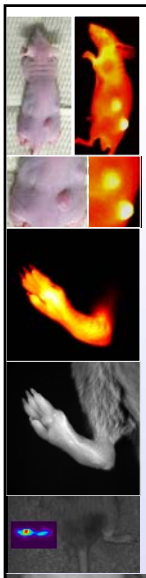
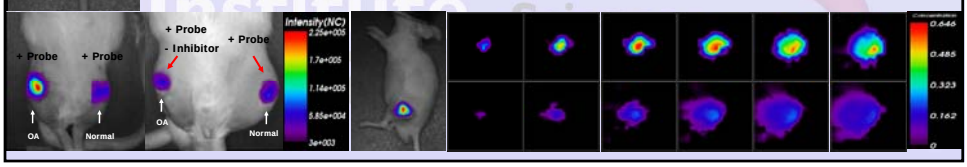


Optical Bio-imaging with Polymer Nanoparticles

Ick Chan Kwon, Ph.D
Biomedical Research Center
Korea Institute of Sci. & Tech.

2008. 4. 17.
US-Korea Nano Forum

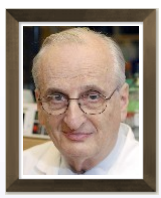


TIME

Wednesday, Jan. 16, 2008

Judah Folkman, Cancer Pioneer

By Alice Park



HarvardScience

M. Judah Folkman, biomedical pioneer, dies at 74

Surgeon, research scientist, teacher and mentor, created field of angiogenesis

The New York Times

January 16, 2008

Judah Folkman, Researcher, Dies at 74

Children's Hospital Boston

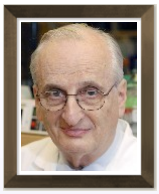
Children's mourns the death of Dr. Judah Folkman

Clinical Cancer Research

In Memoriam

Judah Folkman, MD (1933–2008)

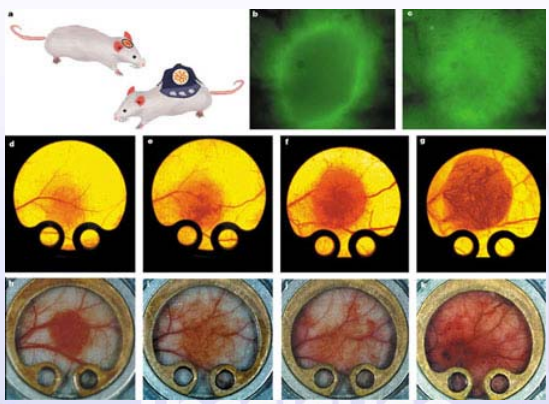
The Editors and Staff of *Clinical Cancer Research* join with the entire cancer research community in mourning the loss of one of the brightest stars in our universe, Judah Folkman. Dr. Folkman was a long-time member and valued friend of the American Association for Cancer Research and a frequent contributor to AACR journals. His most recent contribution appears in this issue (Lee T-Y, Tjin Tham Sjin RM, Movahedi S, Ahmed B, Pravda EA, Lo K-M, Gillies SD, Folkman J, Javaherian K. Linking antibody Fc domain to endostatin significantly improves endostatin half-life and efficacy. Clin Cancer Res 2008;14:1487-93).



"On January 14, Dr. Judah Folkman, **founder of the field of angiogenesis**, died unexpectedly in Denver, Colo., while en route to Vancouver for one of the thousands of lectures that he gave to scientists around the world. A visionary and scientific pioneer, Dr. Folkman was founder and director of the Vascular Biology Program at Children's Hospital Boston, and a professor of Pediatric Surgery and Cell Biology at Harvard Medical School." *from Bess Andrews, Childrens Hospital*

"When Dr. Folkman first proposed, in the 1970s, that a cancer could be kept in check by cutting off its blood supply, **he faced skepticism from a scientific community** that simply wasn't ready for his ideas. But he persevered, even when there were setbacks, and today, more than **1,000 laboratories worldwide** are engaged in the study of angiogenesis, the field he founded. As a result of Dr. Folkman's vision and resilience, more than **10 new cancer drugs are currently on the market**, and more than **1.2 million patients worldwide are now receiving anti-angiogenic therapy."** *from Robert Cook, Harvard Science Correspondent*

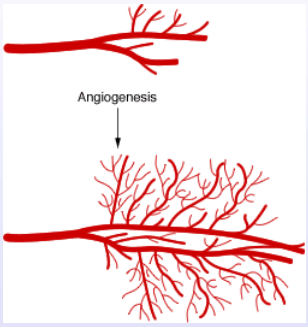
What is Tumoral Angiogenesis



- **Pathological angiogenesis is a hallmark of cancer.**
- **Without blood vessels, tumors can not grow beyond a critical size (~ 5 mm in diameter) due to the lack of oxygen and nutrients for their survival.**

Carmeliet et al. Nature 2000;407:249-257

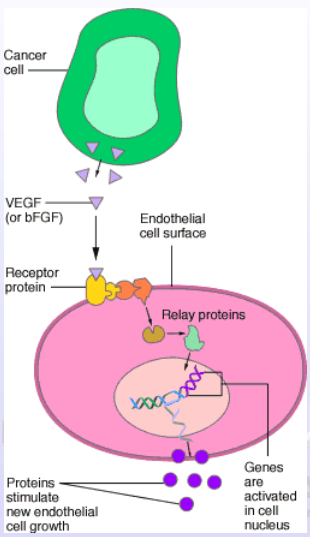
When Tumoral Angiogenesis Starts



Beyond the critical **volume of 2 cubic millimeters**, oxygen and nutrients have difficulty diffusing to the cells in the center of the tumor, causing a state of cellular **hypoxia** that marks the **onset of tumoral angiogenesis**.

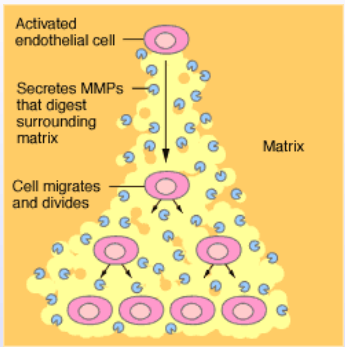
http://www.angioworld.com

The Angiogenesis Signaling Cascade



VEGF and **bFGF** are first synthesized inside tumor cells and then secreted into the surrounding tissue. When they encounter endothelial cells, they bind to specific proteins, called **receptors**, sitting on the outer surface of the cells. The binding of either VEGF or bFGF to its appropriate receptor activates a series of relay proteins that transmits a signal into the nucleus of the endothelial cells. The nuclear signal ultimately prompts a group of genes to **make products needed for new endothelial cell growth.**

Endothelial Cell Activation

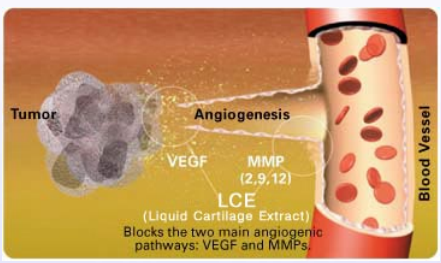


The activation of endothelial cells by VEGF or bFGF sets in motion a series of steps toward the creation of new blood vessels.

First, the activated endothelial cells produce matrix ***metalloproteinases*** *(MMPs)*. The **MMPs** break down the *extracellular matrix*—support material that fills the spaces between cells and is made of proteins and polysaccharides.

Breakdown of this matrix permits the migration of endothelial cells. As they migrate into the surrounding tissues, activated endothelial cells begin to divide.

The Angiogenic Sequence



• A cell activated by a **lack of oxygen** releases angiogenic molecules that **attract inflammatory and endothelial cells** and promote their proliferation.
• During their migration, inflammatory cells also secrete molecules that intensify the angiogenic stimuli.
• The endothelial cells that form the blood vessels respond to the angiogenic call by differentiating and by secreting matrix **metalloproteases** (MMP), which digest the blood-vessel walls to enable them to escape and migrate toward the site of the angiogenic stimuli.

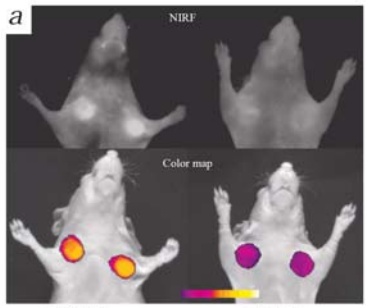
http://www.angioworld.com

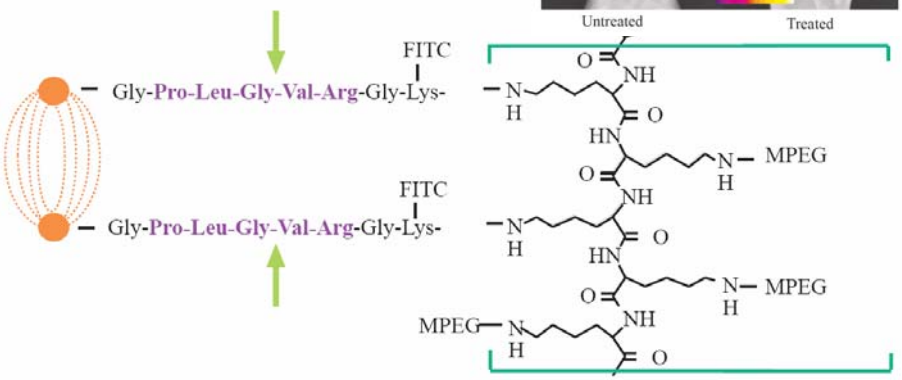
NATURE MEDICINE • VOLUME 7 • NUMBER 6 • JUNE 2001

In vivo molecular target assessment of matrix metalloproteinase inhibition

CHRISTOPH BREMER, CHING-HSUAN TUNG & RALPH WEISSLEDER

Center for Molecular Imaging Research, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts, USA
Correspondence should be addressed to C-H.T. or R.W.:
email: tung@helix.mgh.harvard.edu or weissleder@helix.mgh.harvard.edu





Permeablility of Angiogenic Vessel

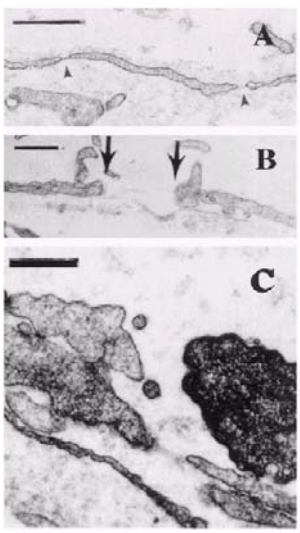


Table 3. Pore cutoff size vs. effective permeability to BSA

Tumor cell line (*n*)	Pore cutoff size, nm	Permeability ($\times 10^7$ cm/sec)
HCa-I (5)*	380–550	2.06 ± 1.44 (1.60–3.99)
LS174T (6)*†	400–600	1.24 ± 0.45 (0.56–1.67)
ST-8 (5)*	550–780	3.73 ± 3.34 (1.67–9.28)
MCa IV (8)*	1,200–2,000	2.5 ± 1.5 (1.2–5.1)
MCa IV (6)§	380–550	1.9 ± 0.5 (1.3–2.5)
U87 (6)‡	7–100	3.8 ± 1.2 (2.4–5.0)

n, number of animals.
*Grown in dorsal chamber.
†Yuan *et al.* (16).
‡Grown in cranial window.
§Yuan *et al.* (12).

Hobbs SK et. al. Proc Natl Acad Sci USA 1998;95:4607-4612.

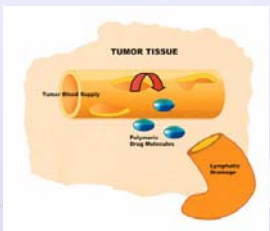
EPR effect
(Enhanced Permeability And Retention)

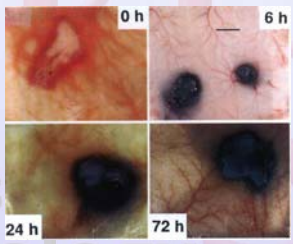
[CANCER RESEARCH 46, 6387–6392, December 1986]

A New Concept for Macromolecular Therapeutics in Cancer Chemotherapy: Mechanism of Tumoritropic Accumulation of Proteins and the Antitumor Agent Smancs[1]

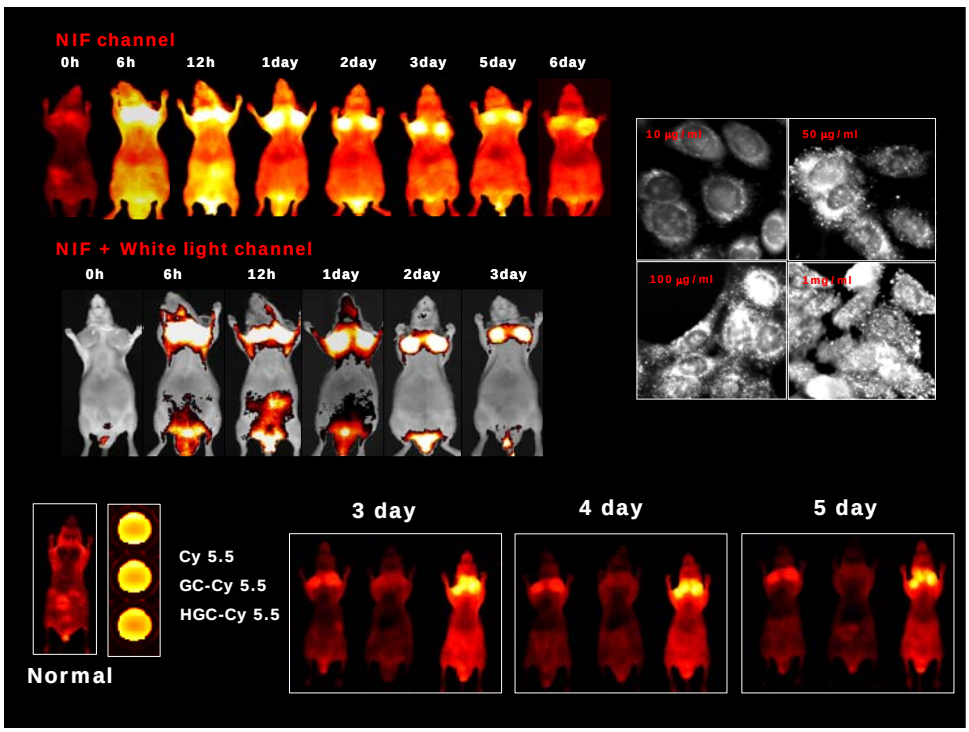
Yasuhiro Matsumura and Hiroshi Maeda[2]

Department of Microbiology, Kumamoto University Medical School, Kumamoto 860, Japan

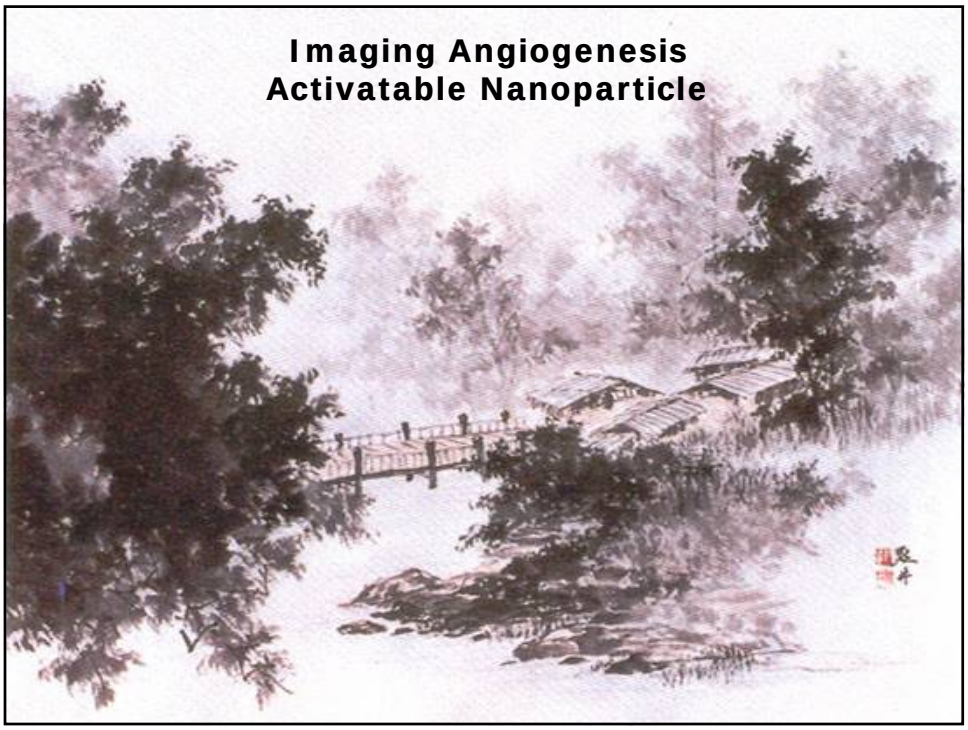




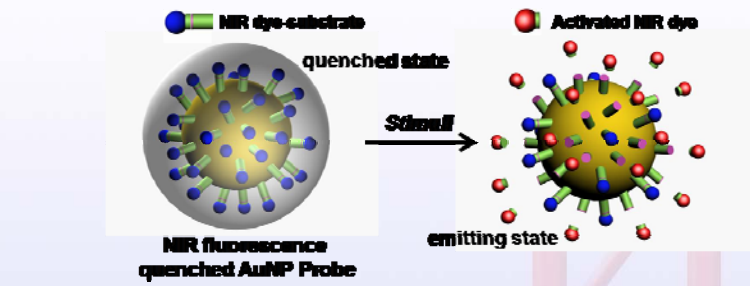
Accumulation of Evans blue-albumin complex in tumor tissue and normal skin in tumor-bearing mice. Tumor S-180 was injected into the skin.

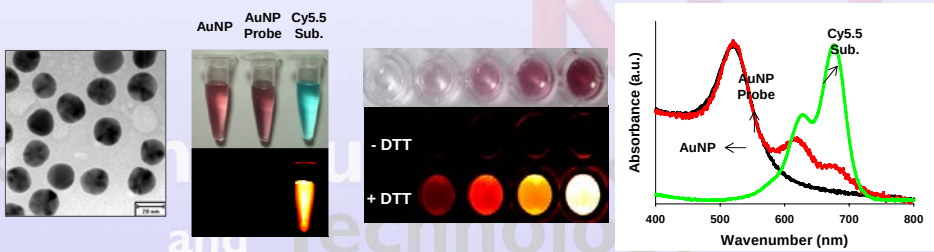


Imaging Angiogenesis Activatable Nanoparticle



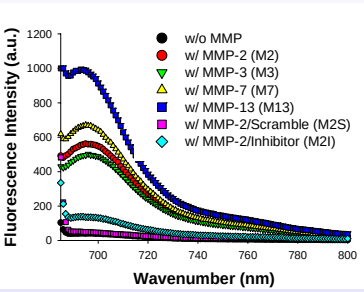
Gold Nanoparticle for MMP Activation

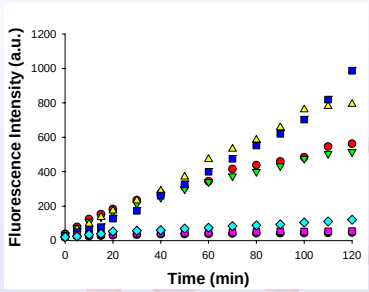


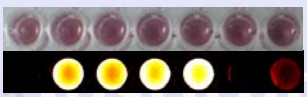


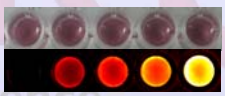
In press, *Angew Chem Intern Ed* (2008)

Gold Nanoparticle for MMP Activation



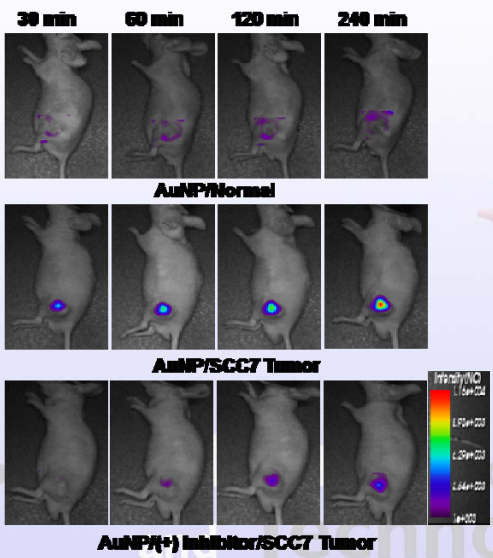


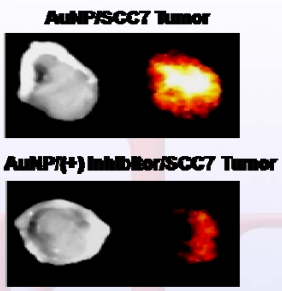


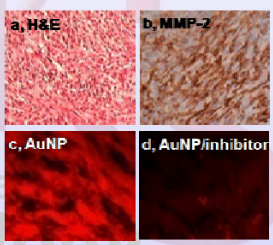


In press, *Angew Chem Intern Ed* (2008)

Gold NP for MMP-2 positive Tumor Imaging

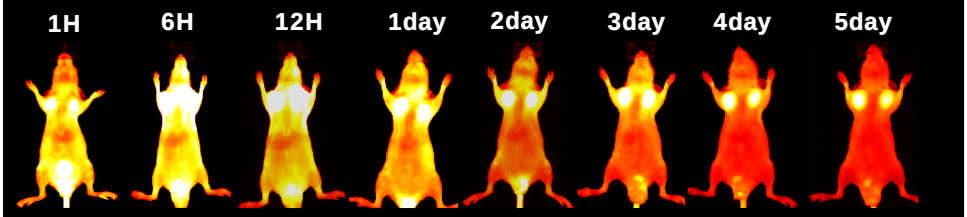


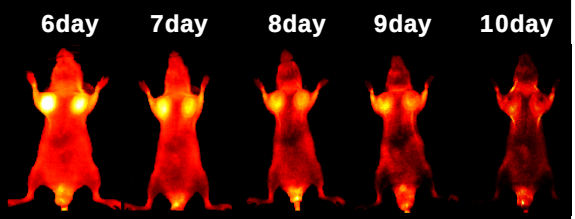




In press, *Angew Chem Intern Ed* (2008)

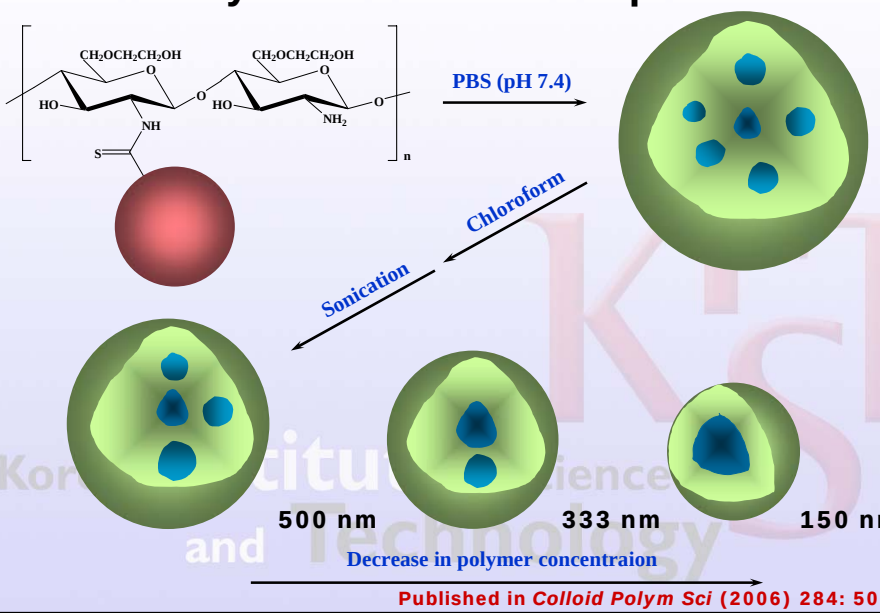
Long Circulating Self-assembled Glycol Chitosan Nanoparticle





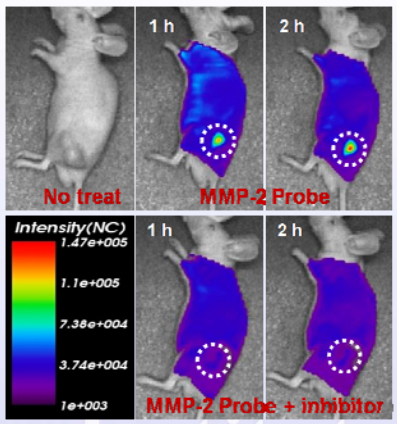
• SCC-7cell (3x106 cell), tail vein injection of HGC-Cy5.5 (5mg/kg)

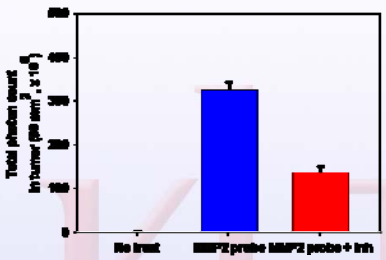
Self-assembled Glycol Chitosan Nanoparticle

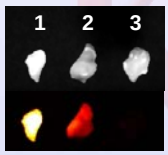


Published in *Colloid Polym Sci* (2006) 284: 506–512

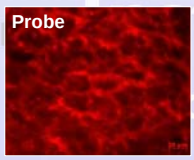
Polymer NP for MMP-2 positive Tumor Imaging

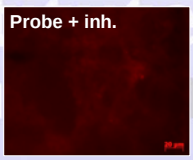


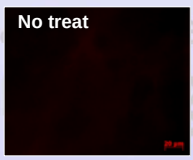




1: MMP-2 probe
2: MMP-2 probe + inh.
3: No treat







Molecular Imaging

- Visualization of biological process
- Molecular events at
  molecular and celluar level
- In living systems
- Using remote imaging detectors

"The characterization and measurement of biological processes in living animals, model systems, and humans at the cellular and molecular level by using remote imaging detectors"

Lucker GD and Piwnica-Worms D *Acad. Radiol.* 2001;8;4

Reduction in Tumor Size

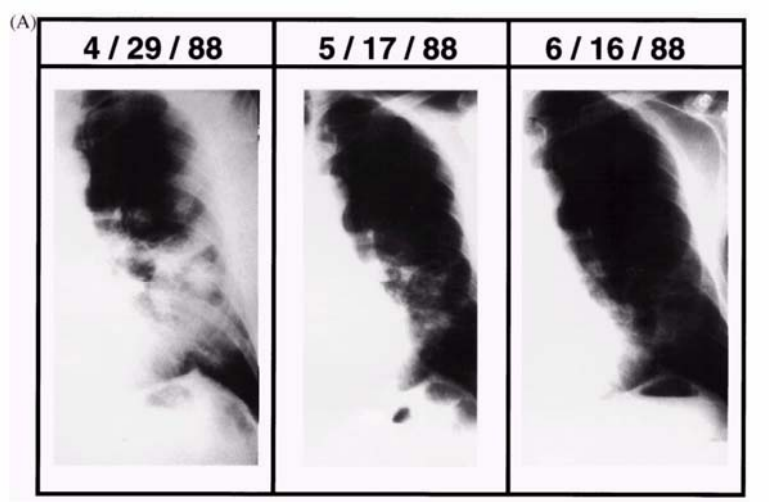
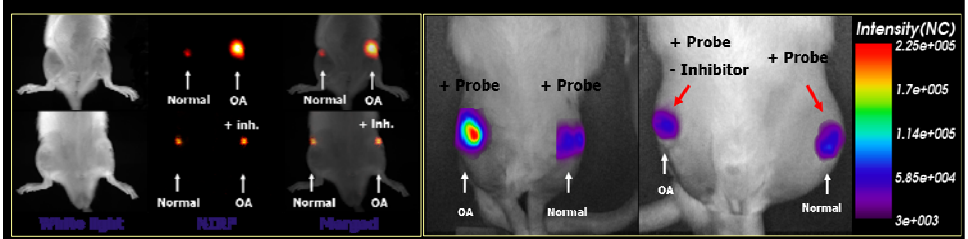
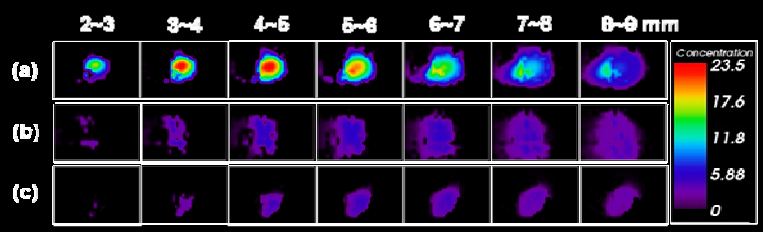


Fig. 5. (A) Chest radiographs from a patient with adenocarcinoma of the lung treated with SMANCS/Lpd via the bronchial artery three times and with aqueous intravenous SMANCS ×3/week during several weeks. A remarkable reduction in tumor size is seen. (B,C) CT scans and (D) chest X-ray images from different lung cancer patients. Please note tumor size reduction between the date given.

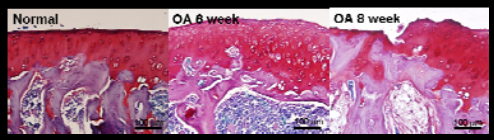
MMP-13 Specific Nanoprobe for OA

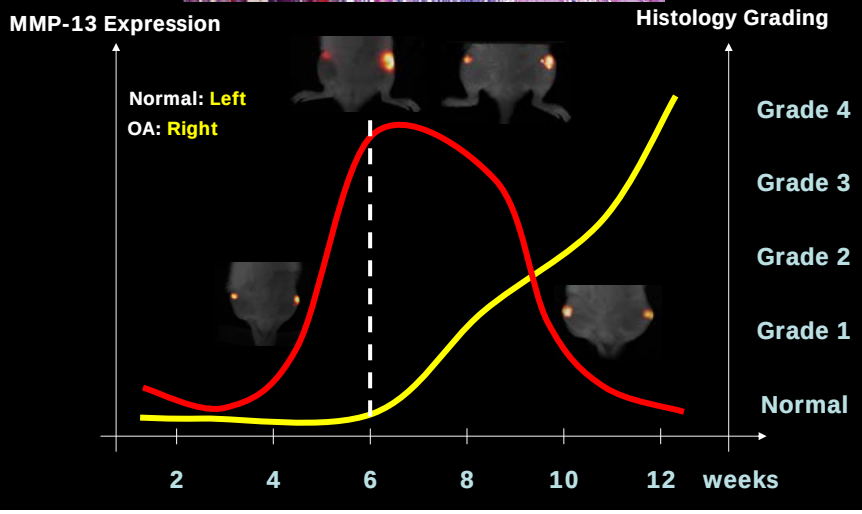




(a) OA + Probe, (b) Normal + Probe, (c) OA + Probe + Inh.

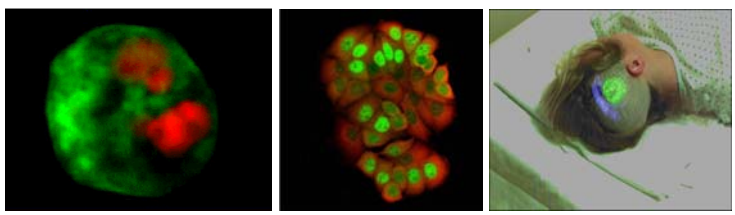
Histology vs. MMP-13 Detection

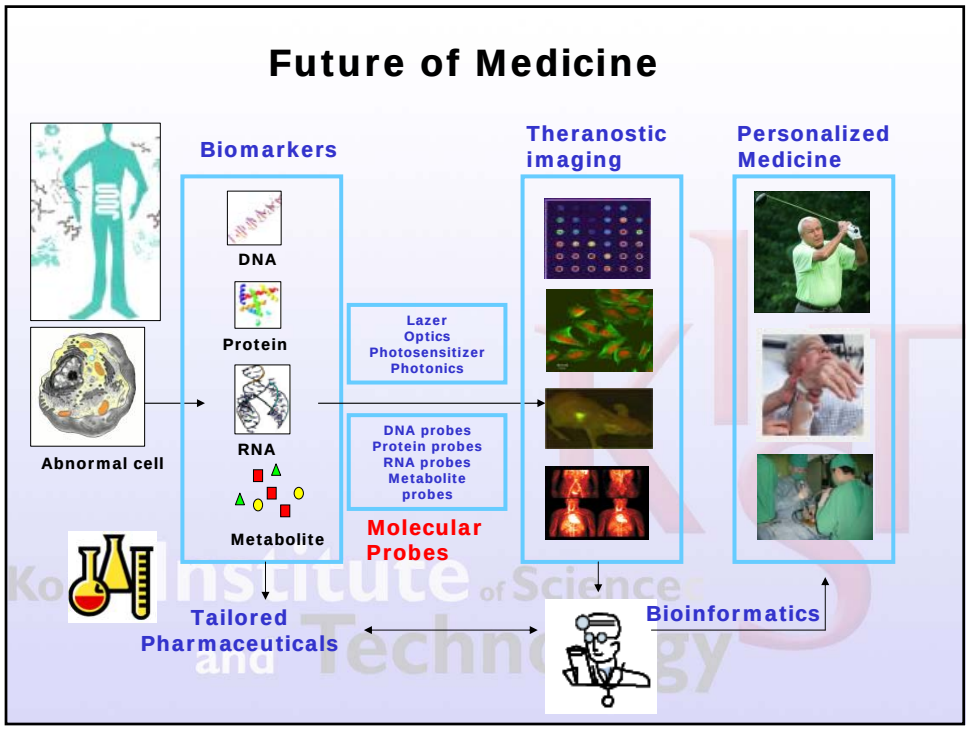




Theragnosis

Diagnosis, Molecular Imaging
Targeted Therapy
Evaluation of Therapeutic Effect




Future of Medicine
Biomarkers
Theranostic imaging
Personalized Medicine
DNA
Protein
RNA
Metabolite
Abnormal cell
Lazer
Optics
Photosensitizer
Photonics
DNA probes
Protein probes
RNA probes
Metabolite probes
Molecular Probes
Tailored Pharmaceuticals
Bioinformatics