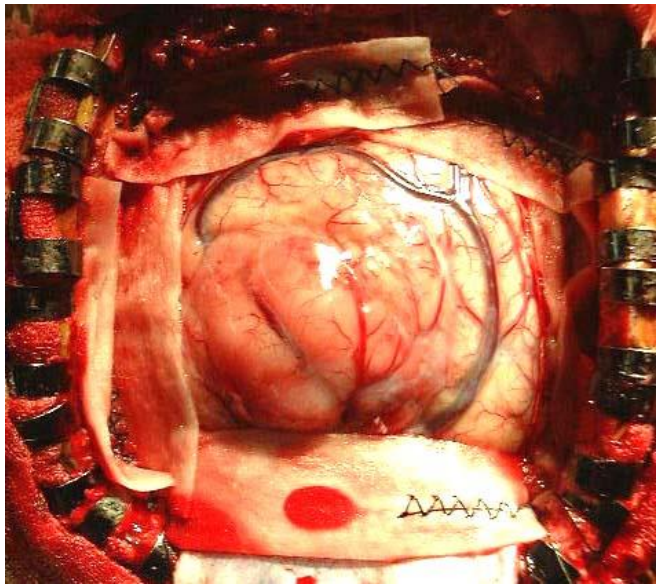
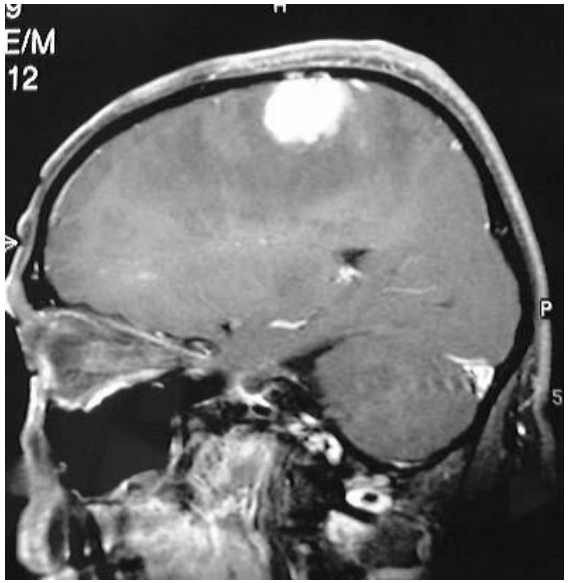
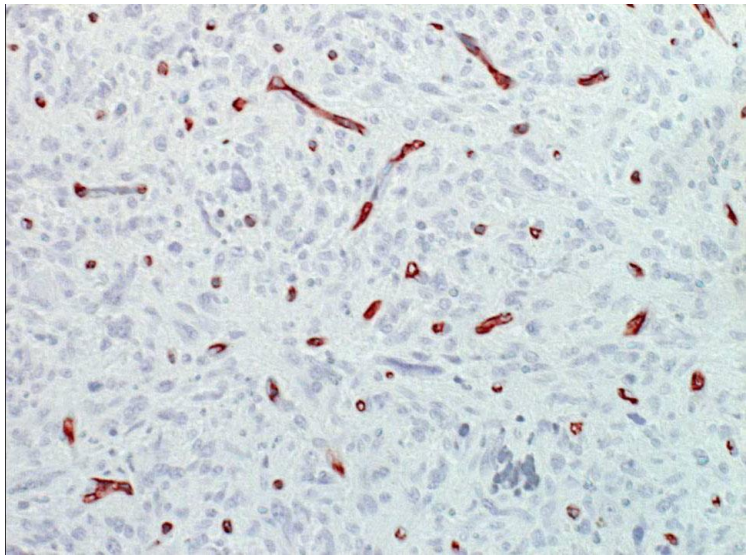
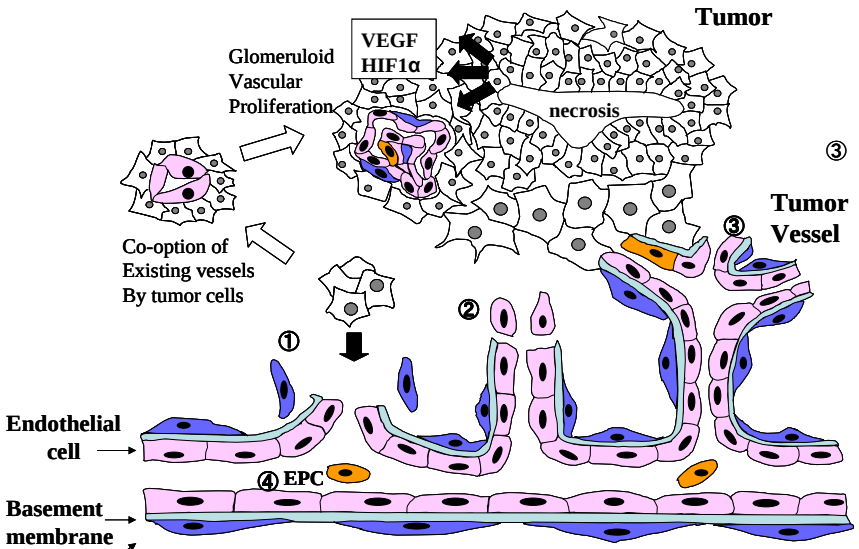
悪性脳腫瘍に対する血管新生抑制療法









栄養源である血管を止めれば腫瘍は育たない

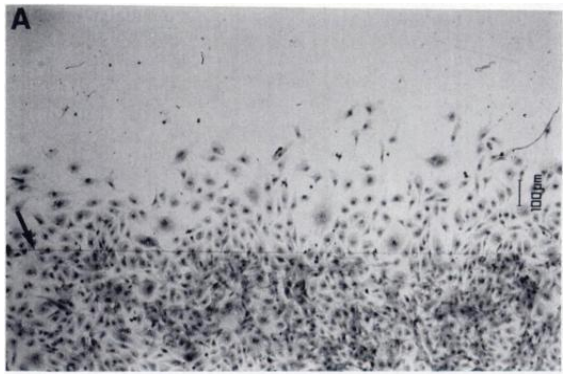
Suramin inhibits glioma angiogenesis

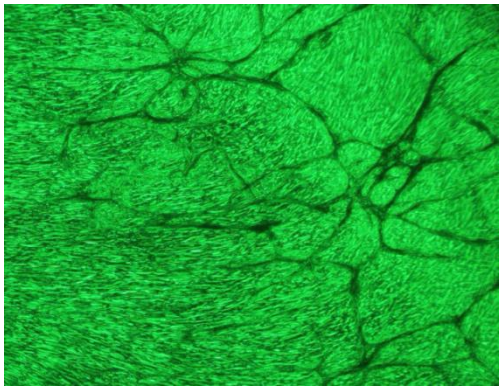
Migration

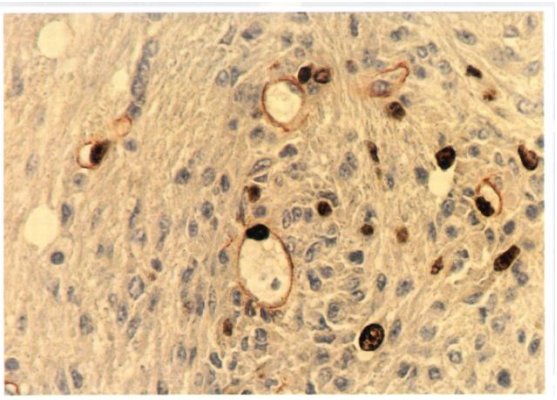
Tube formation

Proliferation (C6 model)

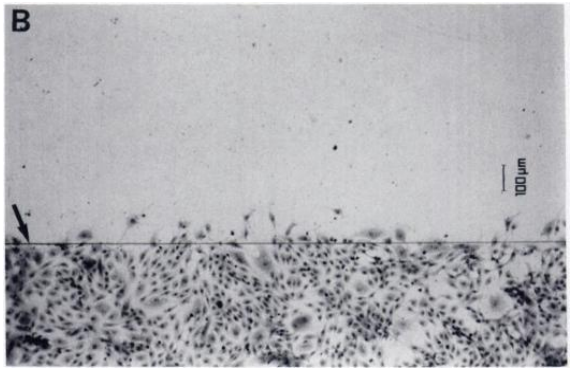
Control

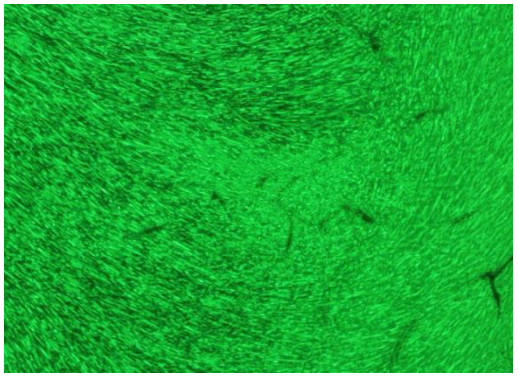


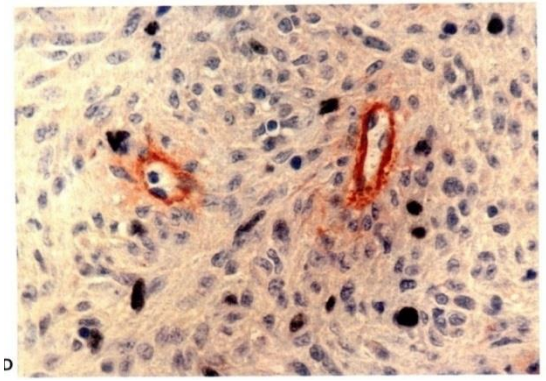




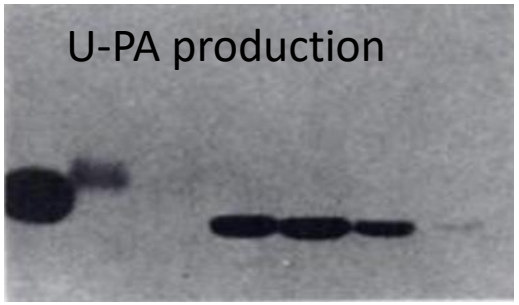
Suramin







U-PA production

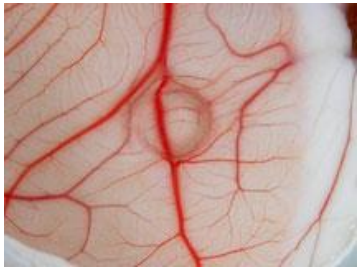


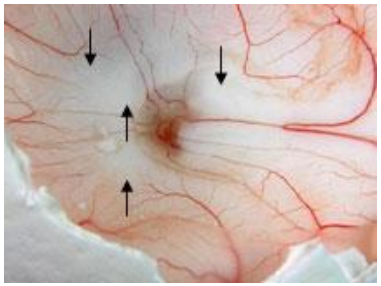
U-PA

bFGF - + + + +

Suramin (ug/ml) 0 0 100 250 500

CAM assay

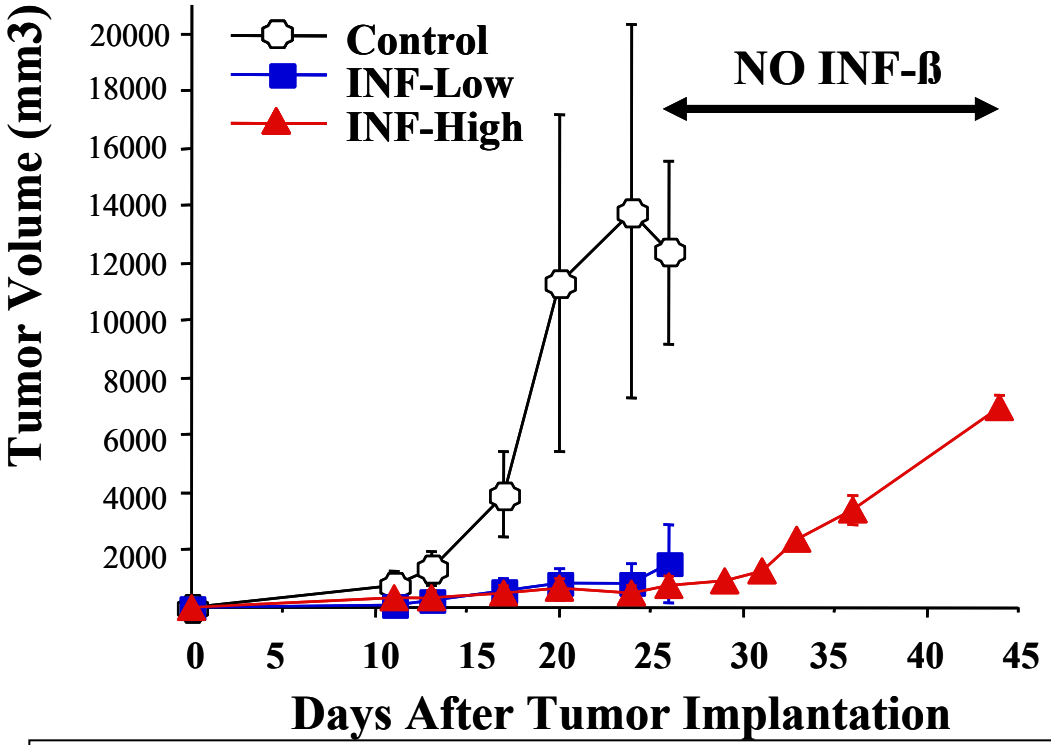




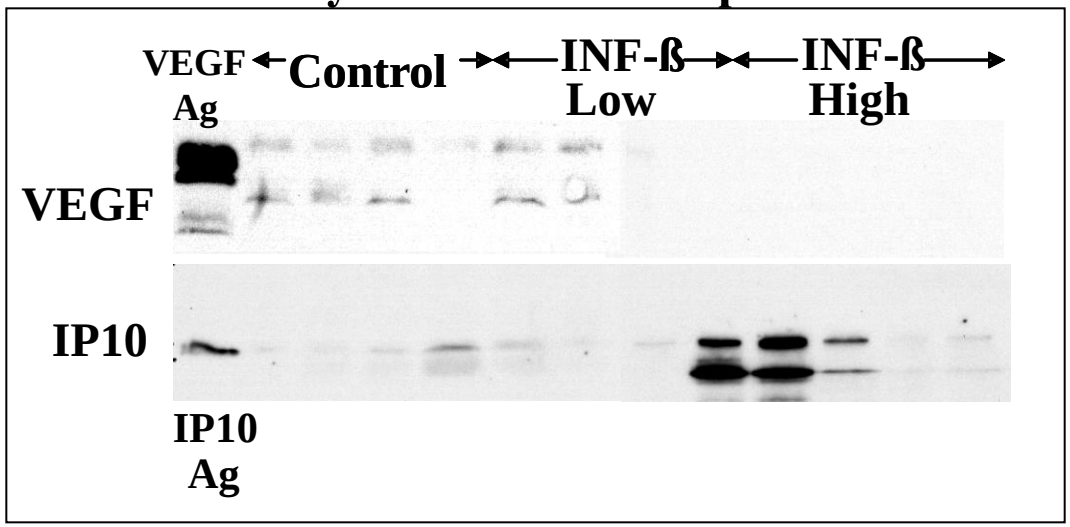
Control

Suramin

Interferon-β inhibits glioma growth



マウス皮下
悪性脳腫瘍モデル



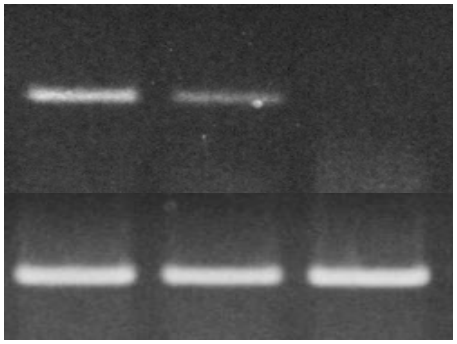
Western analysis

Down-regulation of VEGF
Up-regulation of IP10

TSP-1 Transfectant Tumor Growth

RT-PCR

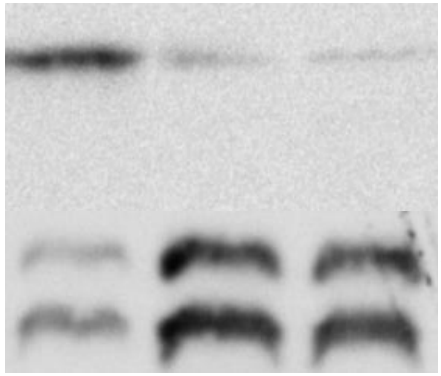
TSP Neo P



TSP1

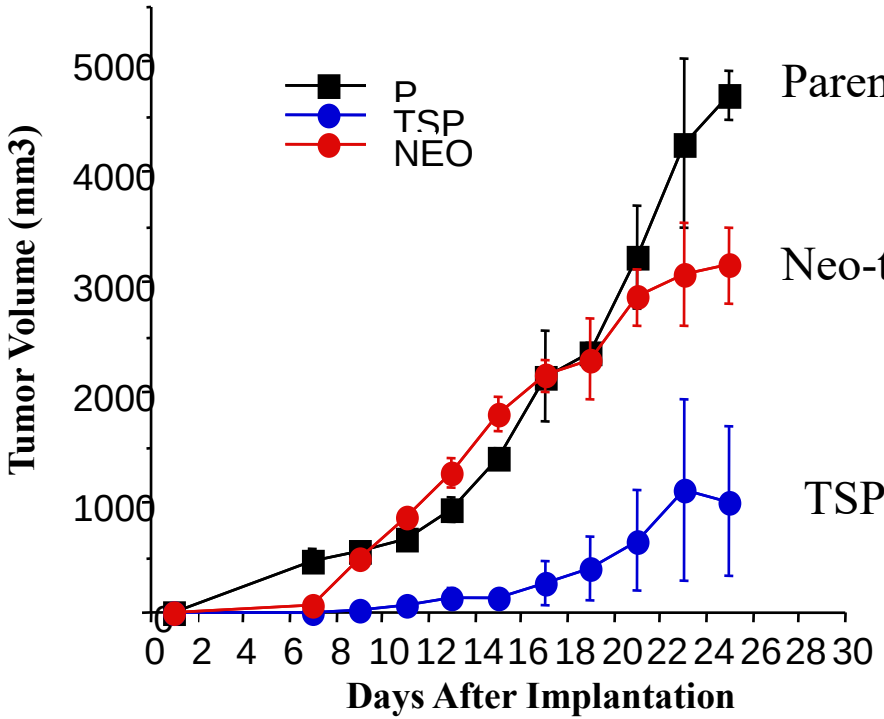
ß-actin

CM Western



TSP1

VEGF



Parent U87 cells

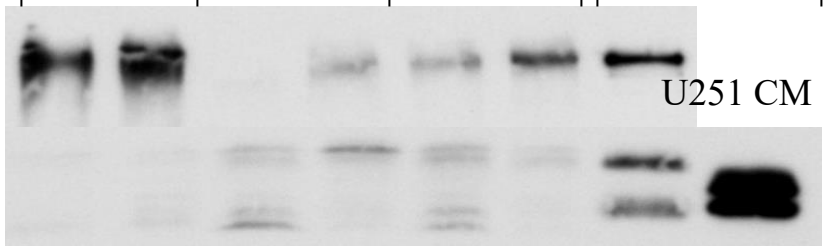
Neo-transfectant

TSP1-transfectant

TSP Neo P Positive control

TSP1

VEGF

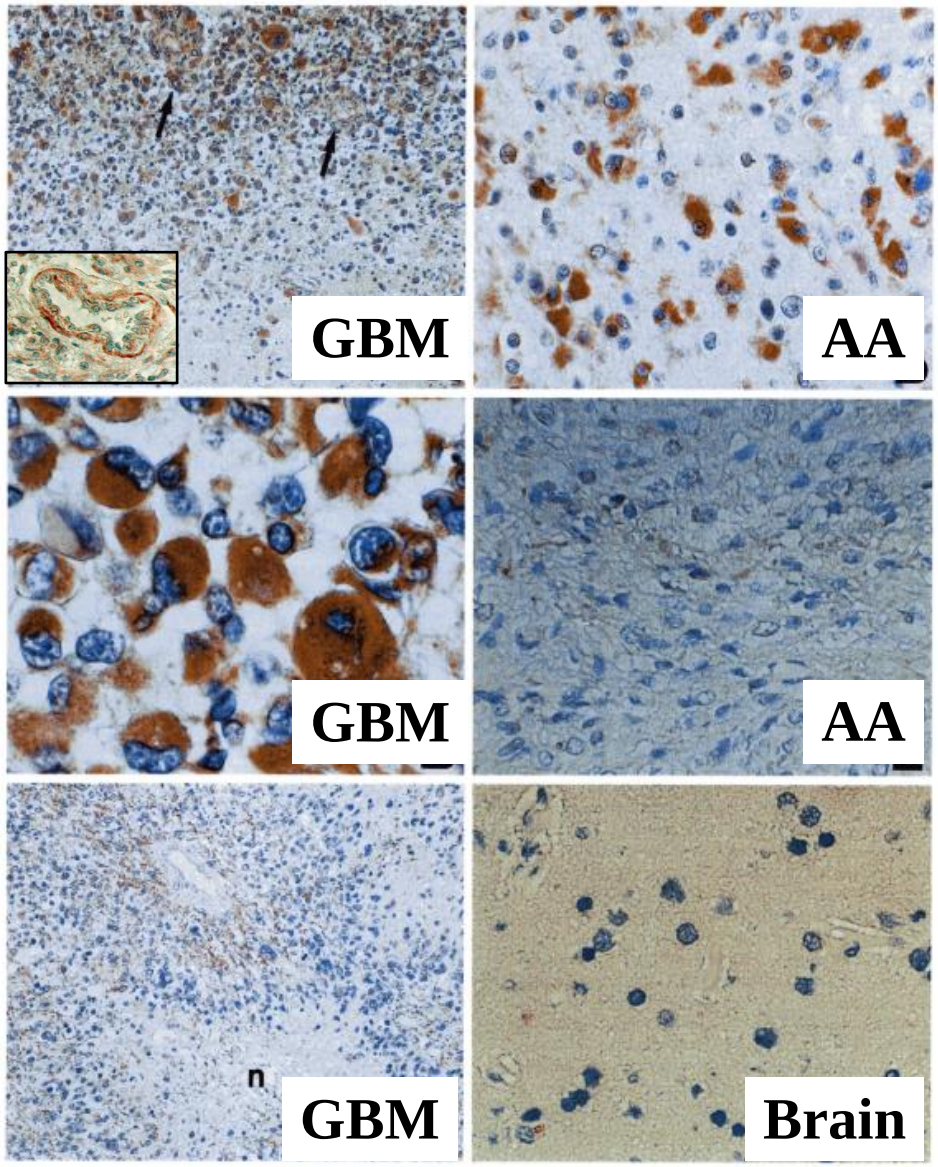


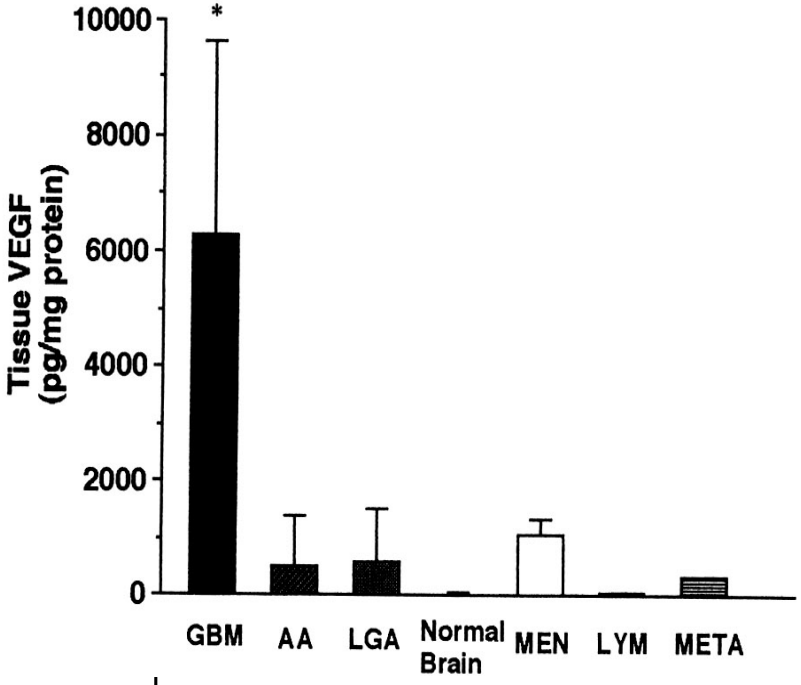
U87 CM

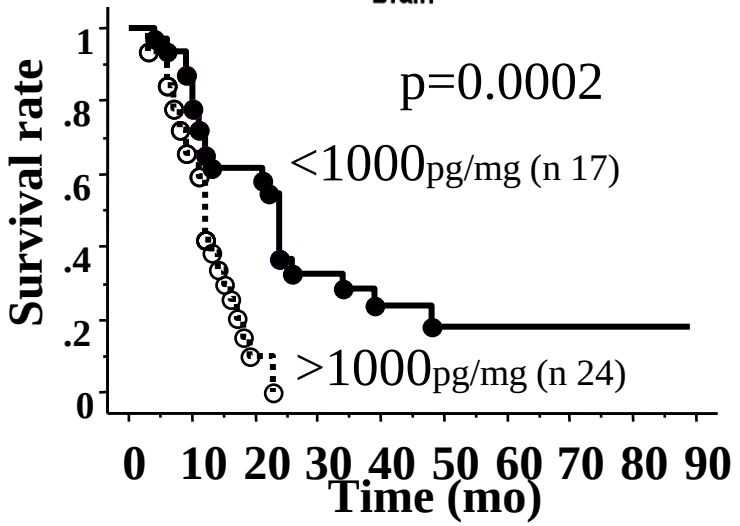
VEGF Ag

TSP1とVEGFのリンク

膠芽腫とVEGF



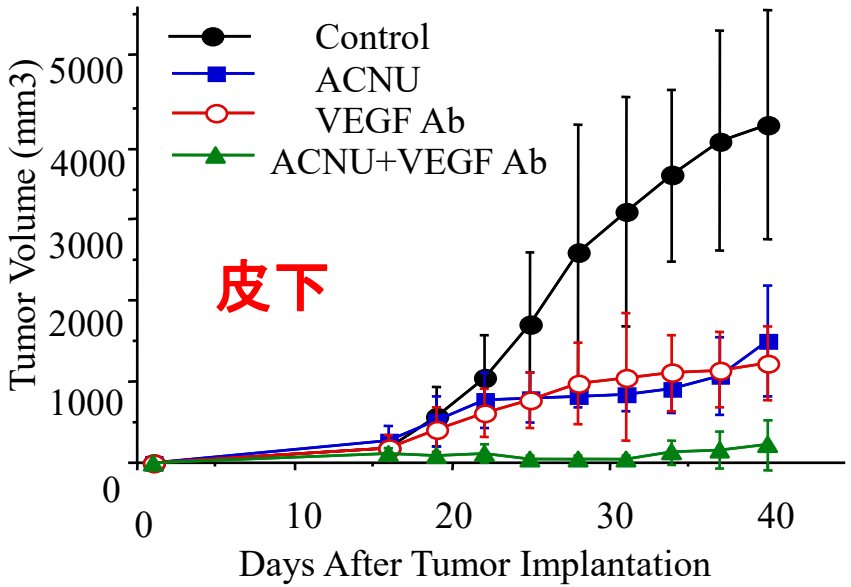


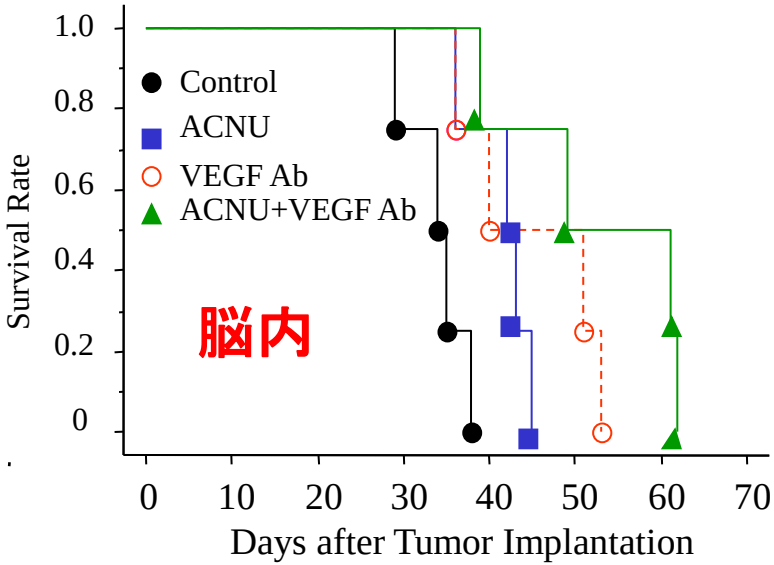


Cancer Res 1996, BTPA 2005

ベバシズマブの膠芽腫への効果（U87 マウスモデル）

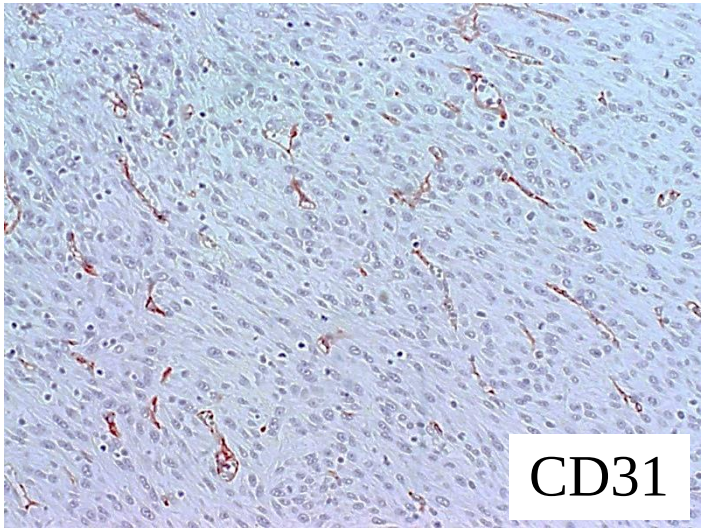
“増殖の抑制と生存期間の延長”





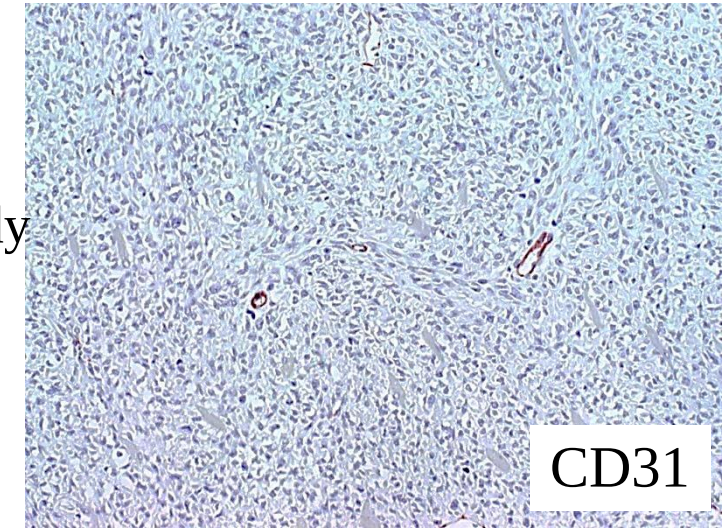
“腫瘍血管新生の抑制”

Control



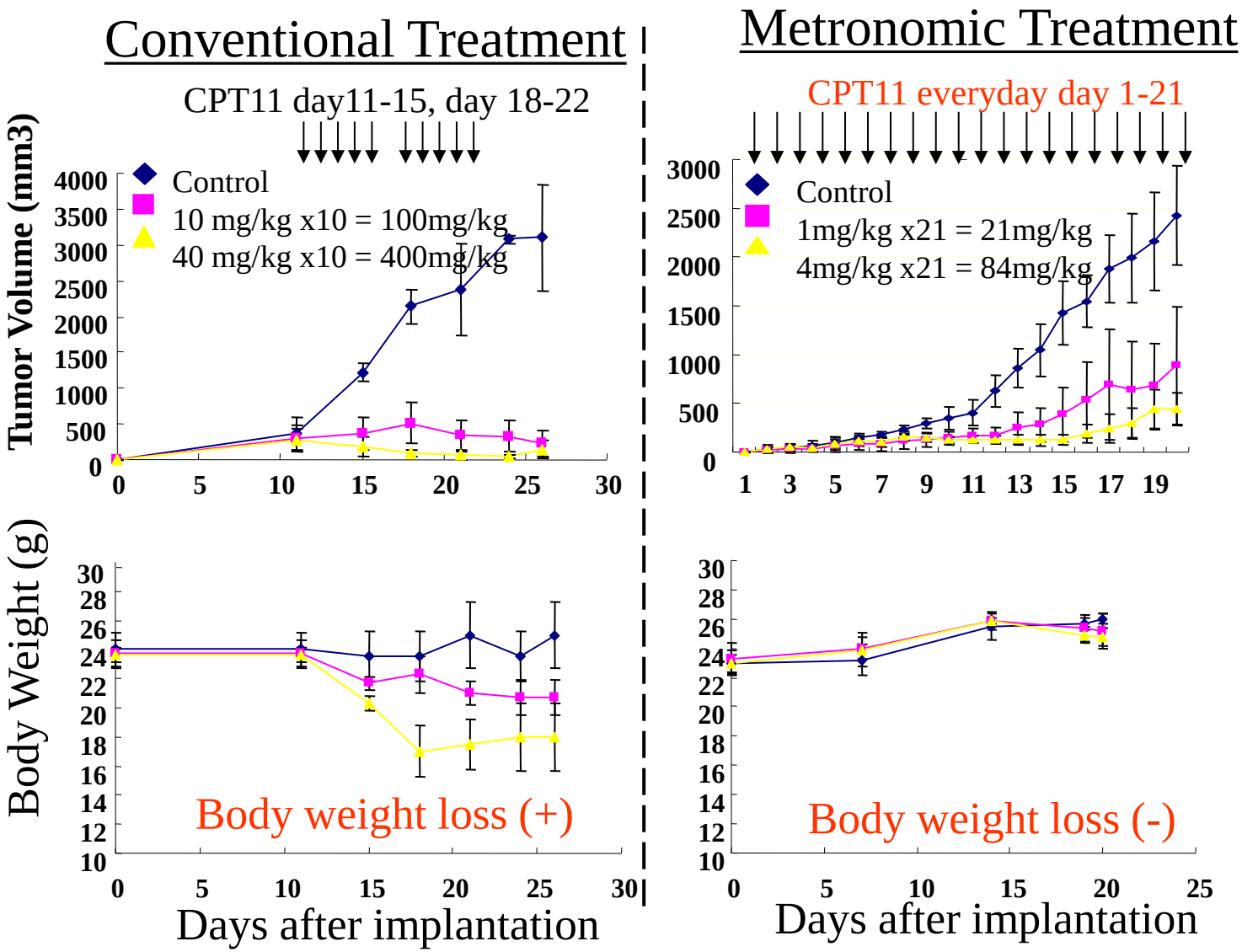
皮下

VEGF Antibody



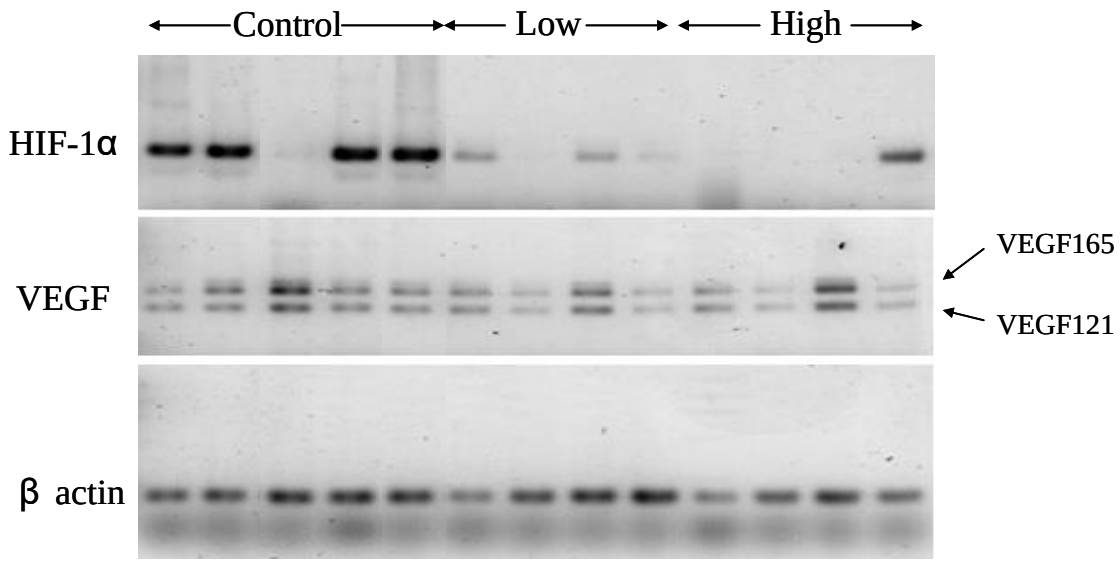
Neuro-Oncol 2003

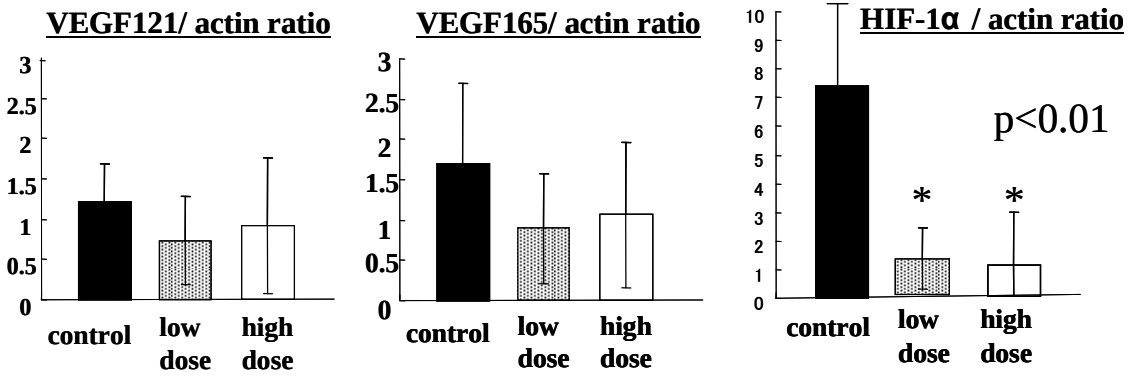
Metronomic CPT11 schedule is effective and not-toxic



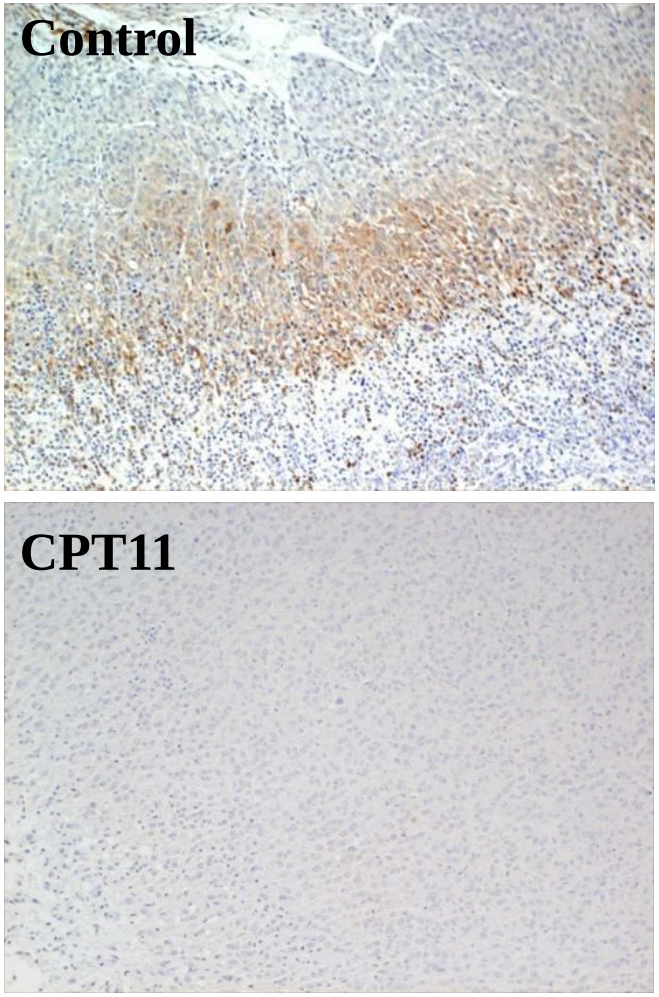
J Neurooncol 2010

Metronomic CPT11 schedule inhibits hypoxia





Hypoxic area (pymonidazole)

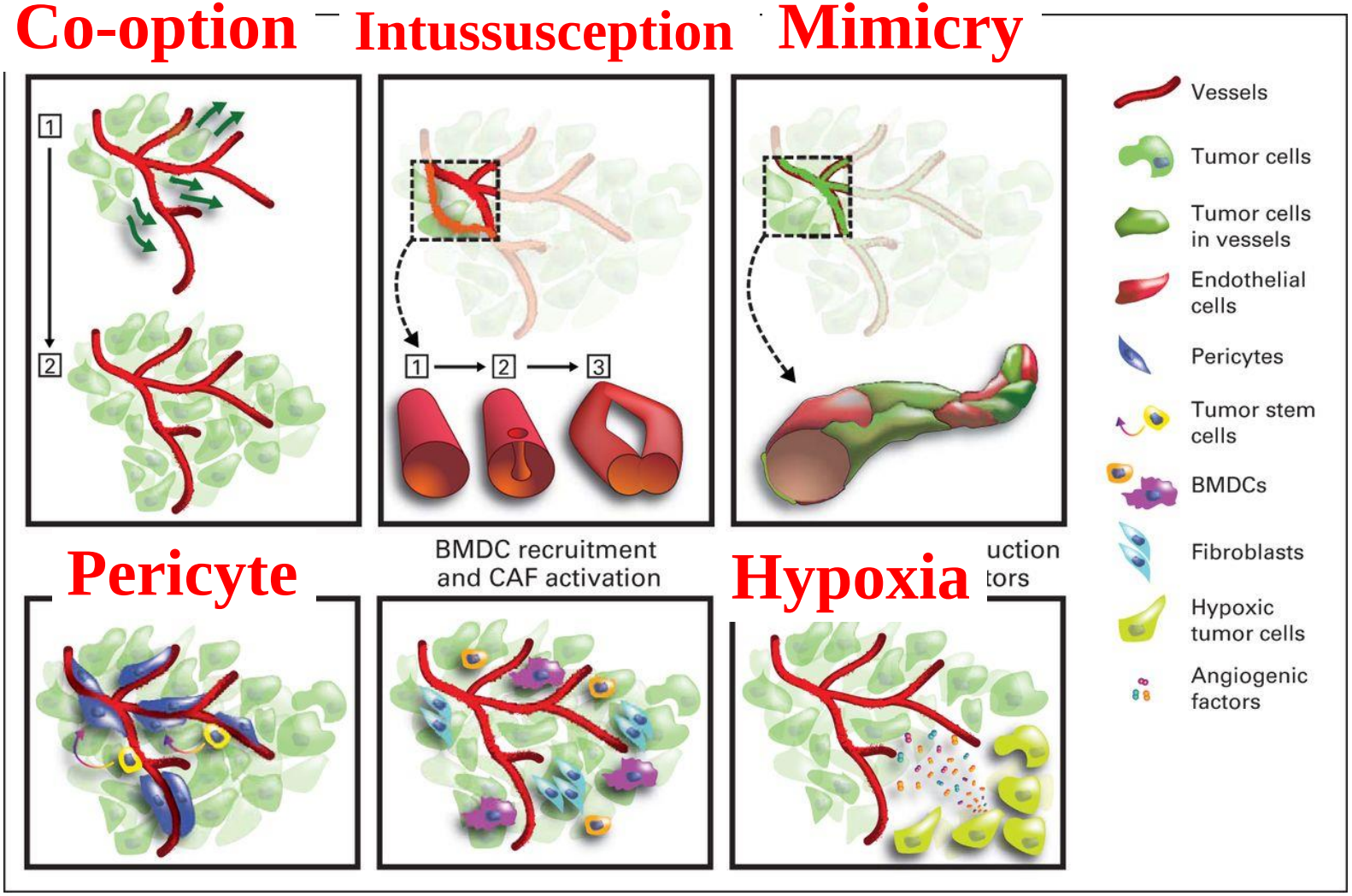


J Neurooncol 2010

脳腫瘍に対する血管新生抑制療法 取り組んでいること

- 血管新生抑制の抵抗性の克服
  - Vessel co-optionの分子メカニズムと抑制
  - Vessel mimicryの分子メカニズムと抑制
  - 低酸素誘導因子の抑制による低酸素の解除
- 免疫療法との併用効果

Resistance to anti–VEGF / VEGFR strategies in glioblastoma (GBM)



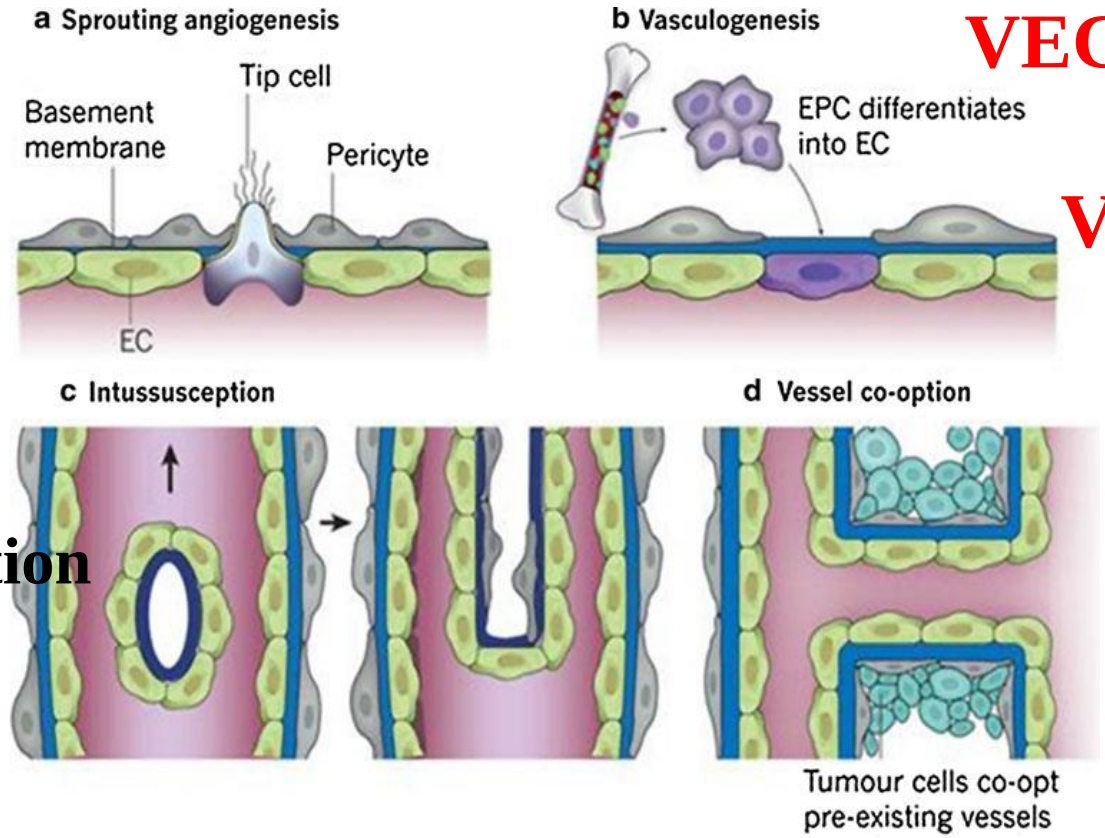
Christine Lu-Emerson et al. JCO 2015;33:1197-1213

Mechanisms of vessel formation

VEGF dependent

Sprouting

Vasculogenesis



Intussusception

Co-option

Infiltrative growth

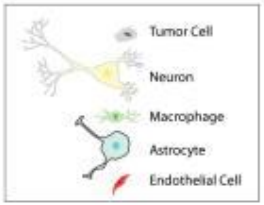
Vascular mimicry

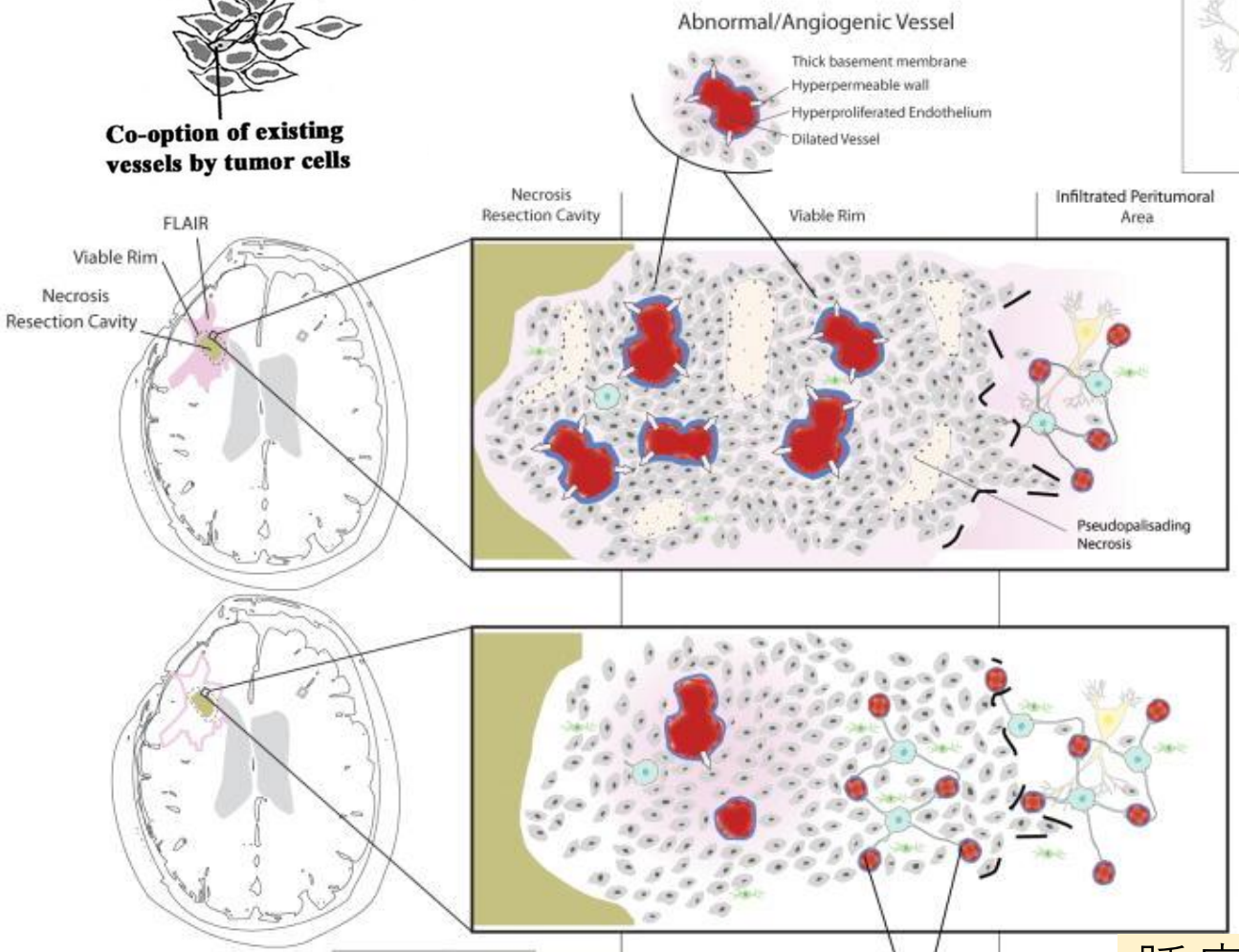
Endothel differentiation

Carmeliet Nature 2011

Vessel co-option

VEGF independent





Standard Tx

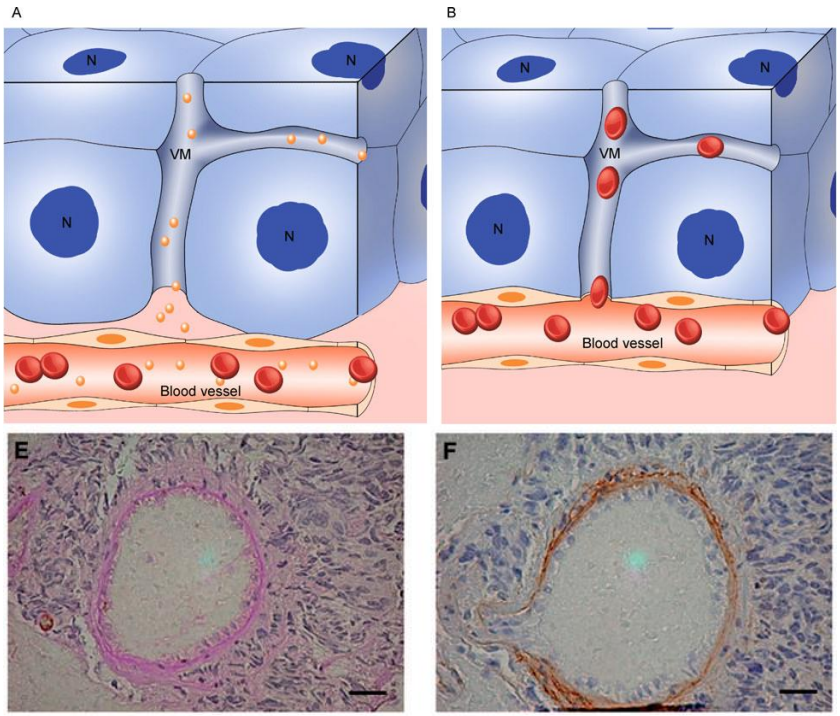
Anti-angiogenic Tx

腫瘍辺縁部でco-optionが増えている

Di-Tomaso Cancer Res 2011

Vasculogenic mimicry in GBM

VEGF independent

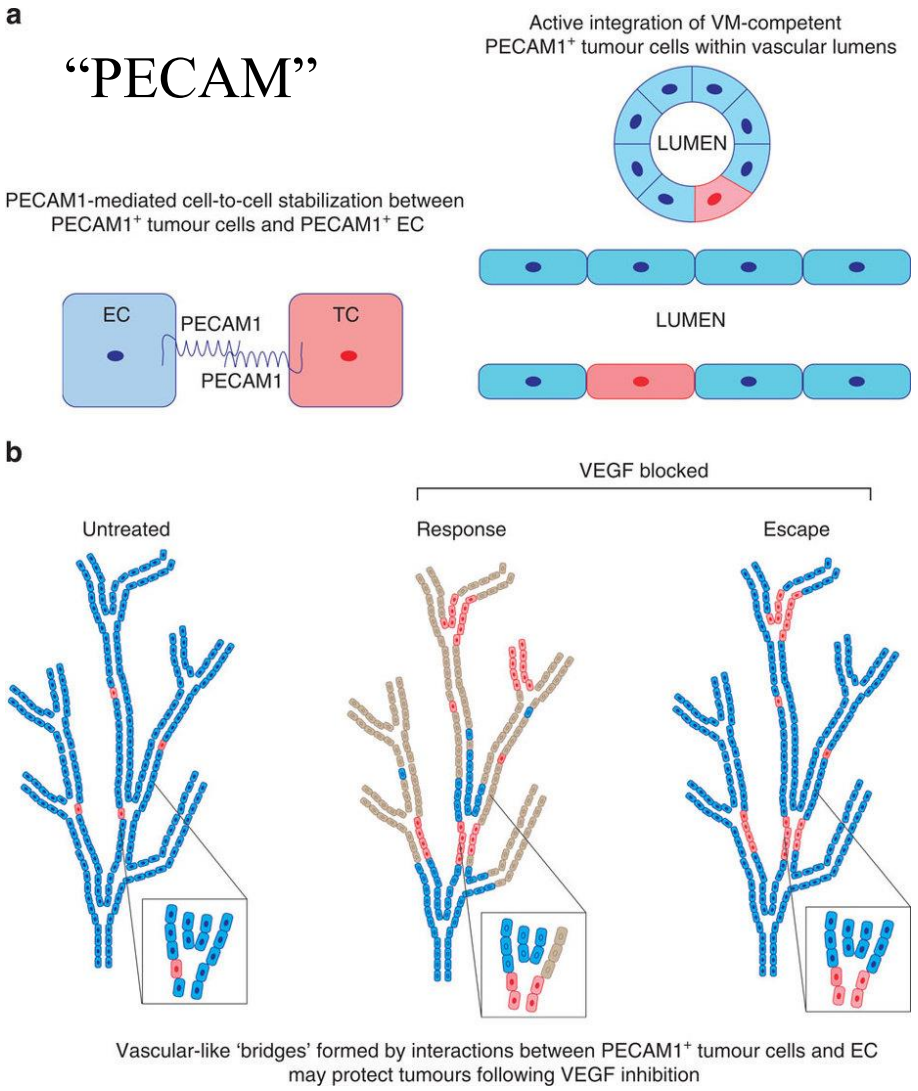


CD34 (-)

Type IV Collagen (+)

Yao Protein Cell 2011
Hallani et al. Brain 2010

"PECAM"



Dunleavey, J Nat Commun 2014