To Video

Enter A New Era In the Management of Diabetic Retinopathy

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29 **Vascular Endothelial Growth Factor (VEGF)**

30 **The VEGF Family**

31 **VEGF-A: Key Mediator of Angiogenesis and Vascular Permeability**

32 **Properties of VEGF: Induces Vascular Permeability**

- Potent vascular permeability inducer (50,000x >histamine)
- Induces vessel leakage via multiple mechanisms
  - Leukocyte-mediated endothelial cell injury
  - Formation of fenestrae
  - Dissolution of tight junctions and transcellular bulk flow
- Vascular permeability may be an antecedent and a necessary step for neovascularization

33 **Properties of VEGF: Proinflammatory**

- Inflammatory cells make and release VEGF
- VEGF binds to leukocytes
- Inflammatory cells participate in Blood-retinal barrier breakdown and neovascularization (NV)
- Leukocytes present at leading edge of pathologic but not physiologic NV (Inflammation)

34 **The VEGF Paradox**

- VEGF required for normal function
- BUT also plays role in pathologic function

35 **Milestones in VEGF Research**

1948-1958	Michaelson, Ashton, and Wise contribute to "Factor X"'	hypothesis
1971	Folkman publishes tumor angiogenesis factor hypothesis	
1983	Dvorak demonstrates tumor secretion of vascular permeability factor (VPF)	
1989	Ferrara clones VEGF and identifies it as an angiogenesis factor	(identity with VPF)
1997	First clinical trials of anti-angiogenic therapy in cancer	patients initiated
1999	Aptamer blocking $VEGF_{165}$ first tested in humans (Macugen for AMD, Eyetech/Pfizer)	
2003	First Anti-VEGF therapy shown to be efficacious in AMD (Macugen for AMD, Eyetech/Pfizer)	
2004	First FDA approved Anti-VEGF therapy for colorectal cancer (Avastin)	

36 **VEGF in Normal Physiology**

- Essential for normal embryonic development
  - Inactivation of single VEGF allele in mice resulted in embryonic death
- Role in female reproductive cycle
  - Follicular growth and development of corpus luteum dependent on new capillary vessels
- Expressed in nonangiogenic tissues in the brain, kidney, and gastrointestinal mucosa

37 ☐ **VEGF in Normal Healing Processes**

- ◆ Corrective role in wound healing and bone repair
  - – Needed for directional bone growth and blood vessel invasion of cartilage
- ◆ Promotes new vessel growth following myocardial ischemia

38 ☐ **Normal Vasculature Regresses**

With Nonselective VEGF Inhibition

39 ☐ **VEGF is found in the Normal Eye**

- ◆ VEGF and VEGF receptors expressed in normal eye
  - – Receptors present in neural elements of inner retina
  - – High VEGF expression in retinal pigment epithelium
- ◆ **Researchers hypothesize VEGF may be important for choriocapillaris survival and/or fenestrae maintenance**

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43 ☐ **Can VEGF effects be blocked in more than one place?**

44 ☐ 1- VEGF Production (Up-regulate VEGF gene) and Release in response to...?

- ◆ **Inflammation**
  - – Complement H?
  - – Elevated lipids?
  - – CRP
  - – Interlukin6
  - – Smoking?

'Combination' Rx
Antioxidants
Lower Lipids
Stop Smoking
Drugs (si RNA)
Plasmapheresis

45 ☐

46 ☐ **SI RNA**

- ◆ Short interfering RNA
  - – Blocks messenger RNA from taking information from the VEGF gene in the cell nucleus to the ribosome where VEGF is produced

47 ☐ **Bee Hive Analogy**

48 ☐ **The Trials**

'Evidence Based Medicine'

49 ☐

50 ☐ **PKC Beta Inhibitor**

- PKC Beta Inhibitor (Ruboxistaurin, Arxxant, Lilly)
  - Eyes with severe NPDR at baseline
  - Had to have DME at baseline
- Did Not Prevent Progression of BDR to PDR (Primary Endpoint)
- Did prevent moderate visual loss (>= 3 lines loss) in severe NPDR (Secondary End Point)

51 ## Pharmocologic Diabetic Retinal Trials

- Does this mean the laser will be used in the future as a door stop?

52 # The Future Isn't What It Used To Be!

53 ## Pharmocologic Diabetic Retinal Trials Enrolling Patients

- PKC Beta Inhibitor (Ruboxistaurin, Arxxant, Lilly) to prevent BDR progression
- Macugen for BDR
- Intravitreal Kenalog for DME
- Intravitreal Kenalog for Rubeosis
- Oral PTK 787 (Novartis-AMD)-Tyrosine Kinase Inhibitor (blocks VEGF receptor)

54 # Avastin

55 ## Avastin

- A very large molecule (VEGF blocker/Ab)
- Too large to cross the blood retinal barrier?
- Same parent compound as Lucentis
- 100x lower affinity than Lucentis
- Much longer half life (systemic concerns)
- Used CA Colon, also lung, breast and others (not for Ivt use)
- Works in the eye!
  - No Animal Studies
  - No Human Studies
  - >10,000 off label intravitreal injections given in last 9 months
  - AMD, PDR, DME, Rubeosis, CRVO, TVO
    - Melamoma? Metastatic?

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61 ## Avasin: Potential Uses For DR

- DME-temporary 6-8 weeks (No traction, several)
- Rubeosis-buys time
- Pre PRP for advanced PDR-less PRP needed?
- Pre PPV for advanced PDR with traction

- Risks?
  - Endophthalmitis, RD from injection
  - Systemic Absorption-HTN, Stroke, MI

62 # Thanks