

Chimeric VEGF₁₂₁-VEGF₁₆₅ Fusion Protein in New Anti-angiogenic Cancer Therapy

Alan Yueh-Luen Lee, Ph.D. (李岳倫)

National Institute of Cancer Research National Health Research Institutes, Taiwan

National Health Research Institutes Contact Person: Shih-hai Wang Tel: +886-37-246166 ext. 33207 E-mail: sea99@nhri.org.tw Address: 35 Keyan Road, Zhunan, Miaoli County 35053, Taiwan Website: http://www.nhri.org.tw

05.09.2017



Do we use the right strategy on cancer therapy?

Trying to control cancer may prove a better plan than just striving to kill it

Conventional Cancer Treatment

- Surgery
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Molecular targeted therapy
 - Small molecule
 - Monoclonal antibody
 - Protein drug
- Immunotherapy: vaccine

Nature (2009) 459: 508

A change of strategy in the war on cancer





Anti-angiogenesis therapy

Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285:1182-1186.

Agents

Avastin/Bevacizumab Iressa/Gefitinib Nexavar/Sorafenib SU11248/Sunitinib GW786034B/Pazopanib VEGF Trap/Aflibercept IMC-1121B/Ramucirumab Anginex, 0118 Angiostatin P Tumstatin Cc AMG-706/Motesanib

Class

(Anti-VEGF Mab)
(RTK inhibitor)
(RTK inhibitor)
(RTK inhibitor)
nib (RTK inhibitor)
ot (VEGFR Decoy)
umab Anti-VEGFR2 Mab
0118 α-Chemokine like compounds
Plasminogen fragment
Collagen XV fragment
(RTK inhibitor)

Dr. Folkman's WAR



Angiogenesis and the Struggle to Defeat Cencer **ROBERT COOKE** Foreword by Dr. C. Everett Koop

Studies/FDA approval Approved (2004) Approved Approved Approved Approved Approved Phase II

Phase I



Challenges

Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis.

Cancer Cell 2009; 15(3):220-31

 Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis.

Cancer Cell 2009;15:232-9.

 Antiangiogenesis therapy might have the unintended effect of promoting tumor metastasis by increasing an alternative circulatory system.

Med Hypotheses 2009.



Escape/Resistance Mechanisms

- Alternative proangiogenic pathways: FGF, PDGF, VEGF-X
- Vascular mimicry: Sprouting-independent vessel growth
- Intratumoral hypoxia
- Increased EMT, invasion
- Suppression of immune surveillance
- Activation of cancer stem cell

Nature Rev Cancer 12, 699-709, 2012 Nature Rev Clin Oncol 9, 378-390, 2012



The Importance of Tumor Microenvironment in Cancer Therapy



Stage 5 – Angiogenesis



VGEF isomers



Highly conserved, homodimeric glycoprotien of 34 to 45 kDa



Signal peptide



Design advantages of Fc region of an antibody

- Enhance dimer formation and receptor binding but not signaling.
- Increase the stability and solubility of the protein drug.

BioDrugs (2015) 29, 215-39

- Fc-Fc Receptor interaction assists drug delivery
- Low immunogenicity TIB (2015) 33, 27-34
- Able to modulate the immune system via Fc Receptor

TIB (2015) 33, 27-34

The Novel VEGF₁₂₁-VEGF₁₆₅ Fusion Attenuates Angiogenesis and Drug Resistance *via* Targeting VEGFR2-HIF-1α-VEGF₁₆₅/Lon Signaling Through PI3K-AKT-mTOR Pathway





Normalizing Tumor Microenvironment to Sensitize Low-dose Therapy and Checkpoint Immunotherapy

