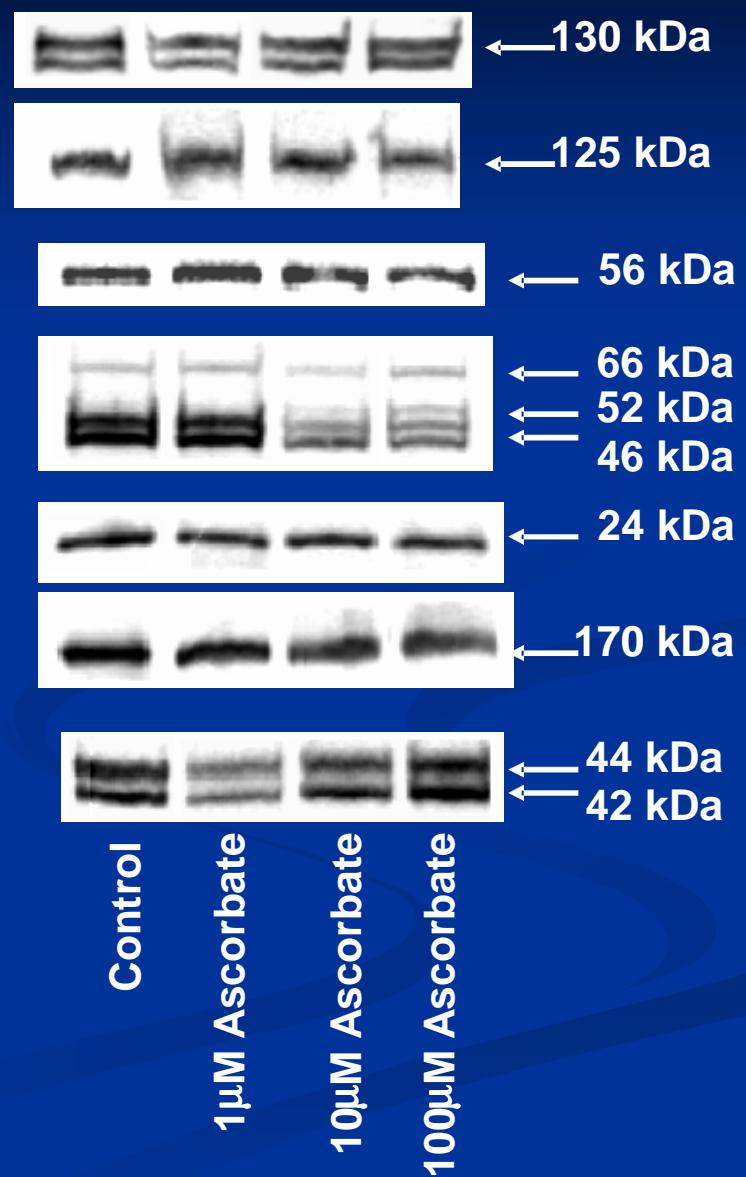
ECHISTATIN



GENISTEIN



ASCORBIC ACID



Snake venom-derived disintegrins:

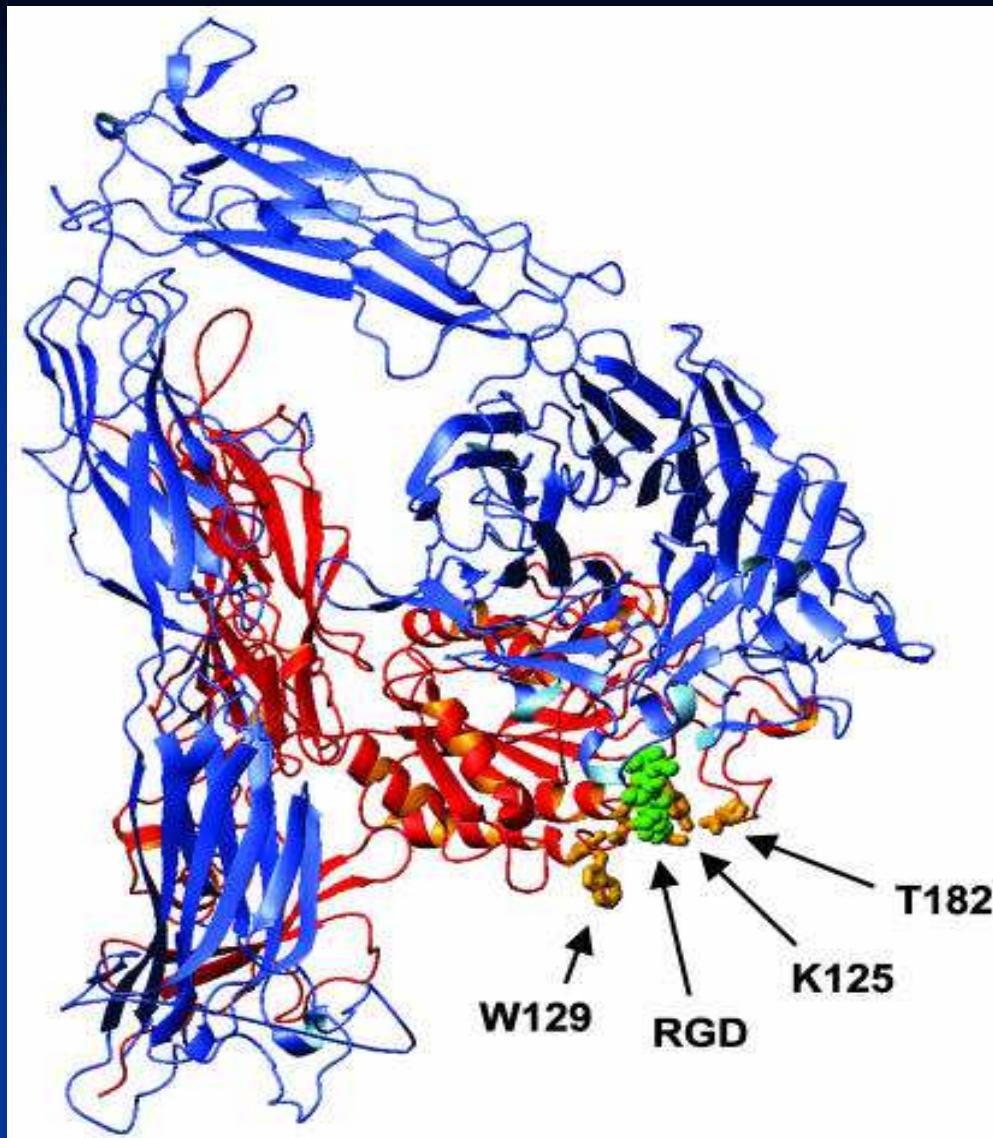
- rhodocetin – non RGD $\alpha 2\beta 1$ integrin inhibitor
- obtustatin - non RGD $\alpha 1\beta 1$ integrin inhibitor
- jararhagin – non RGD competitive inhibitor of $\alpha 1\beta 1$ integrin
- salmosin - non RGD $\alpha v\beta 3$ integrin inhibitor
- crovidisin – snake venom RGD-dependent metalloproteinase
- triflavin - RGD disintegrin (binds several integrins)

Monoclonal antibodies for integrins:

- represented by large number of inhibitory as well stimulatory antibodies

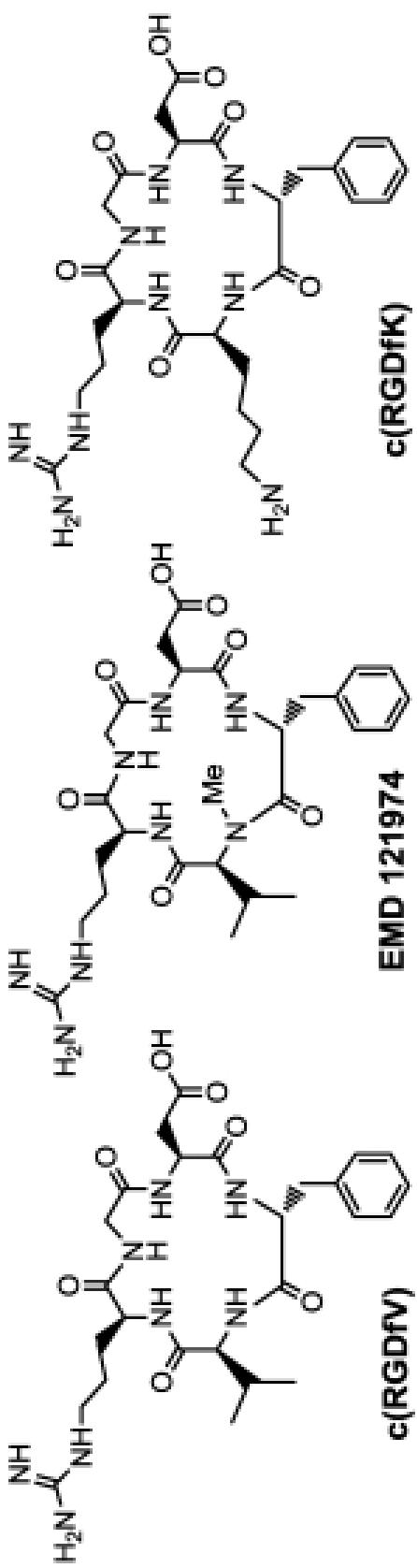
Plant-derived modulators of integrins:

- epigallocatechin gallate – green tea polyphenol that modulate expression of different integrins
- betulinic acid – pentacyclic triterpene that induce apoptosis through modulation of integrin signaling

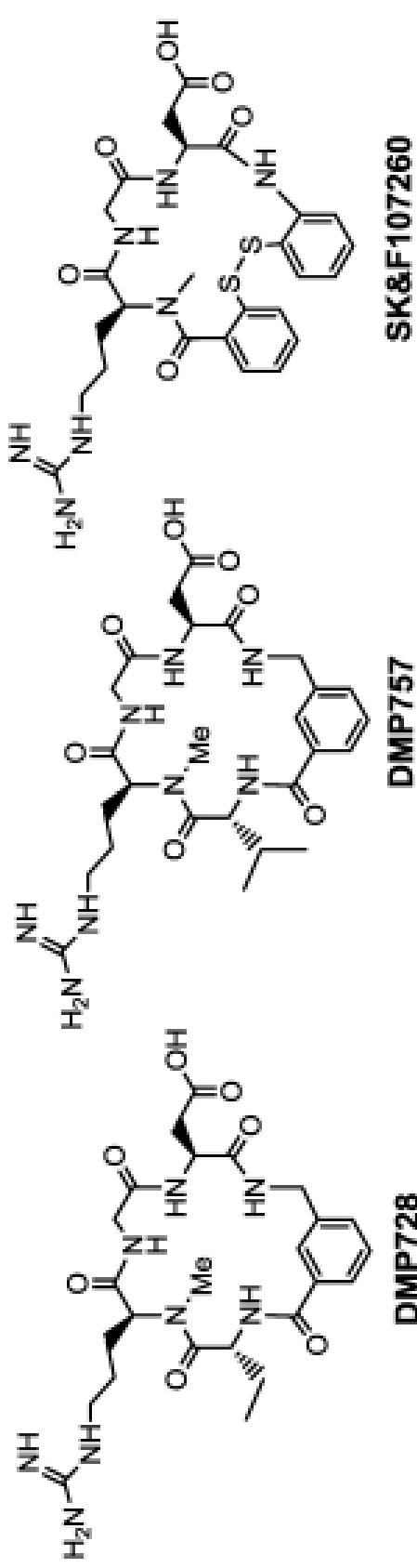


Proc Natl Acad Sci U S A. 2004 Sep 7;101(36):13114-20. Epub 2004 Jul 26.
Integrin beta3 regions controlling binding of murine mAb 7E3: implications for the mechanism of integrin alphaIIbbeta3 activation.
Artoni A, Li J, Mitchell B, Ruan J, Takagi J, Springer TA, French DL, Coller BS.

$\alpha_v\beta_3$ -Targeted Cyclic Pentapeptides



$\alpha_{IIb}\beta_3$ -Targeted Cyclic Hexapeptides

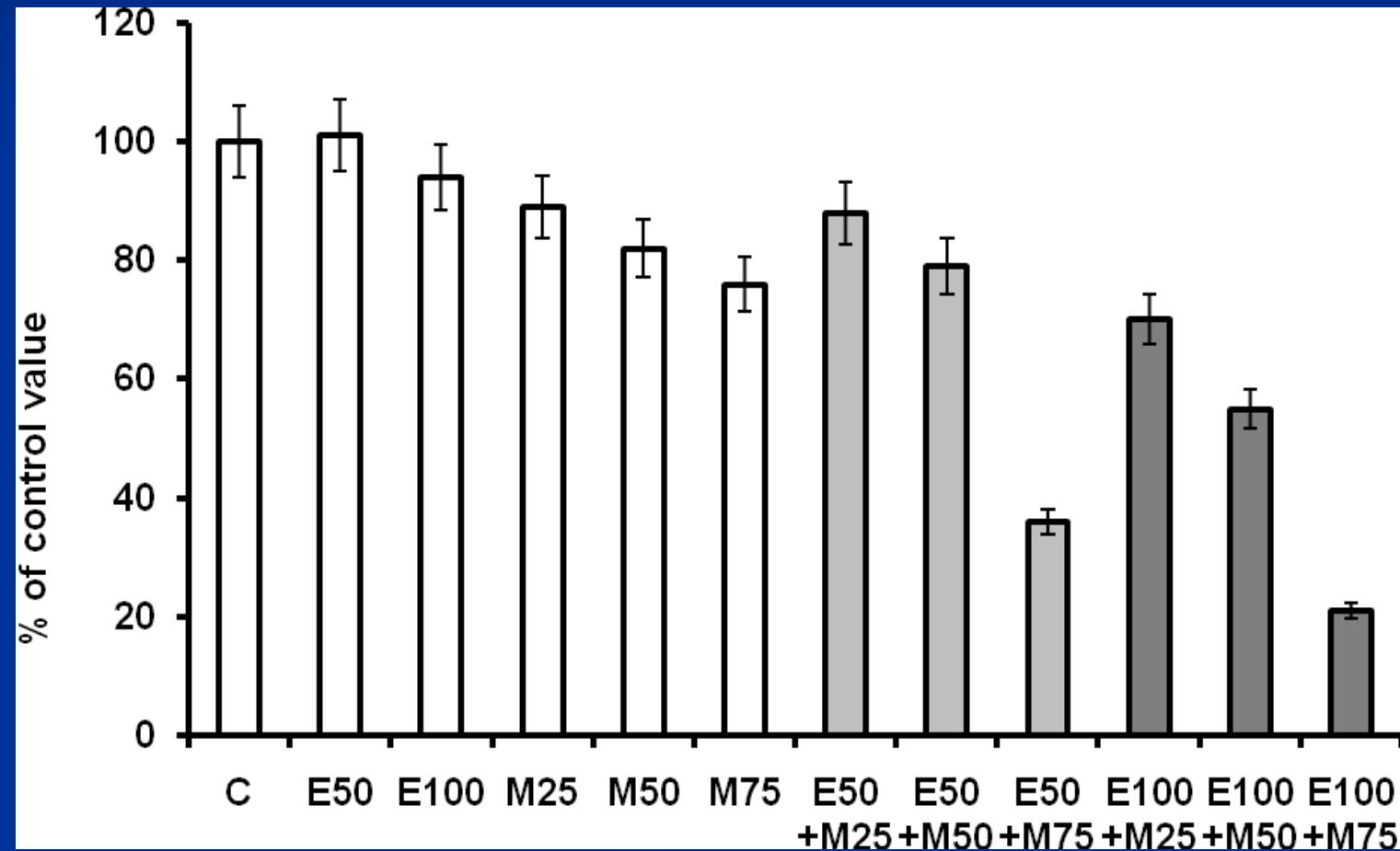


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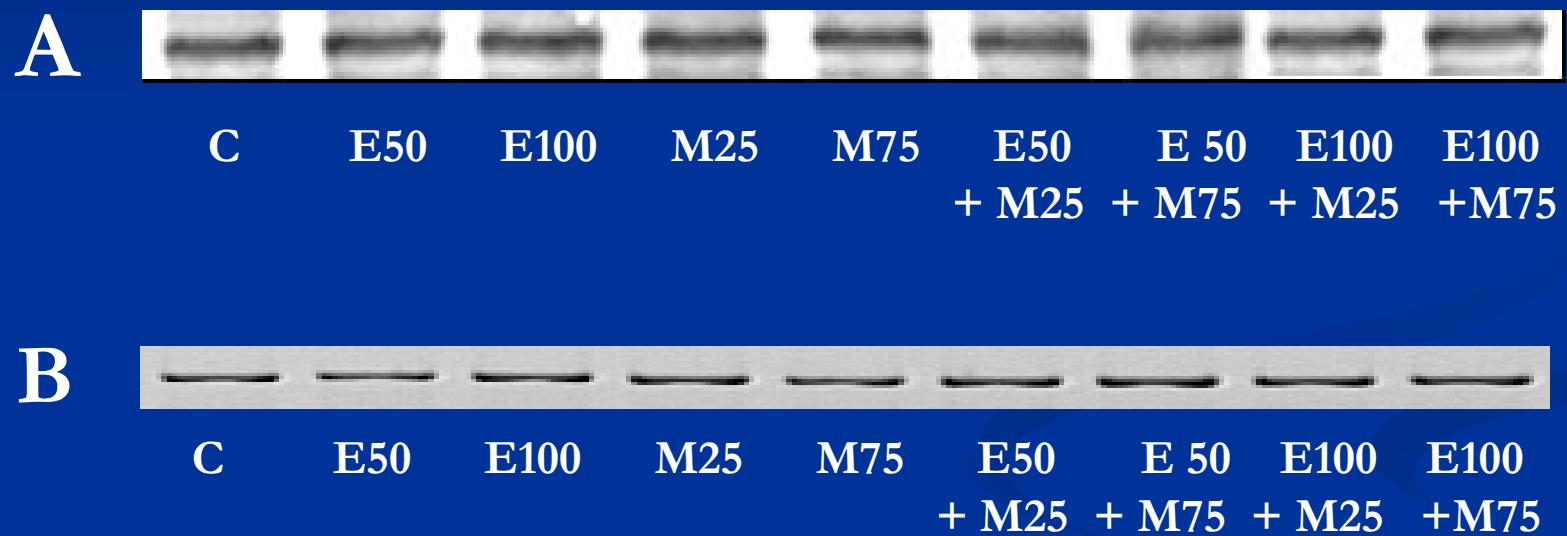
DMP757

DMP728

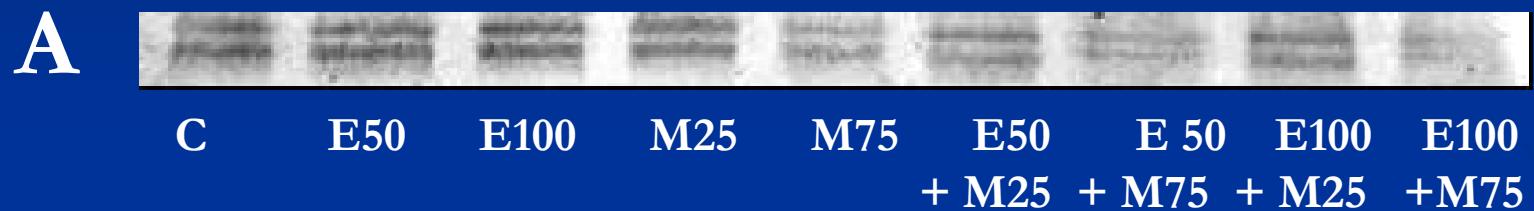
Viability of Ishikawa cells treated with various concentrations of echistatin (E) and malphalan (M)



Western immunoblot analysis for β_1 -integrin receptor (A) β -actin (B) in Ishikawa cells treated with echistatin (E) and melphalan (M)



**Western immunoblot analysis for Shc protein (A),
FAK (B) in Ishikawa cells treated
with echistatin (E) and melphalan (M)**



Western immunoblot analysis for IGF receptor in Ishikawa cells treated with echistatin (E) and melphalan (M)



