Angiogenesis Pathways to Progress?

Kathy D Miller, MD
Sheila D Ward Scholar of Medicine
Associate Professor of Medicine
The Indiana University Melvin and
Bren Simon Cancer Center

Disclosures for Kathy D Miller, MD

Consulting Agreement	Bristol-Myers Squibb Company
Speakers Bureau	Genentech BioOncology, Roche Laboratories Inc

Irrational exuberance

- Therapy “resistant to resistance”
  - Endothelial cells are ‘normal’
- Xenograft models with widespread activity
- BUT
  - Early clinical results ‘disappointing’
  - If tumors grow, there must be resistance

Kerbel RS: A cancer therapy resistant to resistance. Nature 390:335-6, 1997

Resistance mechanisms observed in the clinic

- None observed

Potential mechanisms of resistance

- Heterogeneity in
  - Endothelial cells are ‘normal’
  - Tumor cells
  - Host
- Tumor microenvironment
- Compensatory response
- Growth independent of angiogenesis
- Pharmacokinetics

Endothelial heterogeneity

- Lessons from embryology
  - Brain and testes endothelia express mdr
- Lessons from the lab
  - CXC receptor expression in ‘normal’ endothelia differs based on source
  - Tumor-associated versus non-malignant endothelia
    - Nearly ½ of 170 transcripts differentially expressed
    - Expression similar but not identical between primary and metastatic sites

Barrand et al FEBS Lett 374:179-83, 1995; Gille et al Blood 87:211-7, 1996; St. Croix et al Science 289:1197-1202, 2000

Tumor heterogeneity

- Genetic instability
- Variable sensitivity to hypoxia and hypoglycemia
  - Cyclic hypoxia common
  - Tumor cells farther from vessels may be relatively resistant to hypoxia

Durand et al Cancer Res 58:3547-50, 1998
Brown et al Nat Med 7:864-8, 2001

Host differences

- Up to 10-fold difference in response in corneal micropocket assay among different mouse strains
- VEGF-2578C/A and -1154G/A polymorphisms associated with increased survival with paclitaxel + bevacizumab therapy
  - VEGF-634G/C and -1498C/T protective from HTN

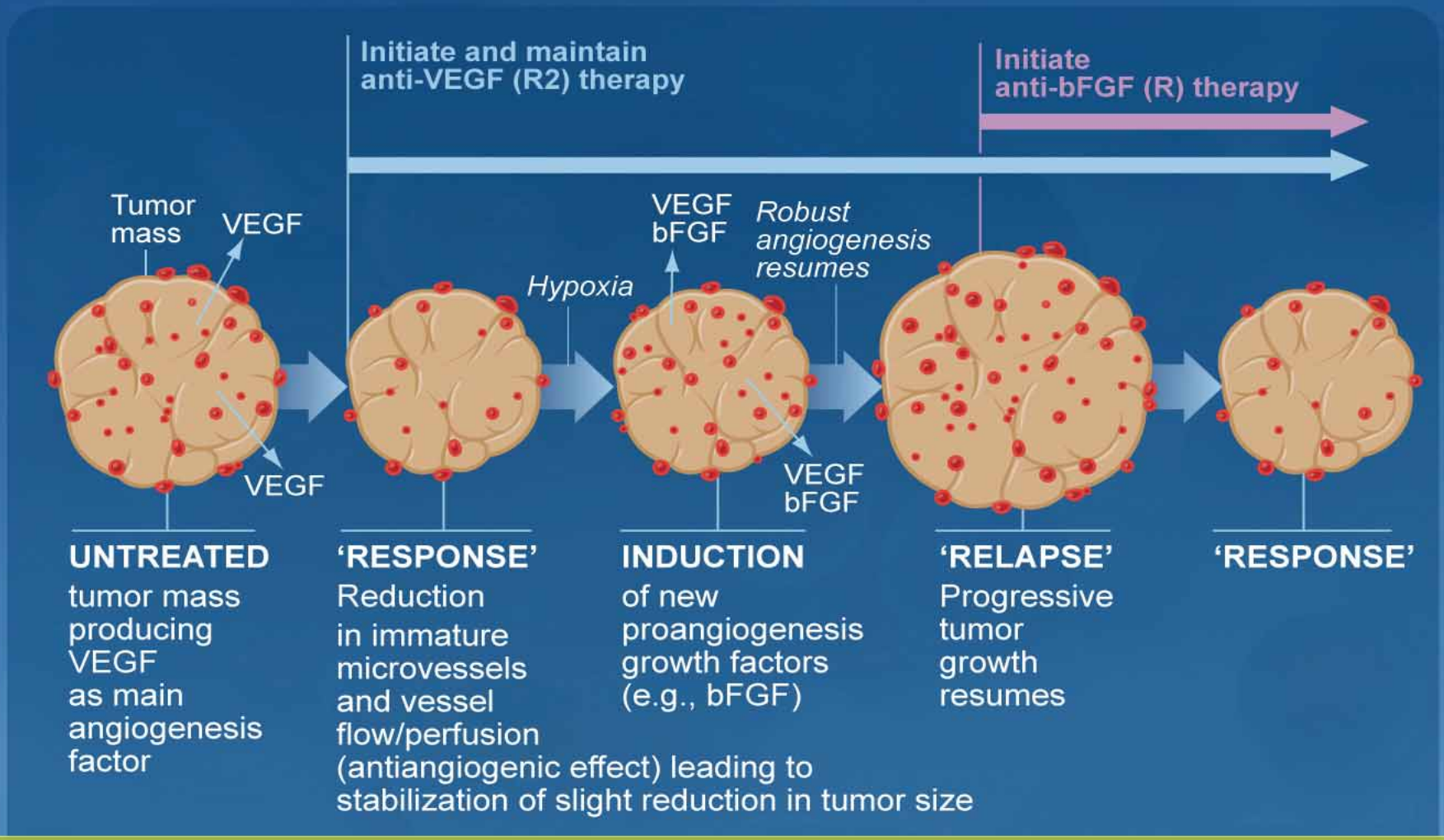
Rohan et al Faseb J 14:871-6, 2000
Schneider et al, JCO 2008

Tumor microenvironment

- Growth and angiogenesis differ in animal model based on site of implantation
- Local production of pro-angiogenic factors induces anti-apoptotic pathways in endothelial cells (ECs)
- Pericyte coverage differs
- Stroma as factor reservoir
- Impact on drug delivery

Pluen et al Proc Natl Acad Sci 2001; Pozzi et al Proc Natl Acad Sci 2000; Gerber et al J Biol Chem 1998; Gohongi et al Nat Med 1999

Compensatory response

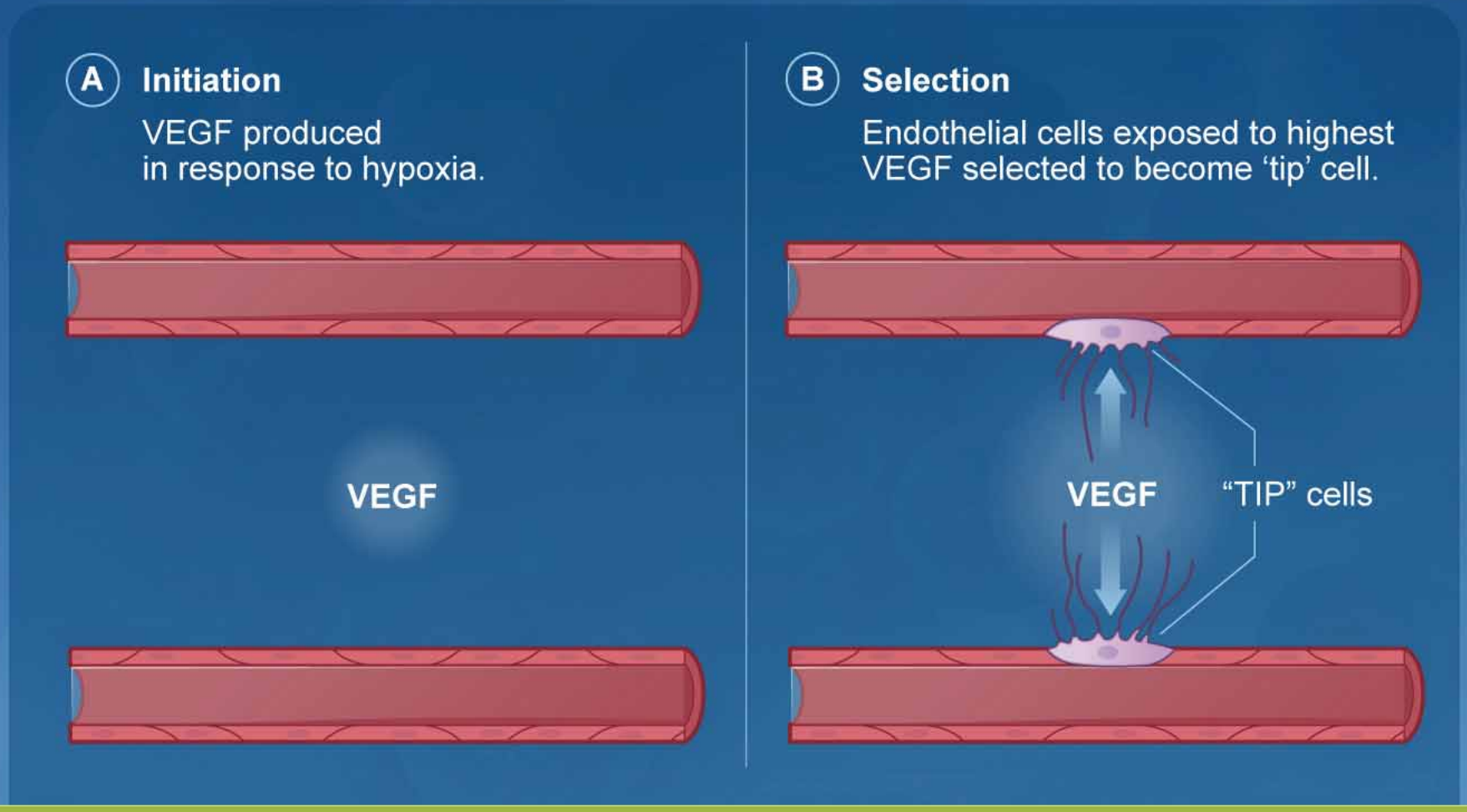


Growth independent of ‘classical’ angiogenesis

- Vascular mimicry
- Vessel cooption
- Intussusception
- Vasculogenesis

Holash et al Science 1999; Patan et al Microvasc Res1996
Hendrix et al Proc Natl Acad Sci 2001; Lyden et al Nat Med 2001

Model of vessel branching



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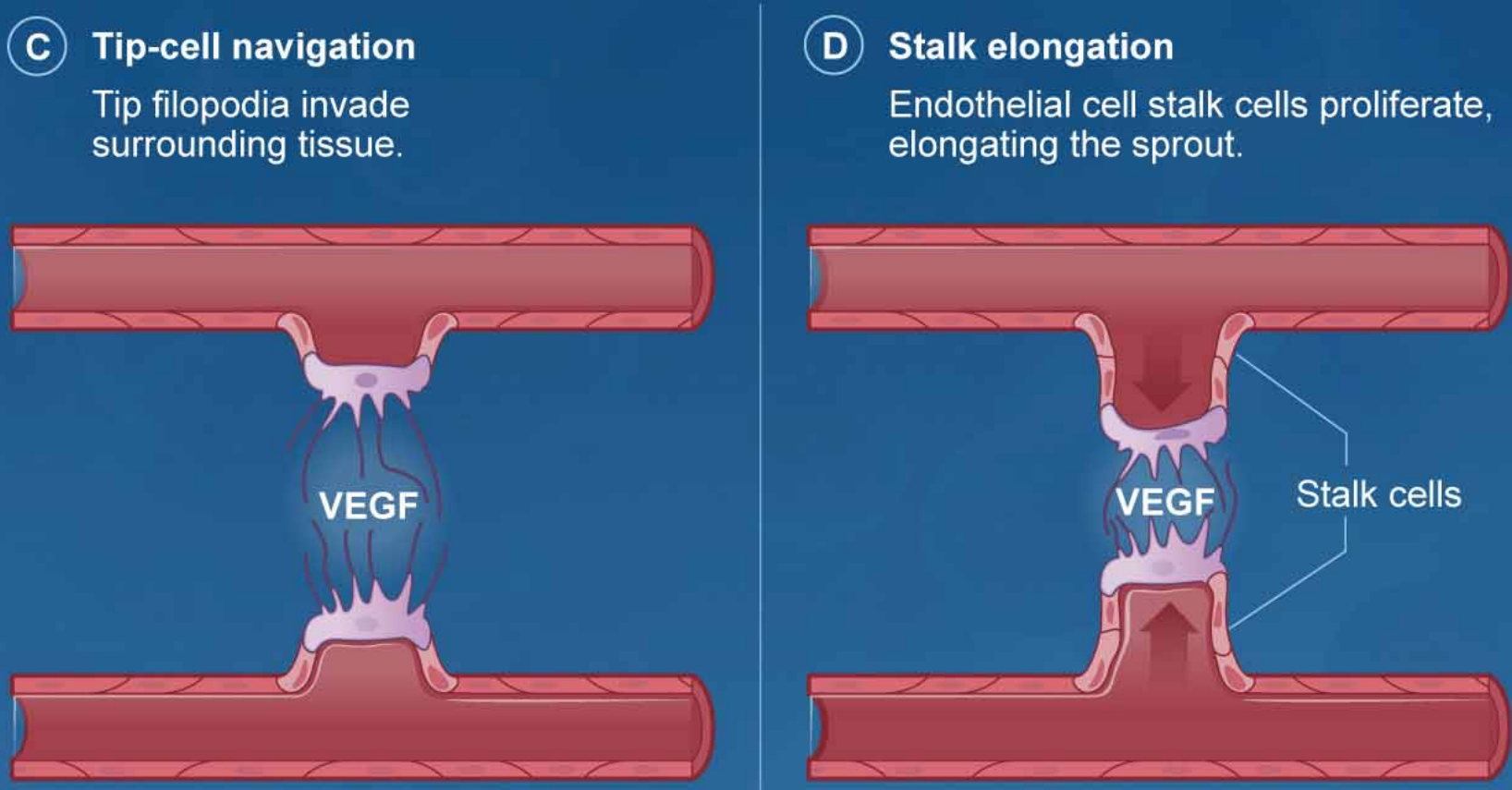
Model of vessel branching



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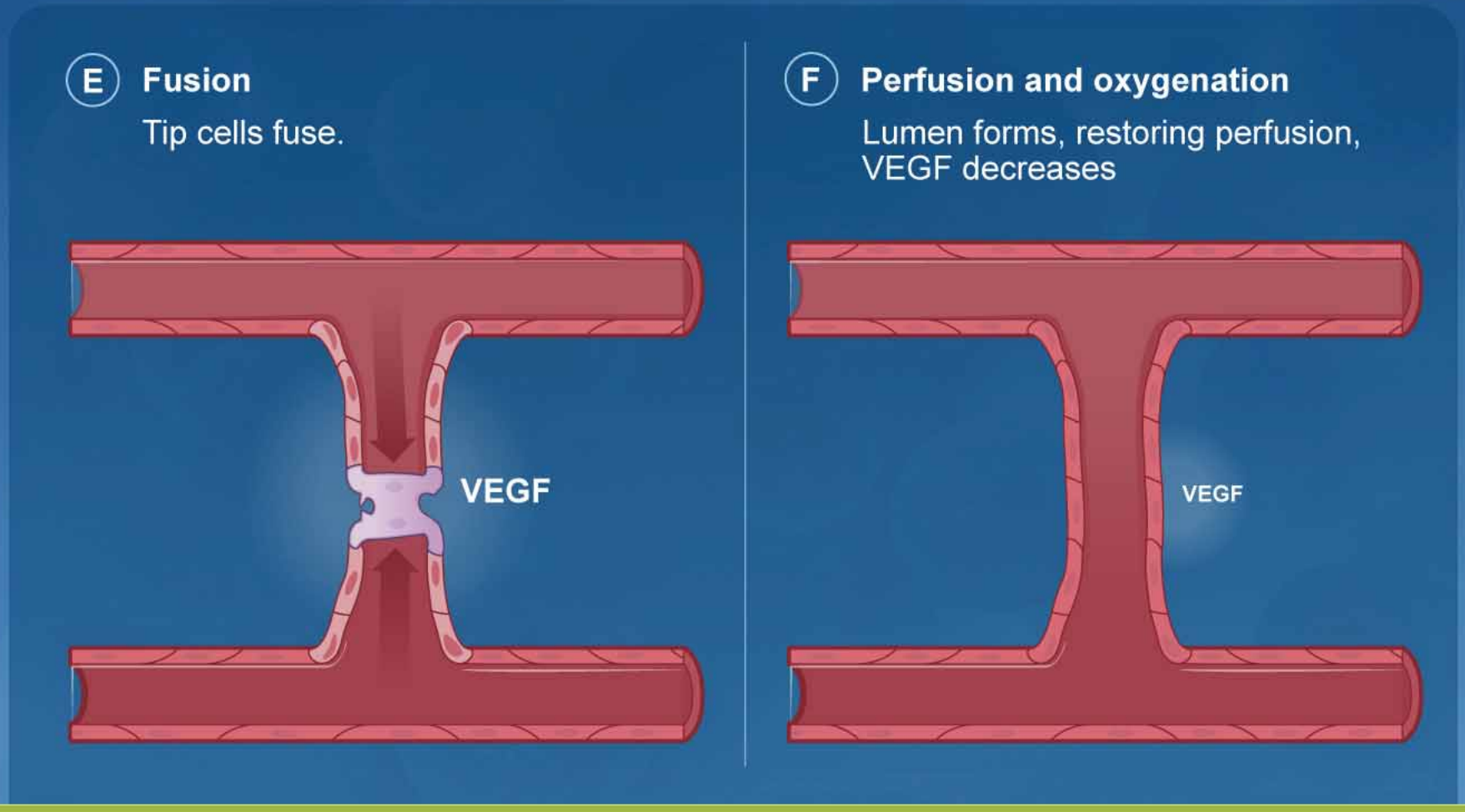
Model of vessel branching



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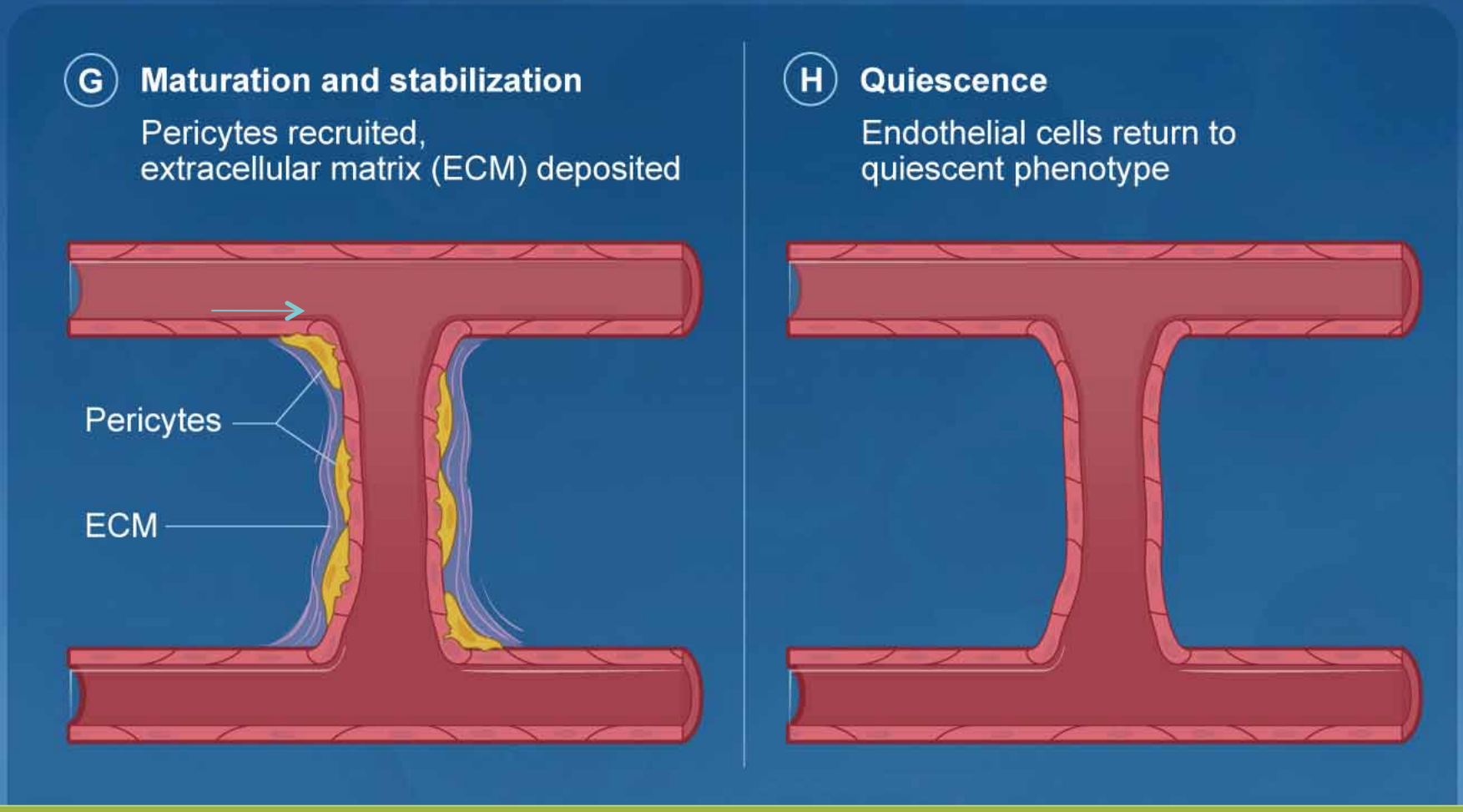
Model of vessel branching



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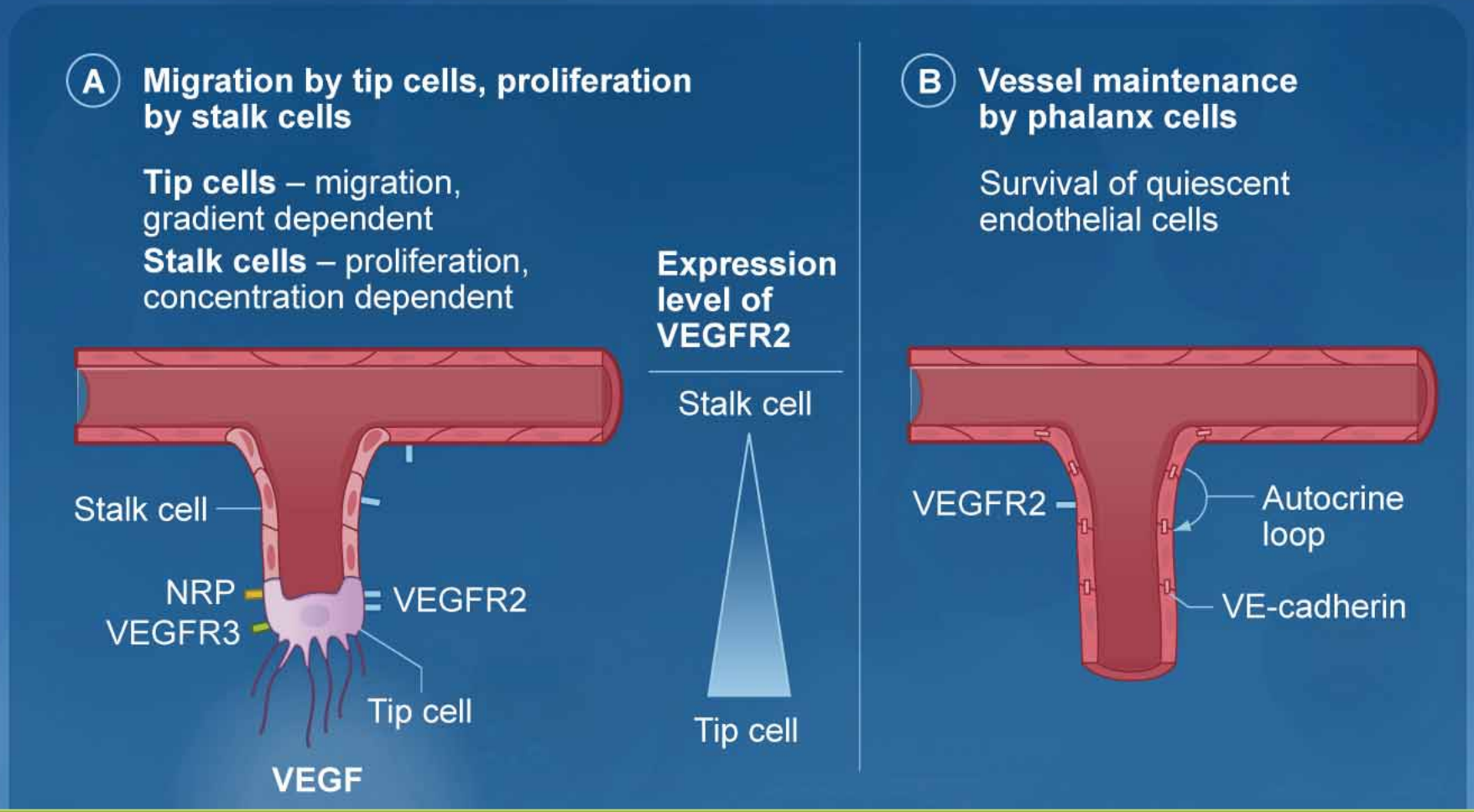
Differential effects of VEGF



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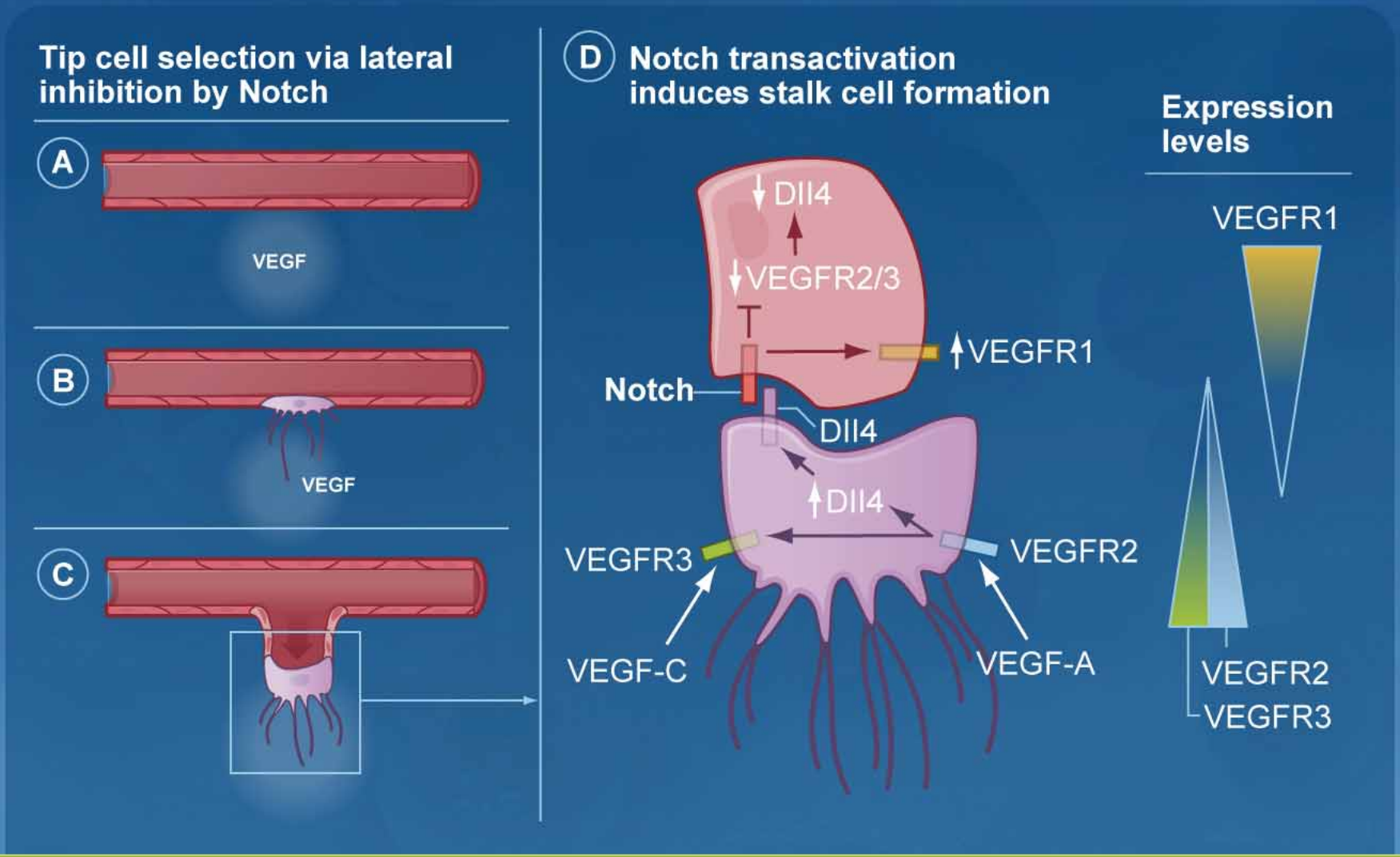
VEGF Inhibition

- Therapeutic effect based on tip and stalk cells
  - Inhibition of tip cell migration
  - Decreased stalk proliferation
  - Apoptosis of ECs without pericyte coverage
  - Impact on marrow derived progenitor release post-chemo
- Toxicity based on quiescent ECs?

Sprouts, not sheets - role of notch



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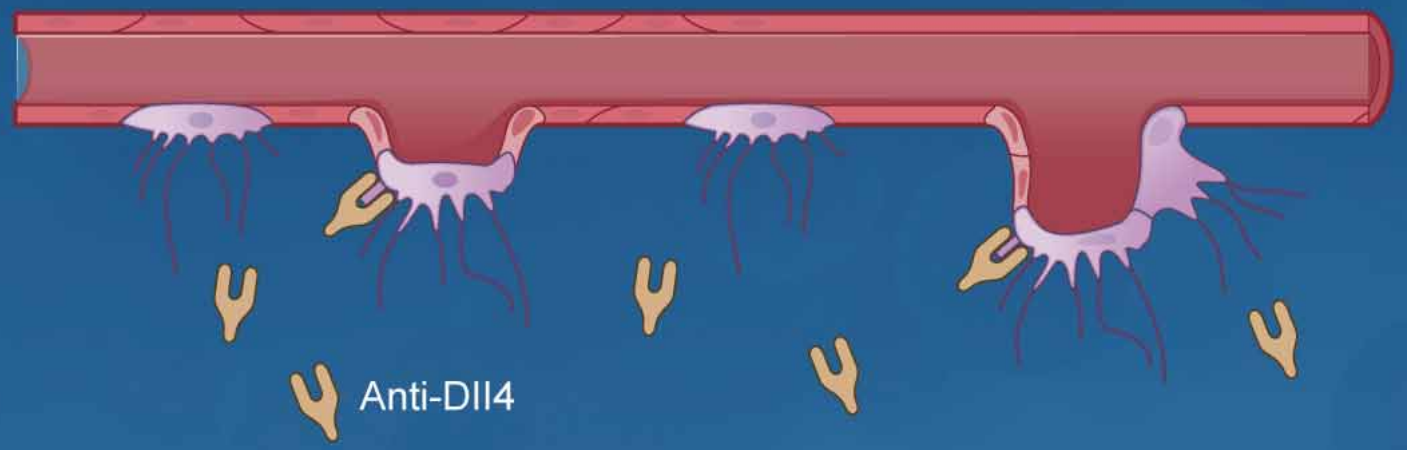
Sprouts, not sheets - role of notch

E **Anti-Dll4 causes non-productive angiogenesis by inducing excess tip cells**

Increased vessel density is not always bad!



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Conclusions

- Early enthusiasm has given way to clinical reality ….resistance continues
- Way forward continues to lie in increased knowledge of fundamental biology