National Institutes of Health Clinical Center

How to Become a Molecular Imager

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Greatest Engineering Achievements of the 20th Century

1. Electrification
2. Automobile
3. Airplane
4. Water Supply and Distribution
5. Electronics
6. Radio and Television
7. Agricultural Mechanization
8. Computers
9. Telephone
10. Air Conditioning and Refrigeration
11. Highways
12. Spacecraft
13. Internet
14. Imaging
15. Household Appliances
16. Health Technologies
17. Petroleum and Petrochemical Technologies
18. Laser and Fiber Optics
19. Nuclear Technologies
20. High-performance Materials

The Nobel Prize in Physiology or Medicine 2003

“for their discoveries concerning magnetic resonance imaging.”

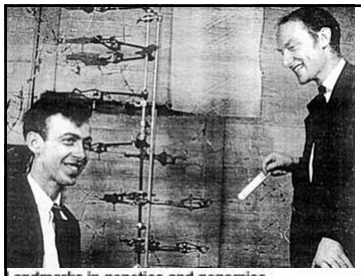
Paul C. Lauterbur

University of Illinois
Urbana, IL, USA

Sir Peter Mansfield

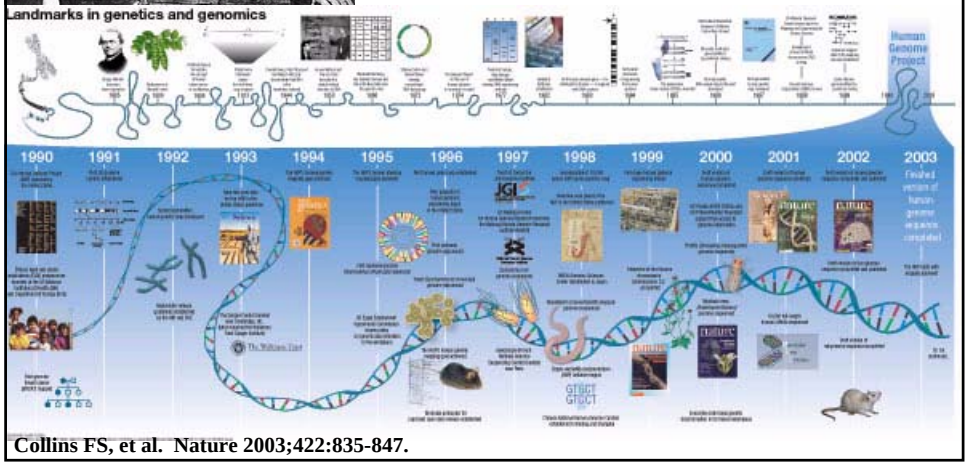
University of Nottingham
Nottingham, UK

www.Nobel.se/medicine/laureates/2003



Deciphering the Secret of Life

Double Helix at 50



Collins FS, et al. Nature 2003;422:835-847.

Learning Objectives

- To learn why radiologists should care about molecular imaging.
- To learn the basic process of becoming a molecular imager.
- To learn how imaging is a key component in the world of “molecular” and “personalized” medicine.

Introduction

- **Why should clinical radiologists learn about “Molecular Imaging” now?**
- **Assumption: It will take years and multi-million dollars to develop new imaging probes and equipment. By the time “Molecular Imaging” is clinically applicable, most radiologists practicing today will be financially independent and happily retired.**

What makes medical imaging clinically useful?

- **To be of clinical value a diagnostic test needs to provide useful information that would affect therapeutic decisions.**
- **A diagnostic test decoupled from therapeutic decisions is not clinically useful.**

What changes can we expect in therapeutics?

- **“Molecular Medicine”**
- **“Genomic Medicine”**
- **“Personalized Medicine”**

Molecular Medicine: The Herceptin Example

- **Herceptin™** (Genentech, Inc.) approve in 1998 for treatment of **HER2 positive** metastatic breast cancer.
- Molecular signature of diseased tissue is critical in patient selection of treatment.

Molecular Medicine: The Gleevec Example

- **Gleevec™** (Novartis, Inc.) approved in 2001 and is designed to specifically block an abnormal protein Bcr-Abl tyrosine kinase which is found in chronic myeloid leukemia (**CML**) cells with a **Bcr-Abl translocation**.

•Breakthrough cancer treatment Avastin receives first approval in the US

•*First anti-angiogenesis treatment approved for cancer*

•Roche today announced that Genentech has received approval from the US Food and Drug Administration (FDA) for Avastin (bevacizumab, rhuMAb-VEGF), an innovative new cancer drug, to be used with intravenous 5-Fluorouracil-based chemotherapy as treatment for patients with previously untreated metastatic cancer of the colon or rectum (first-line treatment). Genentech will market Avastin in the US and expects it to be shipped within three days.

•The US approval is based on data from a pivotal Phase III study in over 900 metastatic colorectal cancer patients which demonstrated that patients treated with Avastin plus IFL chemotherapy had a median survival advantage close to five months, compared to patients on chemotherapy alone (20.3 months versus 15.6 months). This represents the largest improvement in survival time reported in a Phase III clinical study attributable to the addition of a single targeted therapy to conventional chemotherapy.

http://www.eurekalert.org/pub_releases/2004-02/rc-bct022704.php

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

CONCLUSIONS

The recurrence score has been validated as quantifying the likelihood of distant recurrence in tamoxifen-treated patients with node-negative, estrogen-receptor–positive breast cancer.

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

Clinical Definition of a "Molecular Imager"

- **A practitioner of medical imaging in the era of "Molecular Medicine".**
- **The definition is designed to be all inclusive so that we don't get tunnel vision.**

Stages of Development of a "Molecular Imager"

Stage 1	**See morphology think molecular biology**
Stage 2	**Combine imaging & molecular diagnostics information**
Stage 3	**Obtain molecular information using imaging**
Stage 4	**Personalizing Rx with combined imaging & Rx**

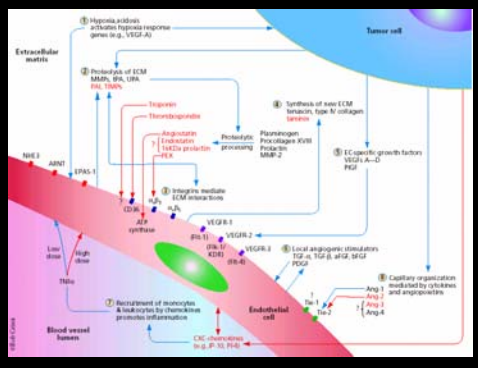
Stage 1. See morphology think molecular biology

- **Biomedical information is widely available to everyone. The onus is on medical practitioners to know more about new developments in biomedicine than our patients.**
- **To many radiologists, molecular biology is easier to learn than MR physics.**
- **Once there is understanding of the molecular basis of the disease processes, it is not difficult to use it in our daily practice.**

Arterial Phase MRI

Venous Phase MRI

DDx: HCC, hypervascular liver metastasis: thyroid, melanoma, breast, renal, neuroendocrine (carcinoid, pancreatic islet cell), and sarcoma metastasis



Vicki Brower. Tumor angiogenesis-new drugs on the block. Nature Biotechnology 1999; 17:963-968.

Stage 2. Combine imaging & molecular diagnostics information

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2003 VOL. 349 NO. 17

Prognostic Value of Myeloperoxidase in Patients with Chest Pain

Marie-Luise Brennan, Ph.D., Marc S. Penn, M.D., Ph.D., Frederick Van Lente, Ph.D., Vijay Nambi, M.D., Mehdi H. Shishehbor, D.O., Ronnier J. Aviles, M.D., Marlene Goormastic, M.P.H., Michael L. Pepoy, B.S., Ellen S. McErlean, M.S.N., Eric J. Topol, M.D., Steven E. Nissen, M.D., and Stanley L. Hazen, M.D., Ph.D.

ABSTRACT

CONCLUSIONS

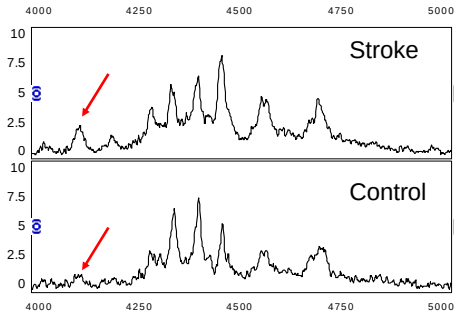
A single initial measurement of plasma myeloperoxidase independently predicts the early risk of myocardial infarction, as well as the risk of major adverse cardiac events in the ensuing 30-day and 6-month periods. Myeloperoxidase levels, in contrast to troponin T, creatine kinase MB isoform, and C-reactive protein levels, identified patients at risk for cardiac events in the absence of myocardial necrosis, highlighting its potential usefulness for risk stratification among patients who present with chest pain.

Stroke Plasma Biomarkers

· Plasma collected from stroke and normal control subjects was run on H50 protein chip arrays (Ciphergen Biosystems, Fremont, CA)

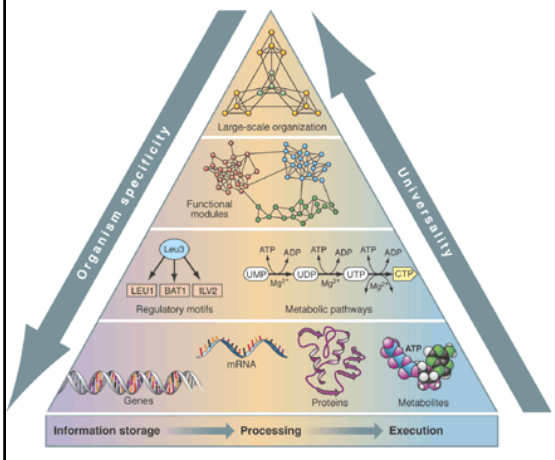
· Multiple peaks were identified in the spectra from stroke patients that were statistically different from controls ($p < 0.05$).

Figure: SELDI-TOF-MS spectra from the plasma of a stroke and normal control. The region between 4000 and 5000 Da is shown. The mass spectrum from the stroke patient contains a more intense peak (arrow) at a mass/charge ratio of 4125 Daltons.



Stage 3. Obtain Molecular Information using Imaging

- This has been done in Nuclear Medicine and PET for years.
- Why is this attracting so much more attention in recent years?



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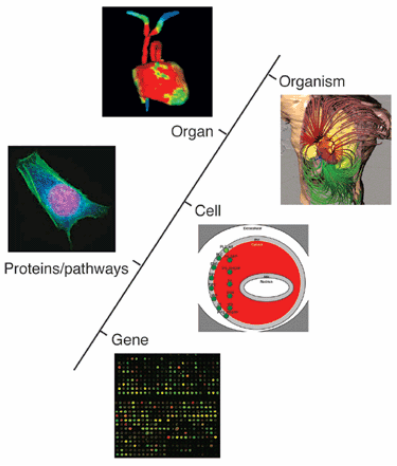

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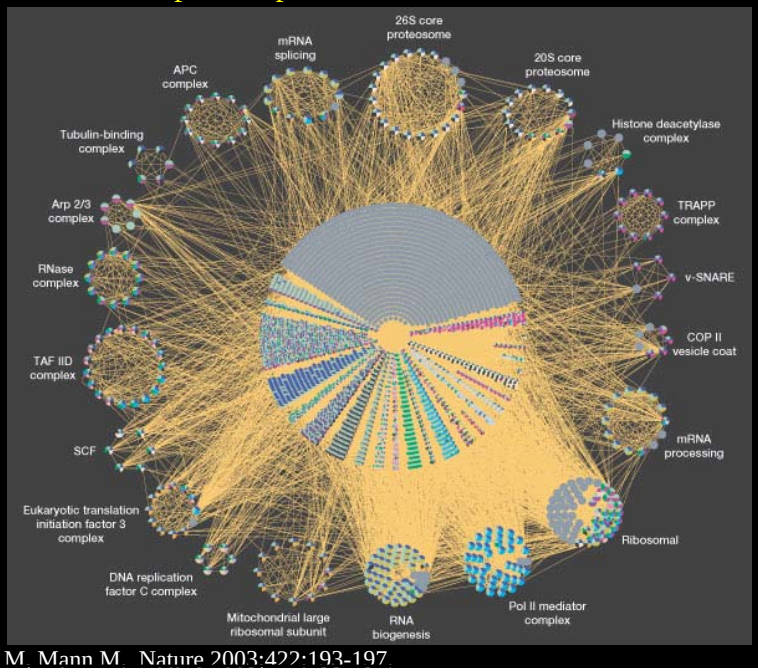
14,000 known protein-protein interactions in Yeast cell



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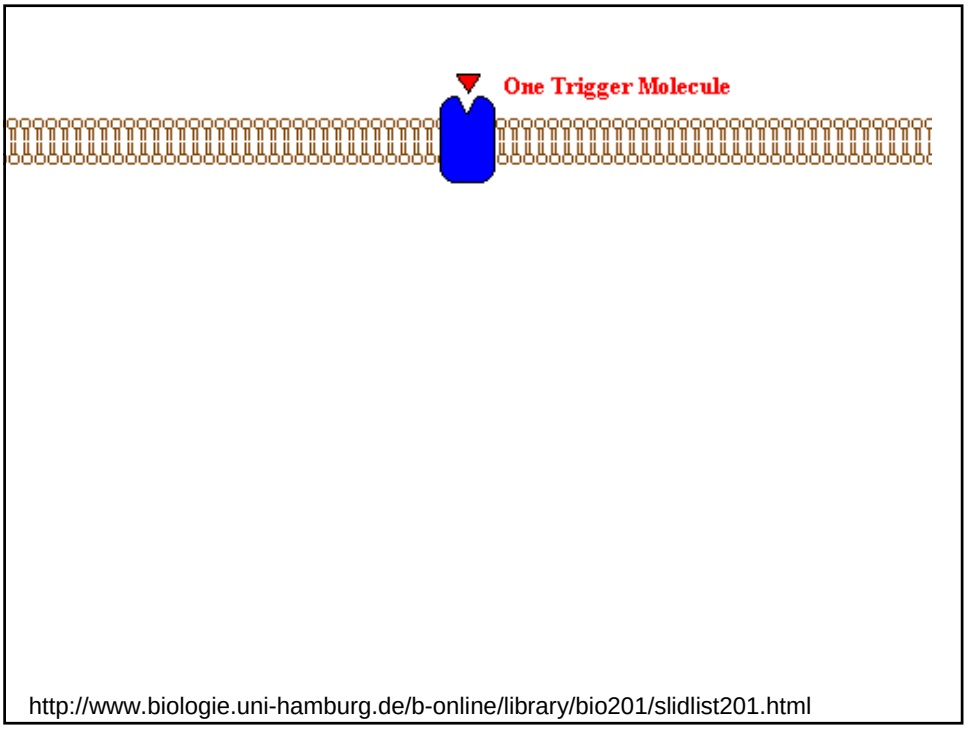
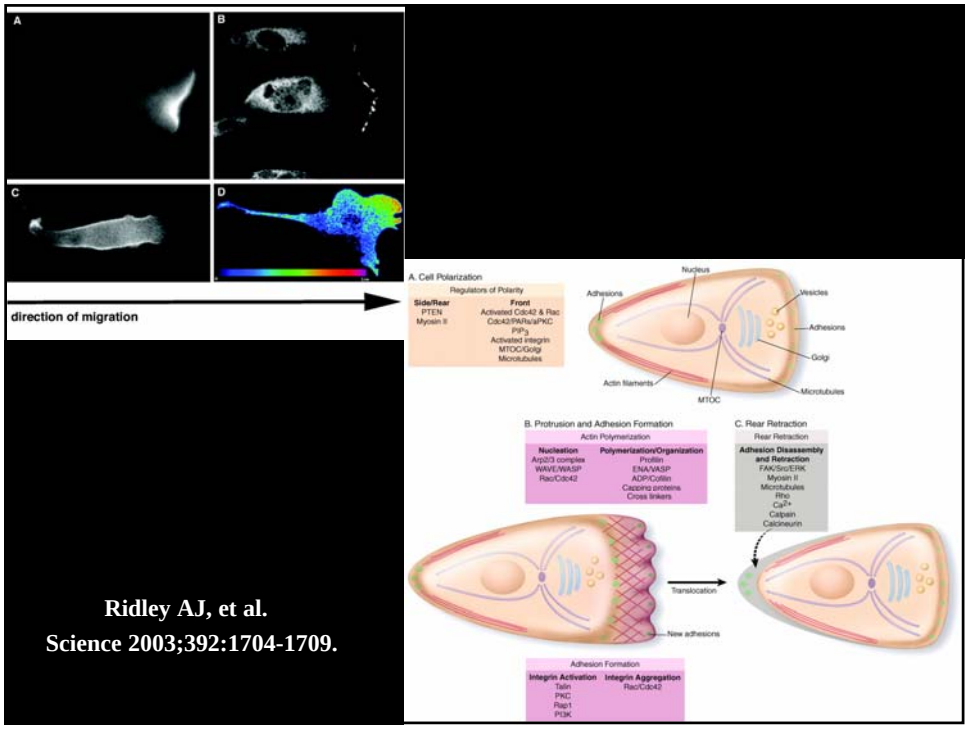


http://www.biologie.uni-hamburg.de/b-online/library/bio201/slidlist201.html



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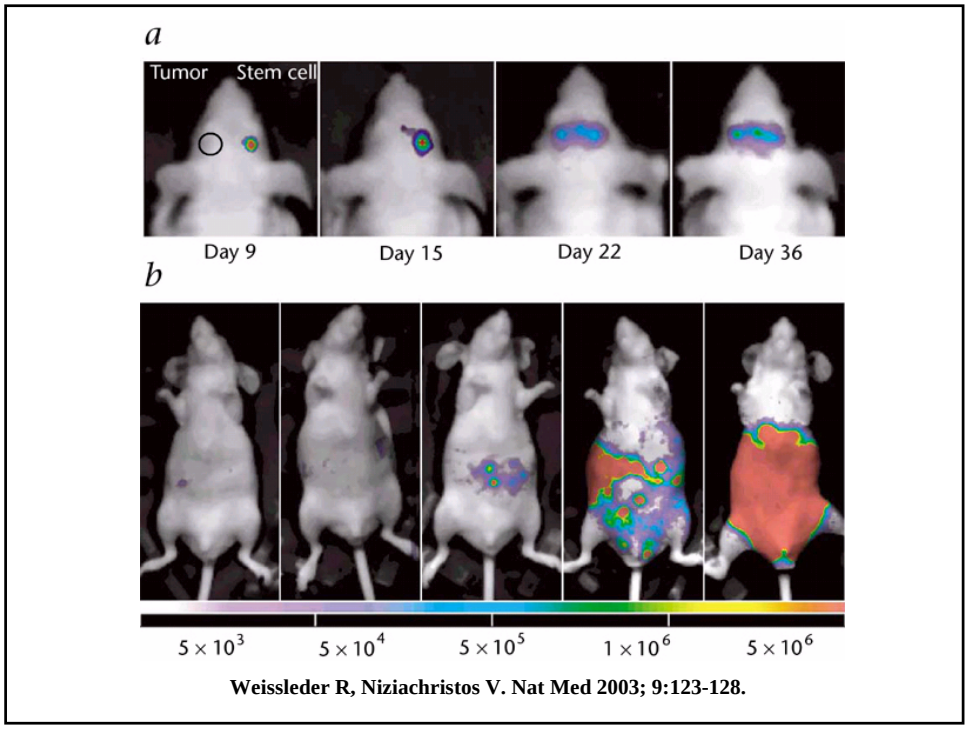

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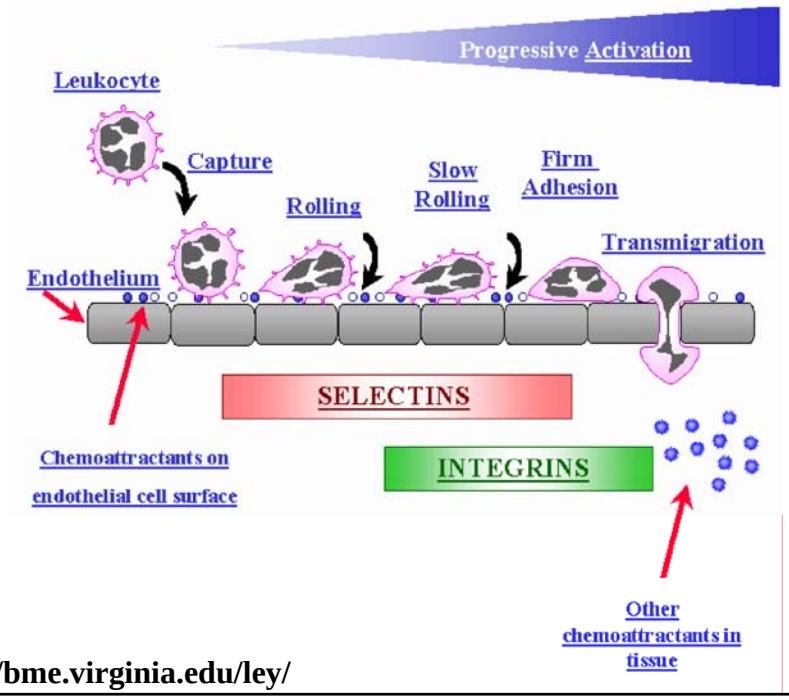
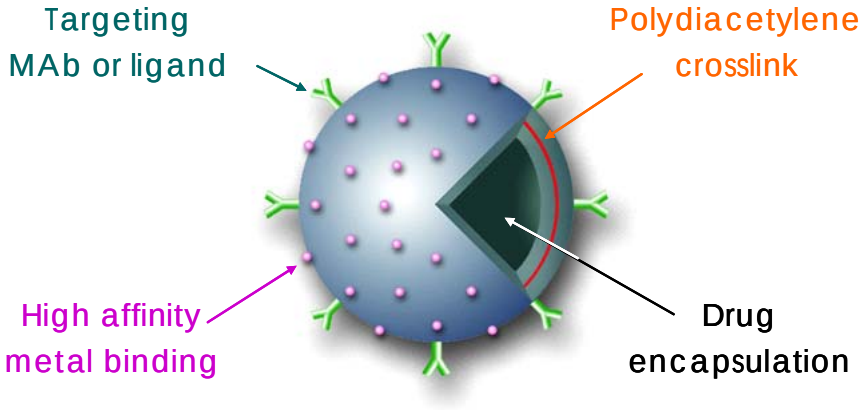
Stage 4. Personalizing Rx with combined imaging & Rx

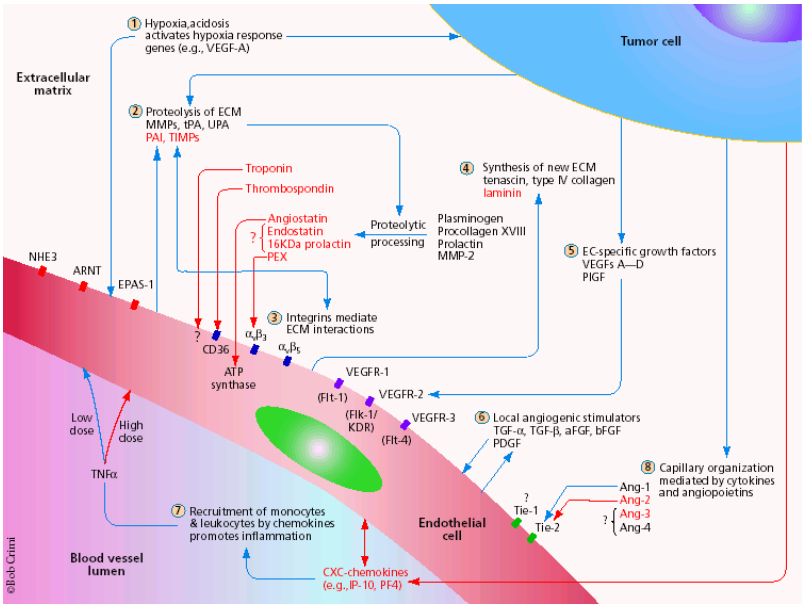
- Zevalin^{TM} (IDEC Pharmaceuticals) is a radioimmunotherapy approved for treatment of some forms of B-cell non-Hodgkin's lymphoma.
- ^{111}In-labeled Zevalin scan is used for patient selection and dosimetry prior to the ^{90}Y-Zevalin Rx.



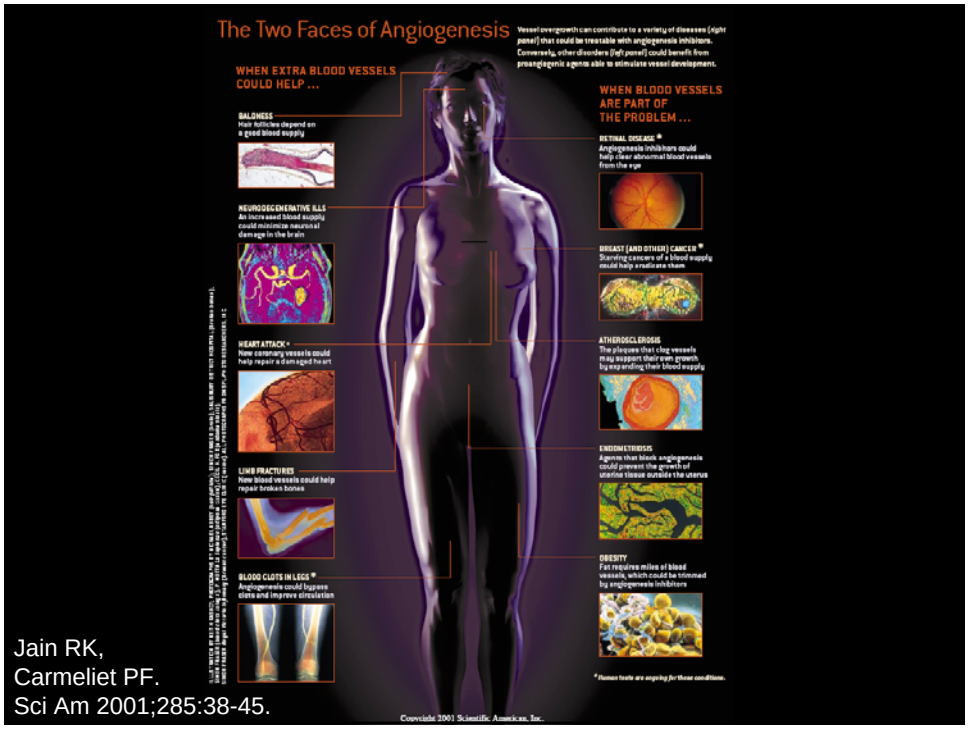
http://bme.virginia.edu/ley/

A Nanoscale Targeted PV





Vicki Brower. Tumor angiogenesis-new drugs on the block. Nature Biotechnology 1999; 17:963-968.



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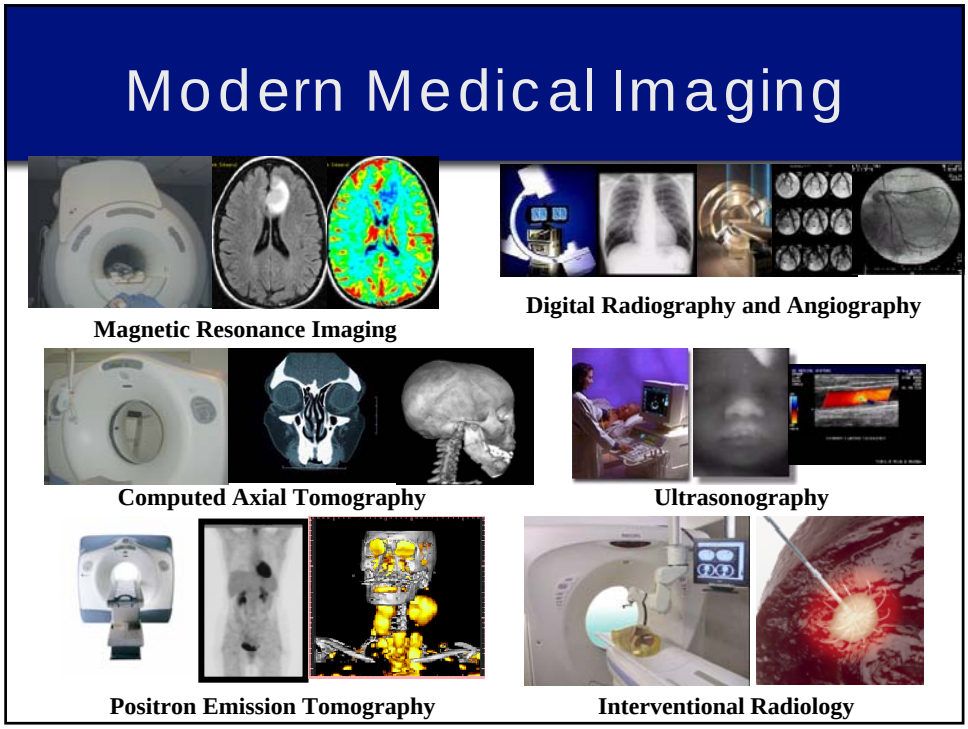
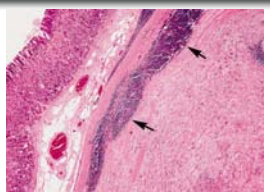


CURRENT CLINICAL PARADIGM



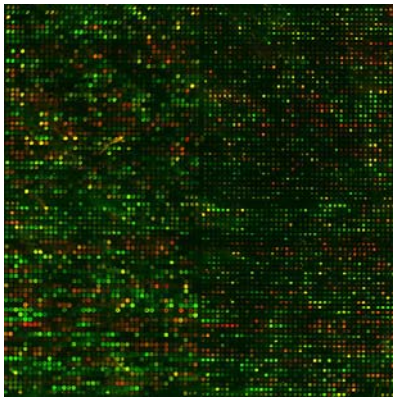
Histology

Imaging

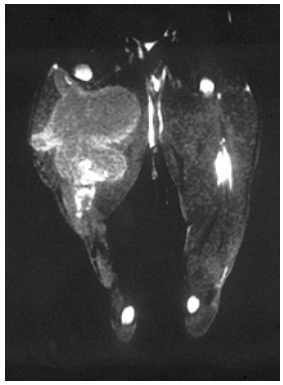
Gross Pathology

Images from Levy AD et al. Radiographics 2003;23:283-304.

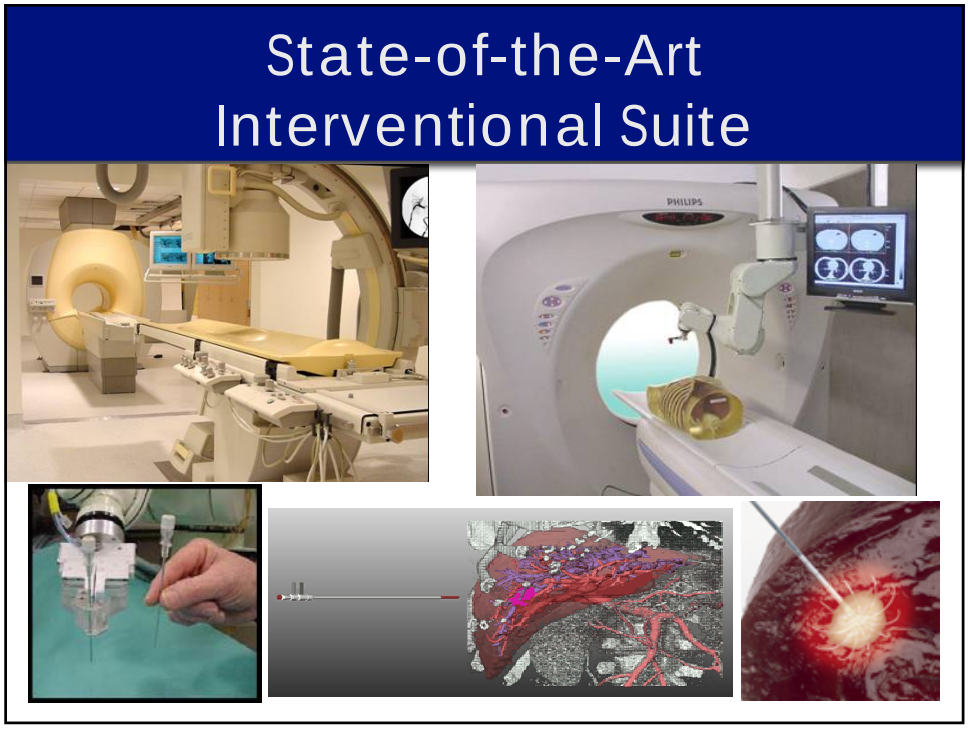
NEW PARADIGM



Functional Genomics



Molecular and Functional Imaging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