Treatment of angiogenesis-dependent diseases

28th May 2013
angiogenesis (an-je-o-JEN-uh-sis):
*angei-, angeio-*, vessel or blood vessel, *genesis-*, origin or birth

angiogenesis:
formation of new blood vessels via extension or remodeling from existing capillaries
Three ways of formation of blood vessels

**Vasculogenesis**
capillaries are formed from vascular progenitor cells

**Angiogenesis**
formation of new blood vessels from pre-existing vessels

**Arteriogenesis**
formation of mature blood vessels; differentiation into veins and arteries
Major growth factors and receptors involved in blood vessels formation

VEGF – vascular endothelial growth factors
VEGF-A – crucial mediator of angiogenesis

VEGF-R – receptors for vascular endothelial growth factors

Angiopoietins (Ang-1, 2)
Tie-2 – receptor for Ang-1, -2

FGFs – fibroblast growth factors

PDGF – platelet-derived growth factor
Physiological angiogenesis in adults is restricted

placenta

uterus

Hair growth

Wound healing
New capillary formation in response to wounding
Angiogenesis may be impaired in many diseases

- Rheumatoid Arthritis
- Blindness
- Stroke
- Heart Disease
- Ulcers
- Scleroderma
- Cardiovascular diseases

Cancer

AIDS complications

Excessive

Insufficient

ANGIOGENESIS

www.angio.org
Treatment of numerous diseases can be improved by pro-angiogenic therapy
Pro-angiogenic therapy

- one of the possible therapy for cardiovascular diseases

- one of the first trial: fibroblast growth factor 1, FGF-1 was used to treat patients with coronary heart disease (Stegmann et al. 2000)

The first clinical study on patients with coronary heart disease treated by local intramyocardial injection of FGF-1 showed a 3-fold increase of capillary density mediated by the growth factor. Also, angiogenic growth factor injection intramyocardially as sole therapy for end-stage coronary disease showed an improvement of myocardial perfusion in the target areas as well as a reduction of symptoms and an increase in working capacity. Angiogenic therapy of the human myocardium introduces a new modality of treatment for coronary heart disease in terms of regulation of blood vessel growth. Beyond drug therapy, angioplasty and bypass surgery, this new approach may evolve into a fourth principle of treatment of atherosclerotic cardiovascular disease.
Delivery of the angiogenic agents: protein, gene and cell therapies.

1. In protein therapy, recombinant proteins are used directly to induce therapeutic effects. However, a major limitation of this approach is the very short half-life of exogenous proteins in target tissues, resulting in only transient therapeutic effects.

2. In contrast, gene therapy uses non-viral or viral vectors to carry a gene construct encoding a therapeutic protein into target tissues, where it is abundantly expressed by the target cells.

3. The idea of cell therapy in its present form is that transplanted cells function as protein factories with the capability of producing multiple endogenous growth factors, meaning that the transplanted cells will induce vascular growth mainly in a paracrine manner, rather than directly replacing damaged cells.
Pro-angiogenic therapy – facts

• Therapeutic angiogenesis with VEGF is a promising approach for the treatment of ischemic myocardium and peripheral skeletal muscles.

• Preclinical studies in large animals have clearly demonstrated safety and efficacy of VEGF gene therapy. However, first clinical trials with intravascular delivery of VEGF vector constructs have only resulted in limited benefits to the patients.

• In order to achieve better transfection efficiency and more targeted effects trials based on direct intramyocardial and intraskeletal muscle injections are performed.

• Phase I/II studies are currently ongoing to test safety, feasibility and efficacy of these improved approaches in patients with severe cardiovascular diseases.
VEGF therapy – first trials - small animal models

Positive results: adenoviral, AAV and lentiviral delivery

VEGF in serum
Local VEGF concentration
Blood flow in muscles
Number of blood vessels

Dulak et al., Eur Surgery 2002, 34: 105-110;
VEGF gene transfer increases number of capillaries in muscles

Ischemic leg after injection with control plasmid

(14 days after injection)

Ischemic leg after injection with VEGF165 plasmid

Dulak et al., Eur Surgery 2002, 34: 105-110;
VEGF gene transfer increases blood flow

Dulak et al., Eur Surgery 2002, 34: 105-110;
FGF4 and VEGF transfer restores blood flow in ischemic leg

Jazwa A et al., unpublished
Wound healing

Angiogenesis in tissue during wound healing

control

100 μm

60 hours after wounding

100 μm
Diabetic wound healing

Ochoa et al., Vascular 2007
Wound healing is delayed in diabetic mice

Grochot-Przeczek et al., PLoS ONE 2009
VEGF stimulates neovascularization and accelerates wound healing in diabetic mice

Jazwa et al., 2010
Why clinical trials are unsuccessful?

- inadequate therapeutic doses, insufficient duration of exposure, compromised delivery and poor vector transduction efficiency

- In addition, potential patient-related issues are proposed: defects in the response to angiogenic stimuli due to existing comorbidities, the use of other medications, circulating angiogenic inhibitors, lack of target receptor expression in target tissues, lack of viable muscle tissue required for a therapeutic response, and growth factor resistance in a chronically ischemic environment

- the lack of animal models that accurately recapitulate key features of the human disease.
Treatment of numerous diseases can be improved by anti-angiogenic therapy.
Tumor growth is dependent on angiogenesis.
Tumor growth is dependent on the blood vessels
Angiogenesis is necessary for tumor growth
Angiogenesis facilitates tumor growth and metastasis

Tumor vasculature

Tumor cells
Angiogenesis is dependent on the balance between pro- and anti-angiogenic mediators.
The Angiogenic Switch is necessary...

for Tumor Growth and Metastasis

Tumor is dormant 

Angiogenic switch

Somatic mutation  
Small avascular tumor

Tumor secretion of angiogenic factors stimulates angiogenesis

Rapid tumor growth and metastasis

Neovascularization:
• Allows rapid tumor growth by providing oxygen, nutrients, and waste removal
• Facilitates metastasis

The balance hypothesis for the angiogenic switch

Hanahan & Folkman, 1996
Blood vessels in tumors are different than in healthy tissue.
Tumors are hypoxic

Hypoxia – one of the strongest inducers of VEGF expression

Half-life of endogenous VEGF mRNA is about 65 min
stability increases ~ 3 times in hypoxia
A new form of cancer treatment using drugs called 'angiogenesis inhibitors' that specifically stop new blood vessel growth and starve a tumor by cutting off its blood supply.
The influence of angiogenesis inhibition on the tumor growth

- Tumor without treatment
  - Tumor increases and metastases

- Tumor treated with antiangiogenic therapy
  - Tumor decreases
Various strategies to inhibit VEGF signaling

Ferrara and Kerbel, Nature 2005
What is the mechanisms of actions of anti-angiogenic drugs?
Normalisation of blood vessels as the mechanisms of action of anti-angiogenic agents

normal  tumor

Jain, Science 2004
VEGF inhibition dramatically affects vessel development

Before VEGF inhibition
Mature and stable

After VEGF inhibition
Disorganised and hyperpermeable

VEGF is over-expressed in a variety of tumors

Inhibitors of angiogenesis

Timeline | Discovery of angiogenesis inhibitors

- Angiostatic steroids
  - Interferon-α/β
  - Tetrahydrocortisol
- Platelet factor 4
  - Protamine
  - TNP-470
- Angiostatin
- Thalidomide
- Endostatin
- Cleaved anti-thrombin III
- 3-amino thalidomide
- DBP-MAF
- Caplostatin


Synthetic angiogenesis inhibitors (orange keyline) and endogenous angiogenesis inhibitors that were identified in the Folkman laboratory are depicted above the timeline. Examples of additional endogenous angiogenesis inhibitors discovered in other laboratories are depicted below the timeline. The first drugs with antiangiogenic activity were approved in 2003 (TABLE 2). DBP-MAF, vitamin-D-binding protein–macrophage-activating factor; EFC-XV, endostatin-like fragment from type XV collagen; PEDF, pigment epithelium–derived factor (also known as SERPINF1); PEX, haemopexin C domain autolytic fragment of matrix metalloproteinase 2; sFLT1, soluble fms-related tyrosine kinase 1; TIMP, tissue inhibitors of matrix metalloproteinase.

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Proteins or fragments of proteins that are formed in the body, which subsequently can inhibit the formation of blood vessels by disrupting the angiogenic process.

They are:
- present in the circulation
- sequestered in the ECM surrounding cells
### List of Angiogenesis Inhibitors in the Body

<table>
<thead>
<tr>
<th>Angiogenesis Inhibitor</th>
<th>Related Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiostatin (plasminogen fragment)</td>
<td>Metalloproteinase inhibitors (TIMPs)</td>
</tr>
<tr>
<td>Anti-angiogenic antithrombin III (aaATIII)</td>
<td>Pigment epithelial-derived factor (PEDF)</td>
</tr>
<tr>
<td>Canstatin</td>
<td>Placental ribonuclease inhibitor</td>
</tr>
<tr>
<td>Cartilage-derived inhibitor (CDI)</td>
<td>Plasminogen activator inhibitor</td>
</tr>
<tr>
<td>CD59 complement fragment</td>
<td>Platelet factor-4 (PF4)</td>
</tr>
<tr>
<td>Endostatin (collagen XVIII fragment)</td>
<td>Prolactin 16kD fragment</td>
</tr>
<tr>
<td>Fibronectin fragment</td>
<td>Proliferin-related protein</td>
</tr>
<tr>
<td>Gro-beta</td>
<td>Retinoids</td>
</tr>
<tr>
<td>Heparinases</td>
<td>Heparin hexasaccharide fragment</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (hCG)</td>
<td>Thrombospondin-1</td>
</tr>
<tr>
<td>Interferon alpha/beta/gamma</td>
<td>Transforming growth factor-beta</td>
</tr>
<tr>
<td>Interferon inducible protein (IP-10)</td>
<td>Tumistatin</td>
</tr>
<tr>
<td>Interleukin-12 (IL-12)</td>
<td>Vasculostatin</td>
</tr>
</tbody>
</table>
### Angiogenesis inhibitors

<table>
<thead>
<tr>
<th>Precursors</th>
<th>Antiangiogenic Fragments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibronectin</td>
<td>H$_2$N [Heparin-binding fragment] COOH</td>
</tr>
<tr>
<td>Prolactin</td>
<td>H$_2$N [16-kD fragment] COOH</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>H$_2$N [Angiostatin (Kringle 1-3, 4)] COOH</td>
</tr>
<tr>
<td>PF-4</td>
<td>H$_2$N [A truncated PF-4] COOH</td>
</tr>
<tr>
<td>Collagen XVIII</td>
<td>H$_2$N [Endostatin] COOH</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>H$_2$N [Kringel 5] COOH</td>
</tr>
<tr>
<td>MMP-2</td>
<td>H$_2$N [PEX] COOH</td>
</tr>
</tbody>
</table>

- **MMP-2**
  - H$_2$N \[Vasostatin\] COOH
- **Calreticulin**
  - H$_2$N \[Kringle 1-5\] COOH
- **Plasminogen**
  - H$_2$N \[aaA\] COOH
- **Antithrombin**
  - H$_2$N \[Restin\] COOH
- **Collagen XV**
  - H$_2$N \[Arresten (NC1 domain)\] COOH
- **Collagen IVα1**
  - H$_2$N \[Canstatin (NC1 domain)\] COOH
- **Collagen IVα2**
  - H$_2$N \[Tumstatin (NC1 domain)\] COOH
- **Collagen IVα3**
  - H$_2$N \[\] COOH
Endostatin

- It was first discovered in 1995 in Dr. Folkman’s lab
- Phase I clinical studies began in 1999
- A naturally-occurring 20-kDa C-terminal fragment derived from type XVIII collagen.
- Interfere with the pro-angiogenic action of growth factors such as basic fibroblast growth factor (bFGF/FGF-2) and vascular endothelial growth factor (VEGF)
Endostatin: An Endogenous Inhibitor of Angiogenesis and Tumor Growth

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Cambridge, Massachusetts 02139
Endostatin treated Lewis Lung Carcinoma
Dose-dependent tumor inhibition

- Graph showing tumor volume over treatment days for saline and endostatin treated groups.
- Images of mice representing endostatin-treated and saline-treated conditions.

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Bevacizumab – Avastin

How Avastin Starves a Tumor

Tumors need blood, and they have a devious way to get it:

1. They secrete a protein called VEGF that docks with receptors in nearby blood vessels, stimulating the growth of new blood vessels.

Genentech foils this plot with Avastin, a drug that binds with VEGF and prevents that protein from attaching to receptors. New blood vessels don’t form, and the tumor starves.
Avastin

- Avastin is a humanized monoclonal antibody (mAb) that targets vascular endothelial growth factor (VEGF)
- Causes regression of tumor vasculature
- Reduces intra-tumor pressure, thereby improving the delivery of cytotoxic agents to the tumor
- Also inhibits new tumor blood vessel formation, restricting tumor growth.

- The first anti-angiogenic agent with demonstrated anticancer benefit in phase III trials.
.....despite its price, which can reach $100,000 a year, Avastin has become one of the most popular cancer drugs in the world, with sales last year of about $3.5 billion, $2.3 billion of that in the United States.
- Recombinant humanised monoclonal anti-VEGF antibody 93% human, 7% murine
- Recognizes all major isoforms of human VEGF
- RhuMAb VEGF binding is restricted to human
- Bevacizumab binds VEGF, preventing interaction with its receptors and activation of downstream signalling pathways
- This ultimately leads to vascular regression, leaving the tumor dormant
Inhibition of experimental human tumor growth by anti-VEGF antibody (precursor of Avastin)

**Fig. 35.3.** Neutralizing antibody to human VEGF inhibits growth of experimental hepatic metastases in the athymic mouse. One day after splenic-portal tumor cell inoculation (2 million HM7 cells), twice-weekly antibody injections were begun, and animals were killed after 4 weeks. Livers of representative animals are shown.
### Avastin in clinical development: overview

#### Phase I
- Combined with chemotherapy in metastatic cancers 3mg/kg every week (n=12) Margolin K, et al. 2001

#### Phase II
- Combined with 5-FU/LV in previously untreated mCRC 5 or 10mg/kg every 2 weeks (n=104) Kabbinavar F, et al. 2003
- Combined with 5-FU/LV in previously untreated mCRC 5mg/kg every 2 weeks (n=209) Kabbinavar F, et al. 2005
- Combined with CP in previously untreated NSCLC (n=99) Johnson DH, et al. 2004
- Monotherapy in previously treated RCC 3 or 10mg/kg every 2 weeks (n=116) Yang JC, et al. 2003
- Monotherapy in previously treated MBC 3, 10 or 20mg/kg every 2 weeks (n=75) Cobleigh MA, et al. 2003
- Combined with gemcitabine in unresectable PC 10mg/kg every 2 weeks Kindler HL, et al. 2004

#### Phase III
- Combined with IFL in previously untreated mCRC 5mg/kg every 2 weeks (n=813) Hurwitz H, et al. 2004
- Combined with either FOLFOX4 or XELOX in previously untreated mCRC (n=1,920)
- **AVANT**: combined with FOLFOX4 or XELOX in stage II/III colon cancer 5mg/kg every 2 weeks or 7.5mg/kg every 3 weeks (n=3,450)
- **AVAIL**: combined with CG in previously untreated stage IIIb, IV or recurrent NSCLC 7.5 or 15mg/kg every 3 weeks (n=830)
- **AVOREN**: combined with IFN-α2a in metastatic RCC 10mg/kg every 2 weeks (n=638)
- Combined with Xeloda® in previously treated MBC 15mg/kg every 3 weeks (n=462) Miller KD, et al. 2005
- Combined with Tarceva™ + gemcitabine in previously untreated PC 5mg/kg every 2 weeks (n=600)

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5-FU = 5-fluorouracil; LV = leucovorin; mCRC = metastatic colorectal cancer; FOLFOX = 5-FU/LV + oxaliplatin; XELOX = Xeloda + oxaliplatin; IFN = interferon; CP = carboplatin/paclitaxel; CG = cisplatin/gemcitabine; RCC = renal cell cancer; MBC = metastatic breast cancer; IFL = irinotecan/5-fluorouracil/leucovorin; NSCLC = non-small cell lung cancer; PC = pancreatic cancer
A Randomized Trial of Bevacizumab, 
an Anti–Vascular Endothelial Growth Factor Antibody, 
for Metastatic Renal Cancer

James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D., 
Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D., 
and Steven A. Rosenberg, M.D., Ph.D.
Increase in survival of patients with renal cell cancer treated with Avastin

Fever, hypertension, proteinuria – adverse effects
The FDA approved Avastin in February 2004 for use in combination with intravenous 5-Fluorouracil (5-FU)-based chemotherapy as a treatment for patients with first-line metastatic cancer of the colon or rectum cancer. In June 2006, the FDA approved Avastin for use in combination with intravenous 5-FU-based chemotherapy for patients with second-line metastatic cancer of the colon or rectum. In October 2006, the FDA approved Avastin in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

So nowadays it is approved for:

- **Metastatic colorectal cancer** for first- or second-line treatment in combination with intravenous 5-fluorouracil-based chemotherapy.
- **Advanced nonsquamous non–small cell lung cancer** in combination with carboplatin and paclitaxel in
- **Metastatic kidney cancer** (with interferon alfa)
- **Glioblastoma** when taken alone in adult patients whose cancer has progressed after prior treatment.
What is AMD?

- Age-related macular degeneration (AMD) is defined as the loss of macular function from the degenerative changes of aging.

- The macula is the most important part of the retina responsible for sharp, central vision.

- AMD is divided specifically into two distinct types: the less severe or “dry” form, and the more severe and debilitating “wet” form.

- The root causes of AMD are still unknown.
Age-related macular degeneration (AMD)
Age-related macular degeneration (AMD)

- Normal Macula
- Dry AMD: Drusen formation under the Macula
- Wet AMD: Macula with abnormal blood vessels
• **Lucentis™ (ranibizumab)** — The FDA approved Lucentis in June 2006 for the treatment of wet AMD.
  - Lucentis (ranibizumab) is a humanized anti-VEGF antibody fragment that inhibits VEGF activity by competitively binding with VEGF.
  - A two-year study showed that **95 percent** of people with wet AMD who received monthly injections of Lucentis experienced no significant loss in visual acuity. Genentech also reported moderate visual **improvement** in 24.8 percent of participants treated with a 0.3 mg dose of Lucentis and 33.8 percent of participants treated with a 0.5 mg dose.
Avastin for treatment an eye diseases

- Avastin is a cancer drug marketed by Roche (Genentech), but some pharmacies repackage Avastin into smaller units to treat an eye condition called macular degeneration. Roche has long warned against the unapproved use of Avastin in the eyes, and the company markets a similar drug called Lucentis that was specifically designed and approved for use in the eyes. However, some eye doctors use Avastin because a much smaller dose is needed compared with that required for a cancer patient. An injection of repacked Avastin costs about $50, while an injection of Lucentis tops $1,000.

- 20 Mar 2013 - **FDA Warns of Eye Infections From Unapproved Avastin** *(The Wall Street Journal)*

- It is not the first time that repacked Avastin syringes have been associated with eye infections. In 2011, the FDA warned about a cluster of serious eye infections in Florida linked to Avastin syringes made by a pharmacy in that state.
The aptamer-based therapeutic, Macugen, is derived from a modified 2′fluoro pyrimidine RNA inhibitor to VEGF and is now being used to treat the wet form of age-related macular degeneration.

**VEGF** binds to its receptors on the cell surface and stimulates angiogenesis.

Macugen binds to VEGF. This prevents VEGF from binding to the receptors on the cell surface. As a result, angiogenesis is not stimulated.

The molecular formula for pegaptanib sodium is

\[ C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28} \text{[C}_2\text{H}_4\text{O}]_n \]

(where n is approximately 900)
and the molecular weight is approximately 50 kilodaltons.
Macugen was demonstrated to be effective in prevention of vision loss in two large clinical trials in patients with AMD.
Macugen – anti-angiogenic drug for treatment of AMD

Inhibition of VEGF binding to its receptors
Macugen effects in AMD

Early and Sustained Treatment Benefit

1 Year Data 0.3 mg

Mean vision change (letters)

Weeks
Macugen effects in AMD

Macugen Treatment Effect Continues for 2 Years

- 2 Years Treatment (N=133)
- Usual Care (N=107)

Mean change in vision (letters)

Week

Year One

Year Two

-9.4 letters

45% Benefit
P<0.01

-17.0 letters

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### Tyrosine kinase inhibitors

**Table 2 - Anti-VEGF therapeutic agents currently in development for breast cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism(s) of action</th>
<th>Molecular target(s)</th>
<th>Stage of clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Anti-VEGF antibody</td>
<td>VEGF ligand</td>
<td>Approved</td>
</tr>
<tr>
<td>Sorafenib (BAY 43-9006)</td>
<td>Tyrosine kinase inhibitor</td>
<td>Raf-1, VEGF receptors-2 and -3, PDGFR-β, Flt-3, c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sunitinib (SU11248)</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-1, -2 and -3, Flt-3, PDGFR-α, PDGFR-β, c-Kit</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Vatalanib (PTK/ZK)</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-1, -2 and -3, PDGFR-β, c-Kit, c-Fms</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vandetanib (ZD6474)</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-2 and -3, EGFR</td>
<td>Phase II</td>
</tr>
<tr>
<td>Motesanib (AMG-706)</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-1, -2 and -3, PDGFR, c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-1 and -2, PDGFR-β, and c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Tyrosine kinase inhibitor</td>
<td>VEGF receptors-1, -2 and -3, PDGFR, c-kit</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor.

Marty et al. 2008
Take-home messages

- Physiological angiogenesis in adults is restricted, however disturbances of this process is a hallmark of many diseases

- One of the strategy to treat tumor/AMD is the anti-angiogenic therapy

- Angiogenesis inhibitors specifically halt new blood vessel growth and starve a tumor by cutting off its blood supply

- Angiogenesis inhibitors prevent VEGF binding to the receptors on the surface of the endothelial cells

- Many anti-angiogenic factors are in the Phase II/III of clinical trails

- On the other hand, proangiogenic therapy could be used as a treatment strategy for cardiovascular disorders