AAPM VISION

Thoughts on the Future of Medical Physics Research in the New Era of Genomic Medicine

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My goal today was to convince you that "wild physics" should be promoted.

It appears I'm a little late!

AAPM characteristics and history

- Celebrating our 55th anniversary this year
- Today is the International Day of Medical Physics
- Over 8,000 members from 25 countries
  - 6,000 full members
  - 70% radiation physics
  - 25% imaging physics
  - 5% other (hyperthermia, etc.)

  - 85% some clinical responsibility
  - 10% primarily research and education
  - 5% government and industry

AAPM characteristics and history

- Prior to 1980, medical physics was a very academic discipline with most physicists working in larger institutions with some academic component.
- Surge in demand for clinical manpower beginning in the 1980's resulted in the AAPM focus being driven by professional needs.
  - Current definition of the Qualified Medical Physicist is an example of this effort.

AAPM characteristics and history

- Today, most research being carried out by AAPM members is translational or clinical and in the areas of radiation therapy and traditional radiological imaging technologies (including nuclear medicine).
  - Science Council spends a lot of effort dedicated to the applications of physics principles in clinical practice (task group reports, reviewing position statements on the safe use of radiation, etc.)

What is *medical physics*?

- According to Wiki
  - Medical Physics is generally speaking the application of physics concepts, theories and methods to medicine/healthcare.
  - Biophysics is an interdisciplinary science that uses the methods of, and theories from physics to study biological systems.

- According to AAPM (from Vision statement)
  - …medical physics, a broadly-based scientific and professional discipline encompassing physics principles and applications in biology and medicine.

Disruptive question for AAPM

What other areas of medical physics science should the AAPM be promoting in the future?

What's driving cancer research?

- **GOOD NEWS**
  - Death rates for the four most common cancers (prostate, breast, lung, colorectal), and all cancers combined, continue to decline.
  - The rate of cancer incidence has declined since the early 2000s.
  - Length of cancer survival has increased for all cancers combined.
- **BAD NEWS**
  - Incidence rates of some cancers are rising including melanoma, non-Hodgkin lymphoma, childhood cancer, leukemia, thyroid, pancreas, liver, testis.
  - Death rates for pancreas, esophagus, thyroid, and liver are increasing.
- **FACTS**
  - Cancer treatment spending continues to rise.
  - Research funding is flat from all sources!
  - Few *cures*…

U.S. Cancer Burden
2009 Estimates

Based on data from NAACCR 1995-2005 & CDC NCHS 1969-2006; NCI statistical models

1,479,350 Cases

- 219,440 Lung
- 192,370 Breast (female)
- 192,280 Prostate
- 146,970 Colon/rectum
- 70,980 Bladder
- 65,980 NHL
- 68,720 Melanomas
- 57,760 Kidney
- 44,790 Leukemia
- 42,470 Pancreas
- 42,160 Corpus uteri
- 37,200 Thyroid

562,340 Deaths

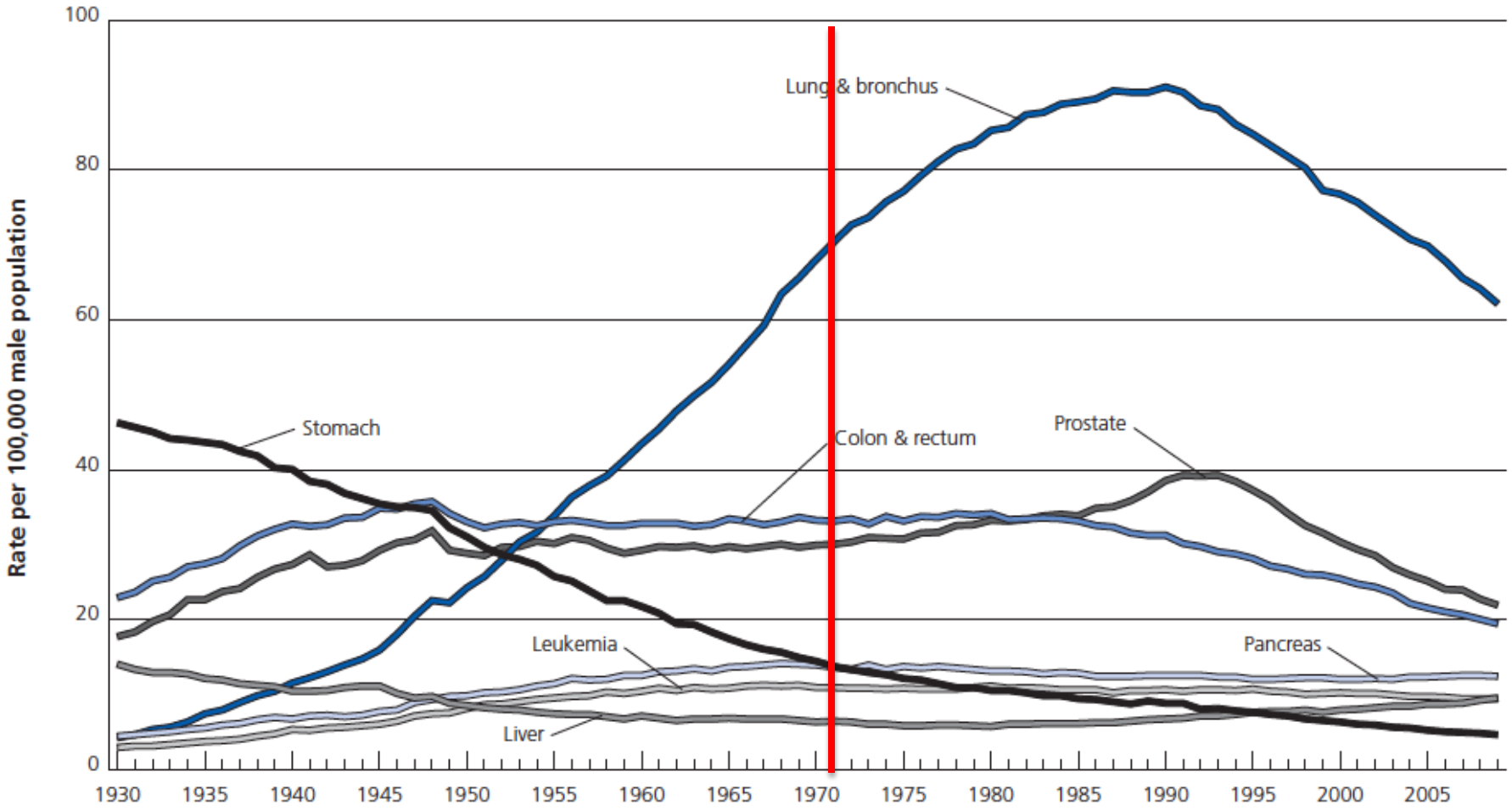
- 159,390 Lung
- 49,920 Colon/rectum
- 40,170 Breast (female)
- 35,240 Pancreas
- 27,360 Prostate
- 21,870 Leukemia
- 19,500 NHL
- 18,160 Liver & IHBD
- 14,600 Ovary
- 14,530 Esophagus
- 14,330 Bladder
- 12,920 Brain

Sources: American Cancer Society, Facts & Figures, 2009.

National Cancer Act of 1971

- Signed into law by President Richard M. Nixon
- The act was created as a mechanism to make the elimination of cancer a national priority
- The press dubbed this the *War on Cancer*
- In 2003, NCI Director Andrew von Eschenbach issued a challenge to cure cancer by 2015
  - This position was supported by AACR in 2005
- **It's 2013 and we are not close to a cure!!!**

Age-adjusted Cancer Death Rates*, Males by Site, US, 1930-2009

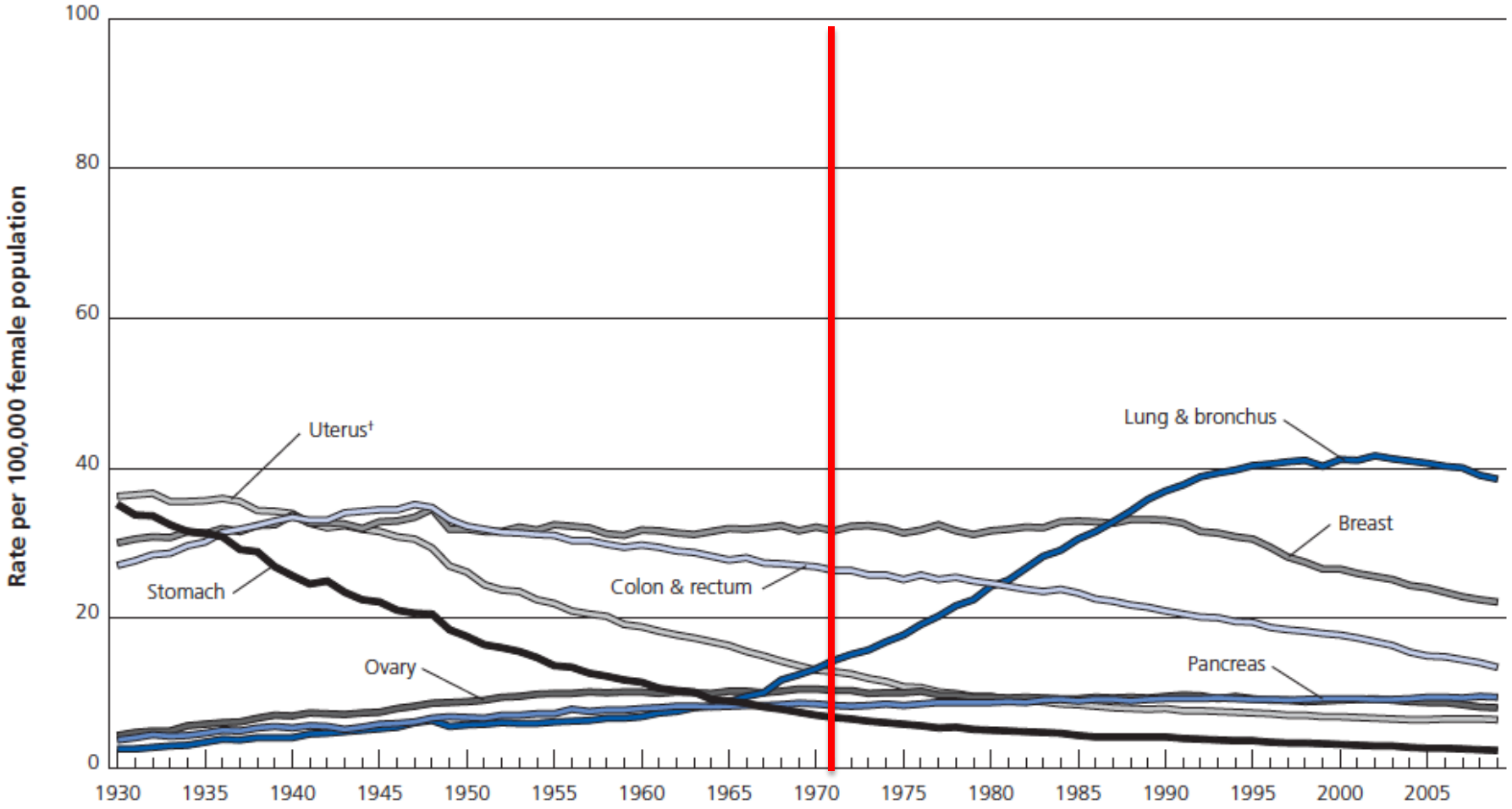


*Per 100,000, age adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Age-adjusted Cancer Death Rates*, Females by Site, US, 1930-2009



*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the lung and bronchus, colon and rectum, and ovary are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Current funding priorities at NCI

- Much more **impact** focused.
  - *So it's a great idea. If it is successful, what will be the impact on patient mortality and morbidity?*
- Instrumentation development will need a very well defined outlet.
  - *Difficult to get funding for platform technologies or incremental advances.*
- Biology orientation
  - ***For cancer, that's really genomics!***

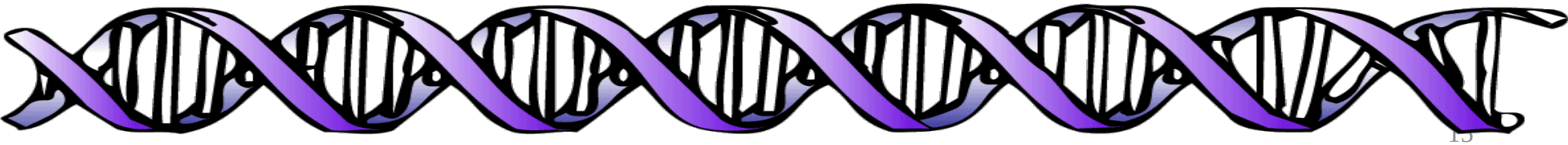
Human Genome Sequencing

Santa Fe 1986: Human genome baby-steps

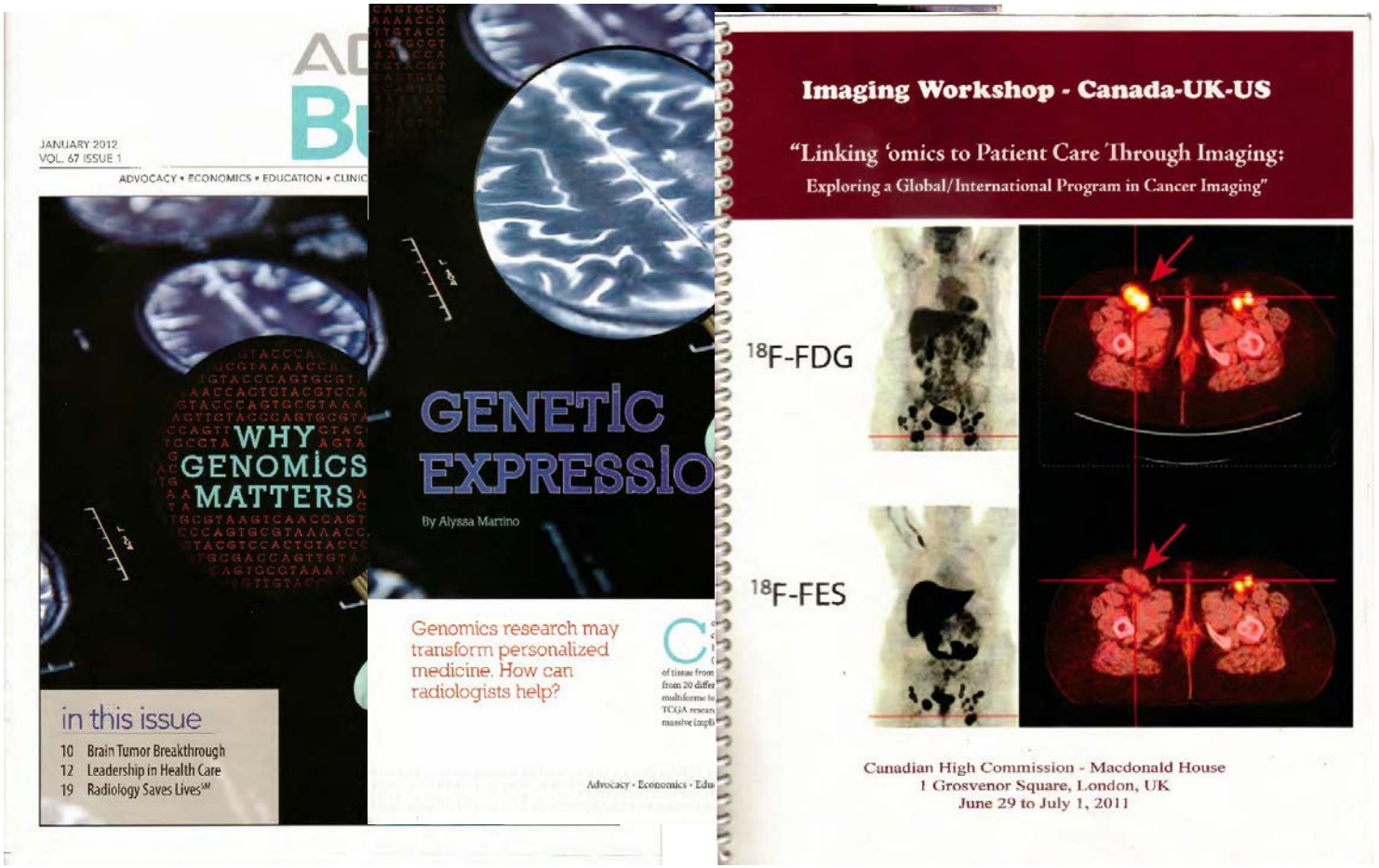
The 1980s saw plenty of discussion on sequencing the human genome. But, according to **Charles DeLisi**, one conference was crucial for converting an idea to reality.

Human Genome Project

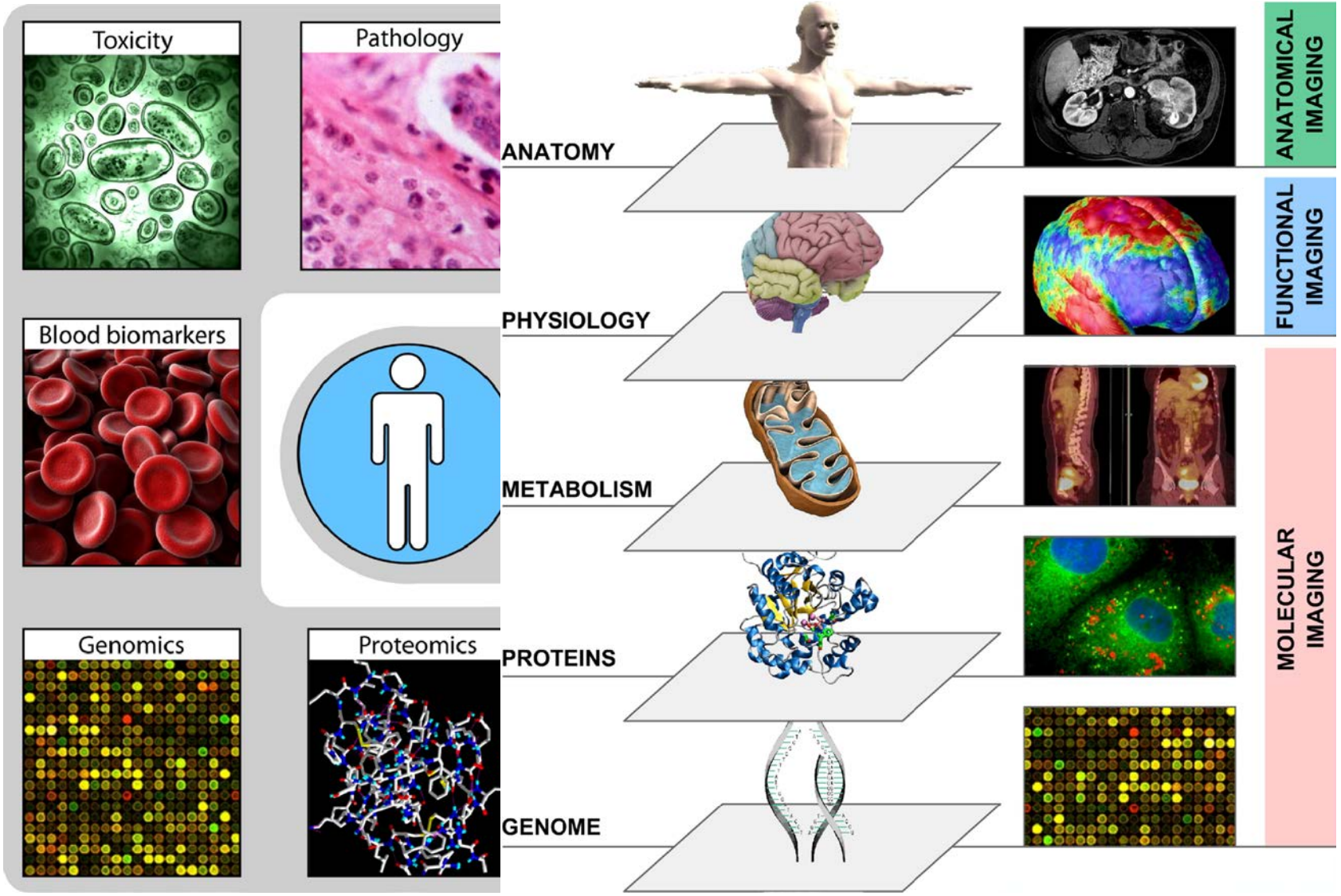
- The project to sequence the human genome evolved from a DoE sponsored meeting in Santa Fe in 1986.
- Funding for the project was provided by the Reagan administration in 1987.
- In 1990, the DoE and NIH signed an MOU coordinating their funding efforts and set 1990 as the starting point of a 15 year clock.
- The project was declared complete in 2003.
  - *99% of the genome was known to 99% accuracy*

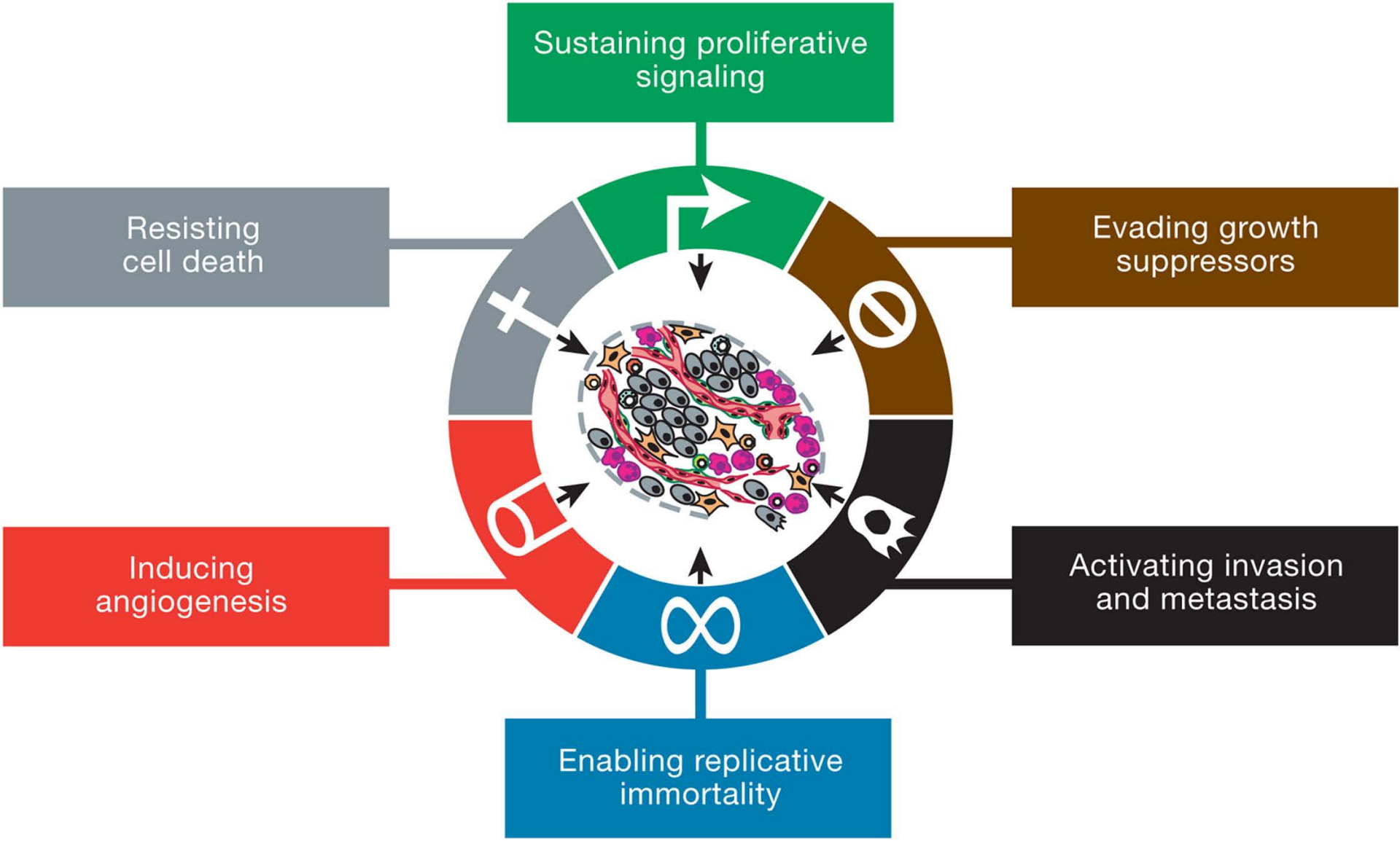


WHAT IS THE FUTURE OF MEDICAL PHYSICS RESEARCH IN A GENOMIC WORLD?

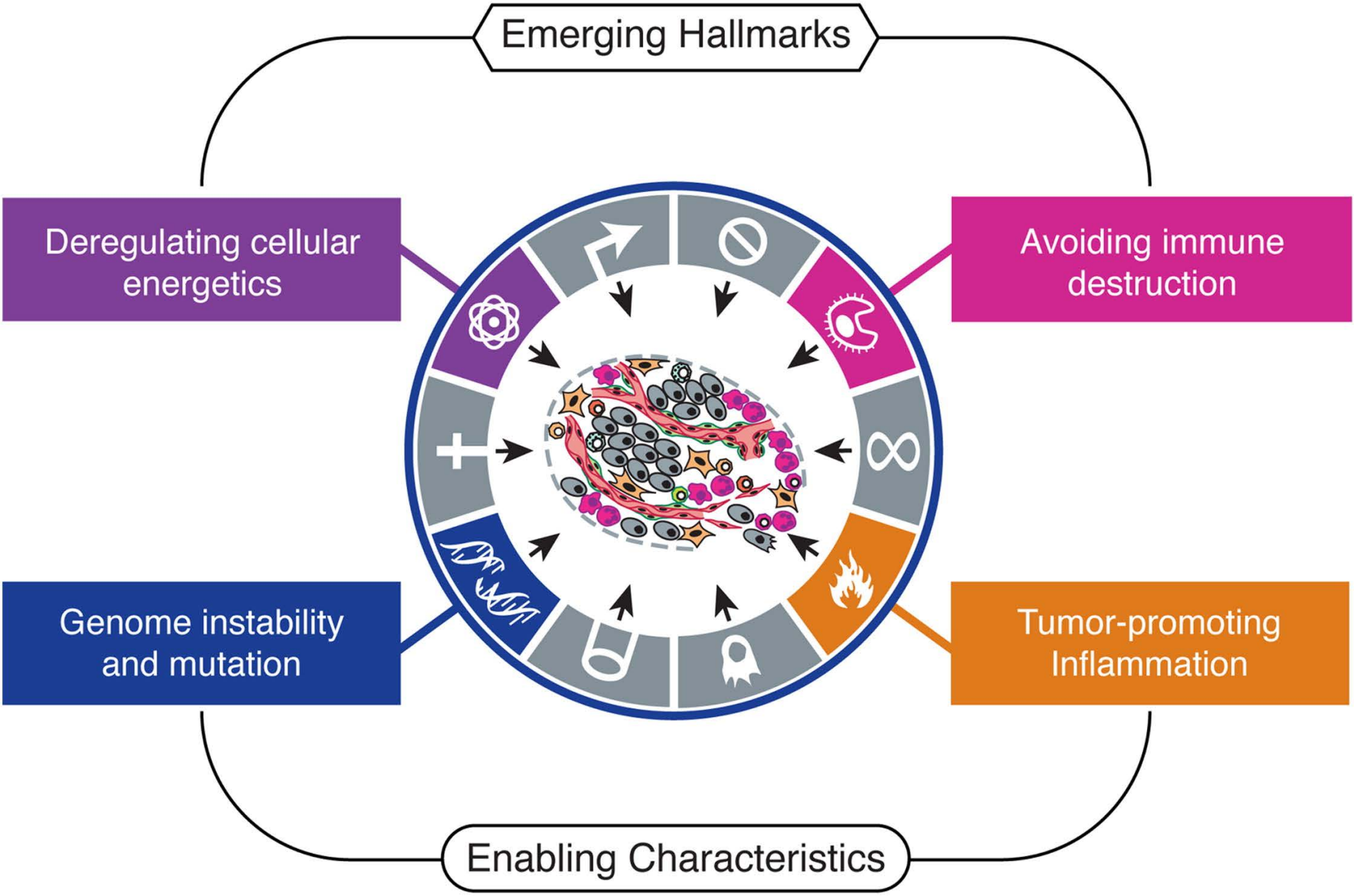


The omics of cancer





Hanahan & Weinberg, Cell 57-70, 2000



Hanahan & Weinberg, Cell 646-671, 2011

NCI provocative questions project

- How does obesity contribute to cancer risk?
- Are there ways to objectively ascertain exposure to cancer risk using modern measurement technologies?
- What are the molecular and cellular mechanisms by which patients with certain chronic diseases have increased or decreased risks for developing cancer, and can these connections be exploited to develop novel preventive or therapeutic strategies?
- Why do certain mutational events promote cancer phenotypes in some tissues and not in others?
- Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with *in vivo* imaging modalities?
- Are there definable properties of a non-malignant lesion that predict the likelihood of progression to invasive or metastatic disease?

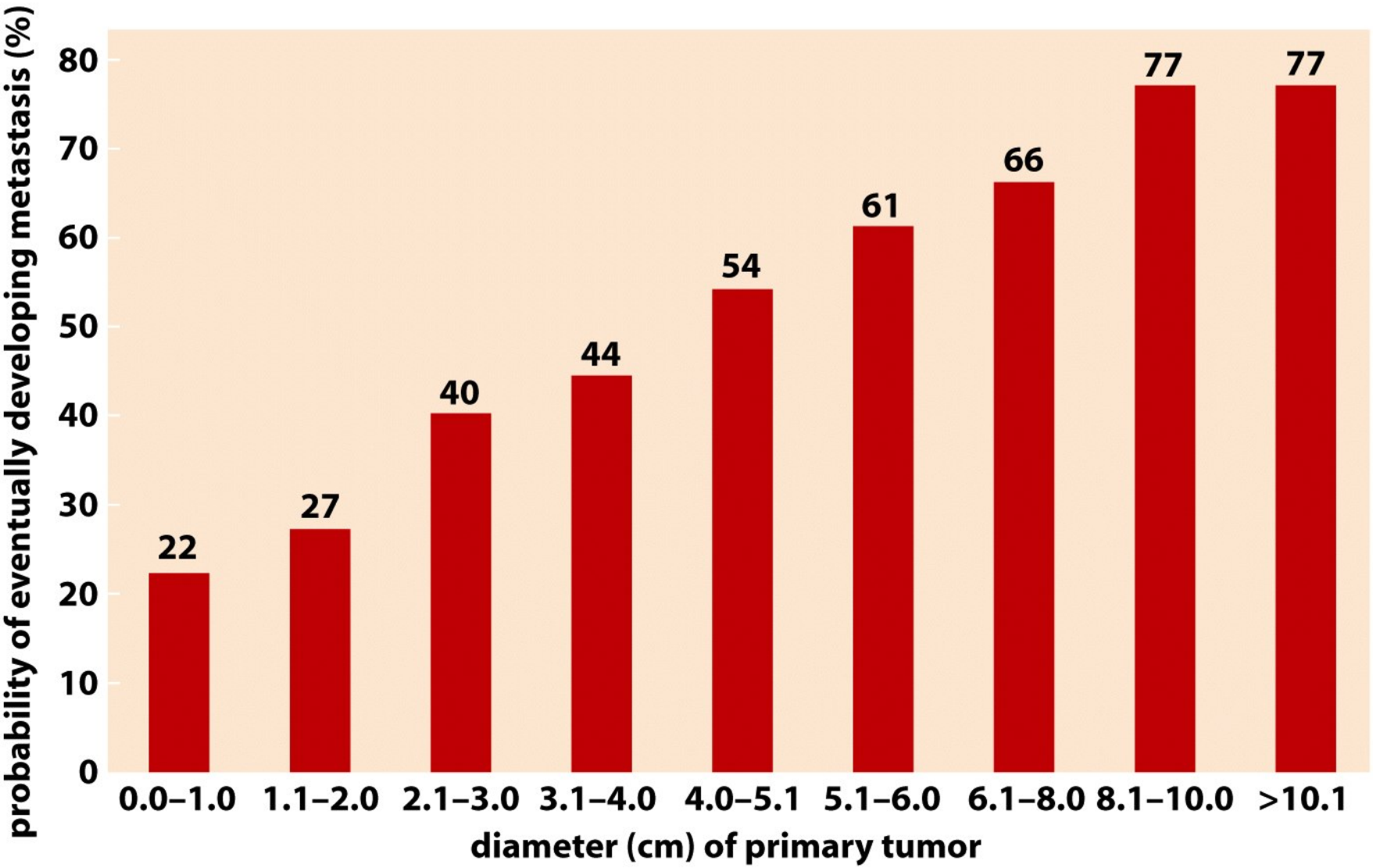


Figure 14.3 *The Biology of Cancer* (© Garland Science 2007)

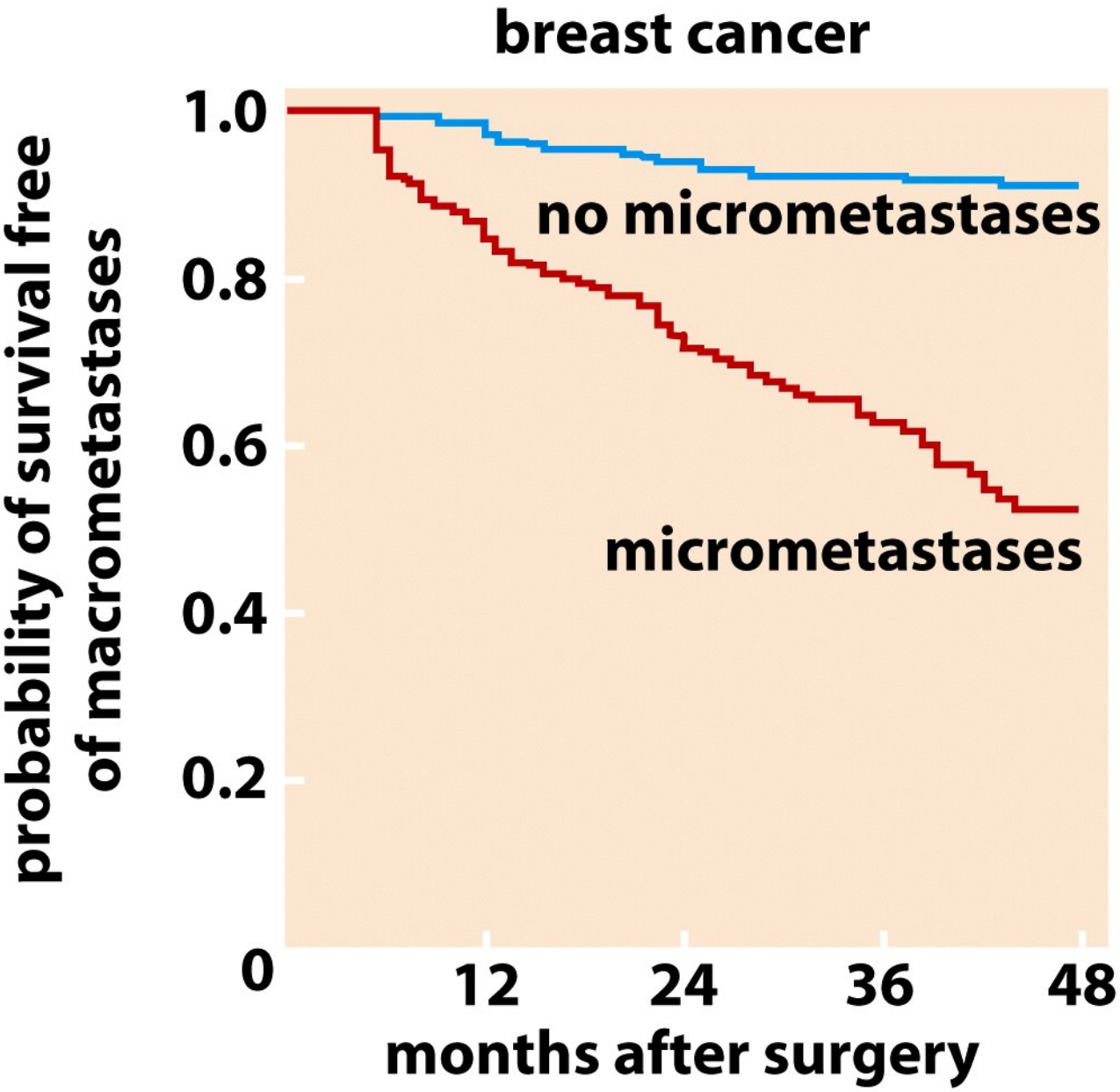


Figure 14.50a *The Biology of Cancer* (© Garland Science 2007)

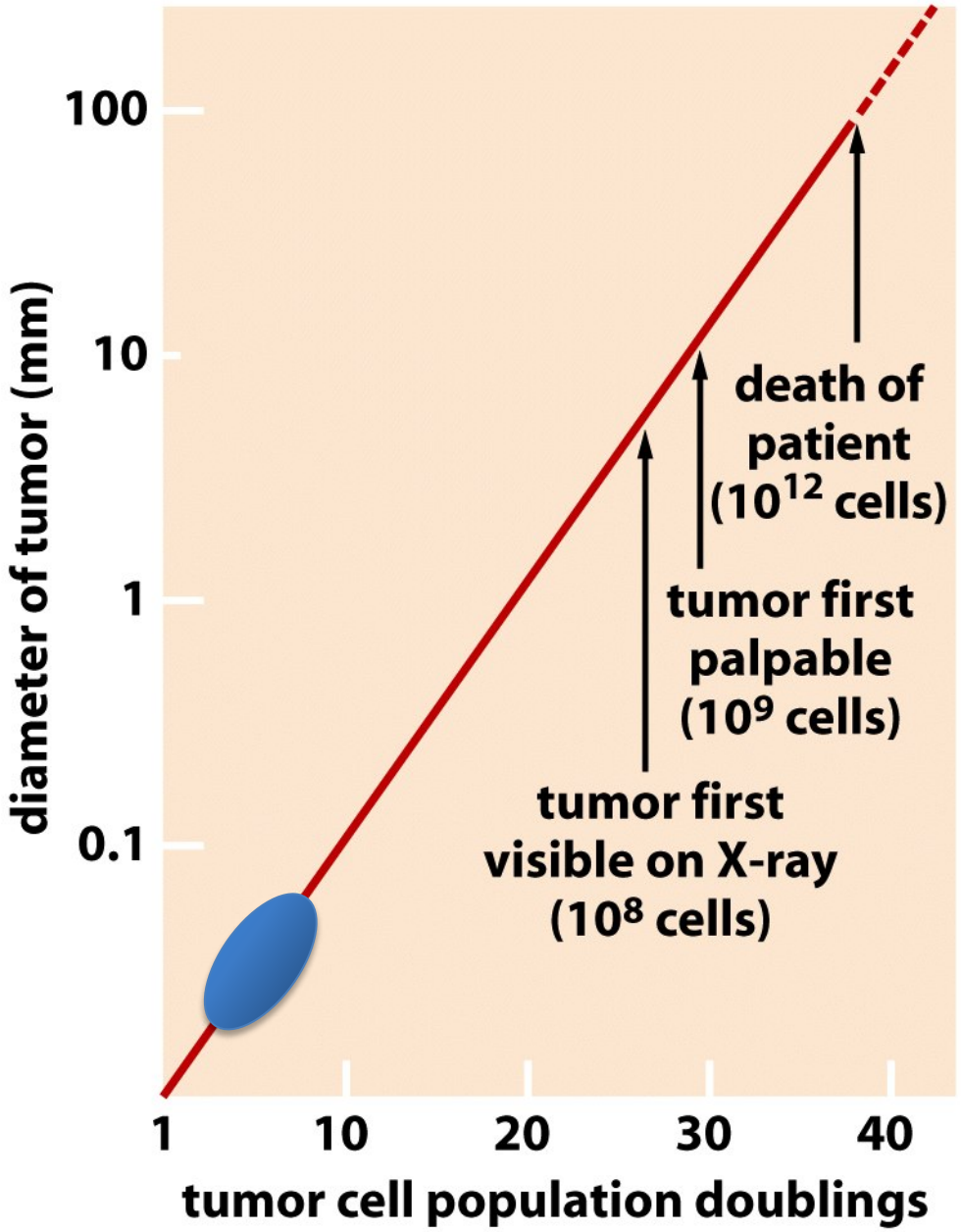
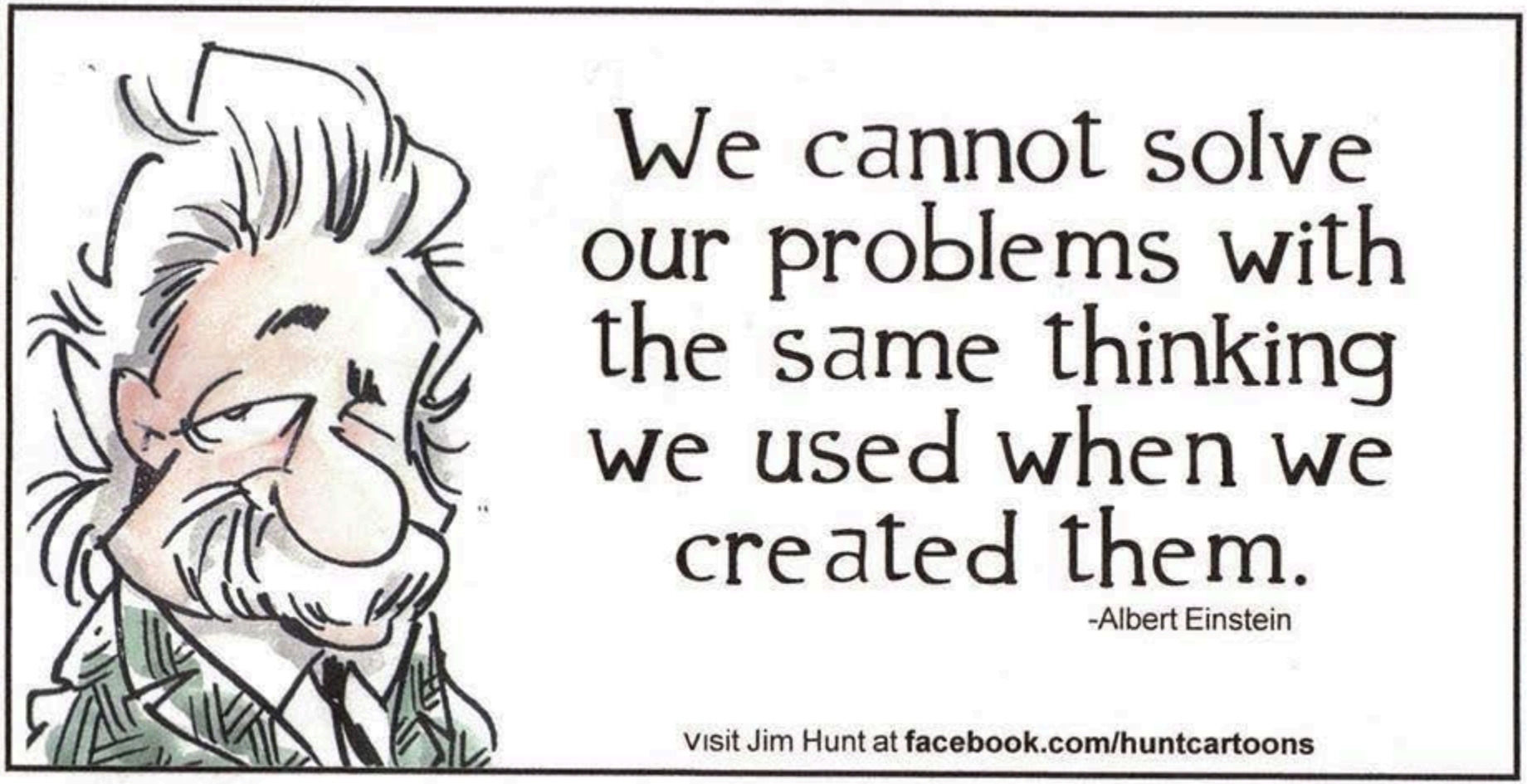
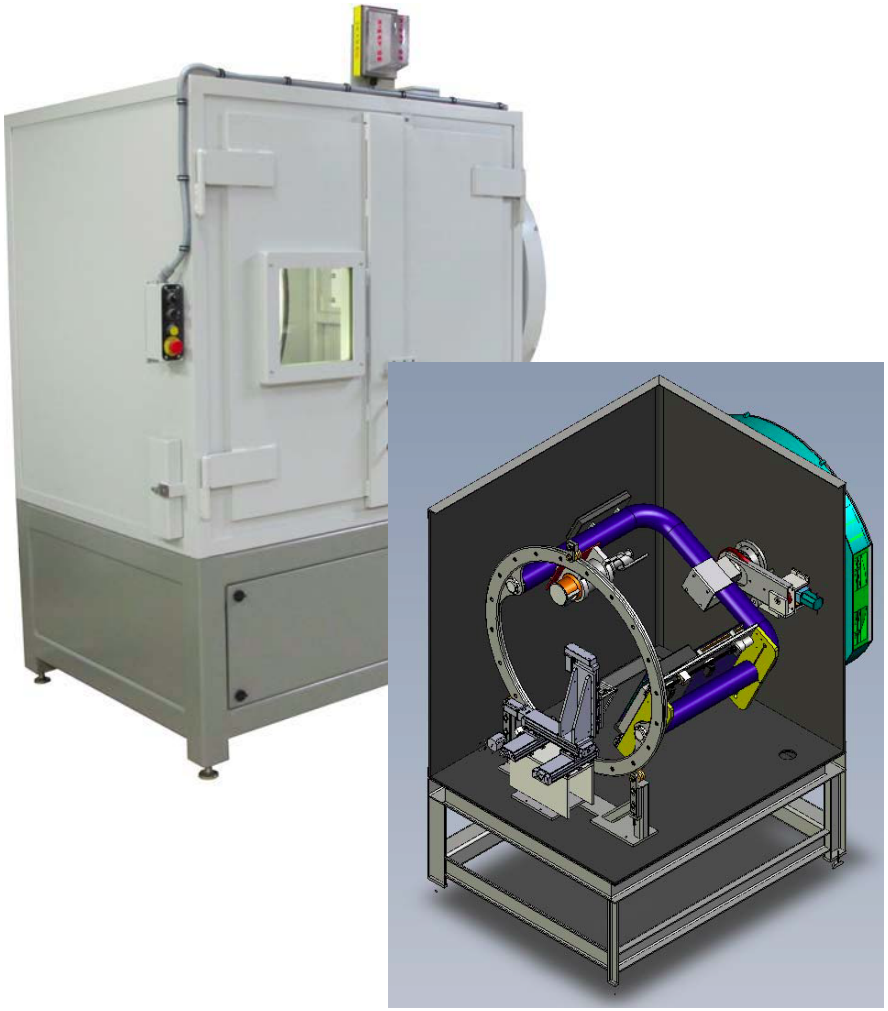


Figure 10.5a *The Biology of Cancer* (© Garland Science 2007)


We cannot solve our problems with the same thinking we used when we created them.
-Albert Einstein
visit Jim Hunt at facebook.com/huntcartoons

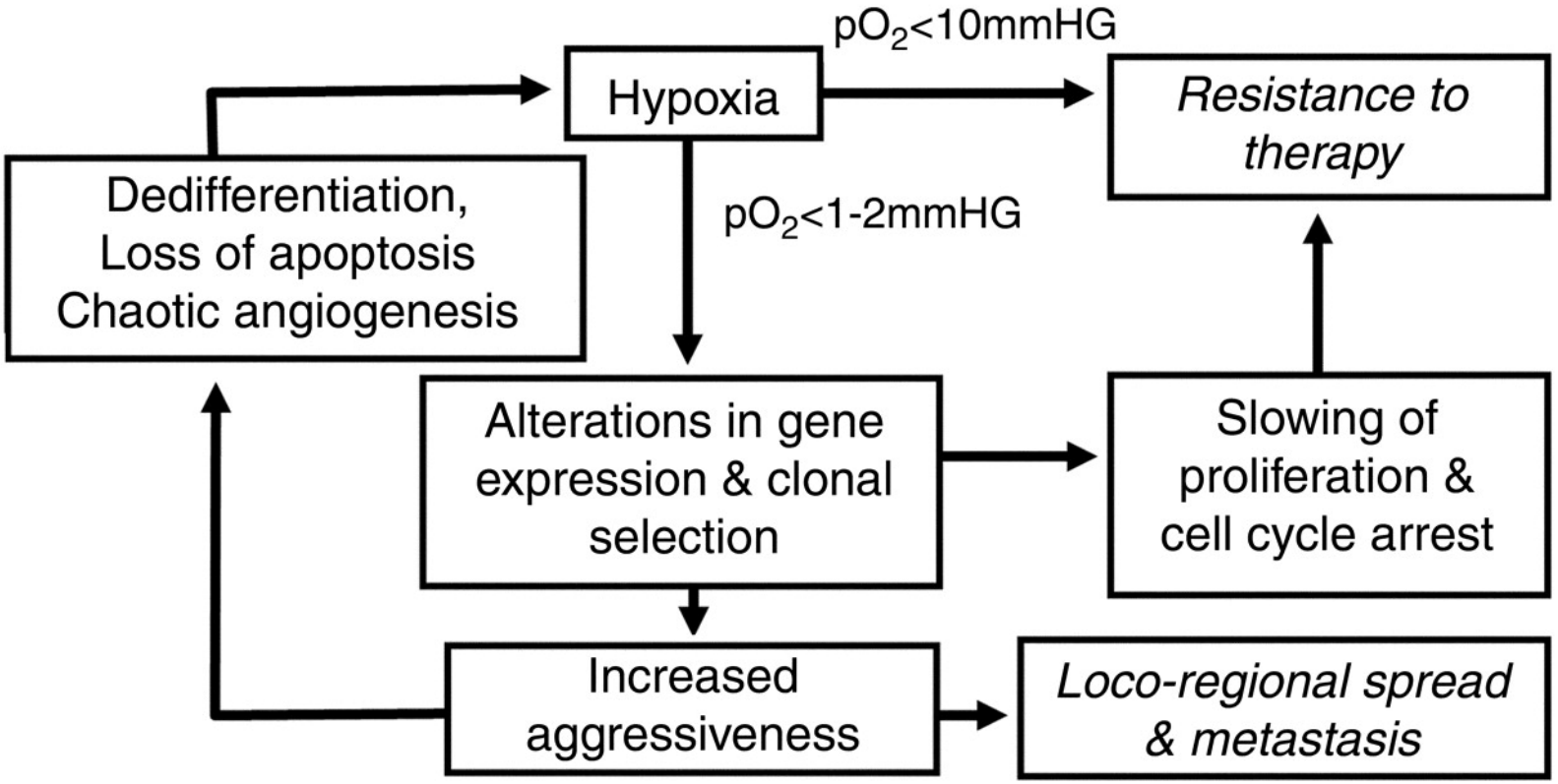
Small animal IGRT platforms



Precision X-ray 225Cx

Xstrahl SARRP

Linking hypoxia to malignant progression: hypoxia (Po2 ≤ 1 mmHg) promotes genomic instability, thereby increasing the number of mutations (genetic variants).



Padhani A R , Miles K A Radiology 2010;256:348-364

Radiology

Cancer Metabolism & Tumor Biology by Hyperpolarized $^{13}C/^{15}N$ MRSI: Prospects for Translation to Clinic Research

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Abstract

A major challenge in cancer biology is to monitor and understand cancer metabolism *in vivo* with the goal of improved diagnosis and therapy. Because of the complexity of biochemical pathways, multi-parametric tracer methods are required for detecting specific enzyme-catalyzed reactions, ideally simultaneously. Stable isotopes such as ^{13}C or ^{15}N with detection by nuclear magnetic resonance spectroscopy (MRS) provide the necessary information about tissue biochemistry, but the crucial metabolites are present in low concentration and therefore are beyond the detection threshold of traditional magnetic resonance methods. A solution is to improve sensitivity by a factor of 10,000 or more by temporarily redistributing the populations of nuclear spins in a magnetic field, a process termed hyperpolarization. Although this effect is short-lived, hyperpolarized molecules can be generated in an aqueous solution and infused *in vivo* where metabolism generates products that can be imaged. This discovery lifts the primary constraint on magnetic resonance imaging for monitoring metabolism—poor sensitivity—while preserving the advantage of biochemical information, and leads to the development of an enabling imaging technology for clinical investigations and discovery research. Hyperpolarized (HP)-$^{13}C/^{15}N$ MRS Imaging (MRSI) may provide real-time high resolution metabolic quantitative imaging of biological molecules with temporal resolution measured in seconds for tracing multiple metabolites. All the published work to date has been performed at the pre-clinical level, and only a few sites are planning to extend the work to clinical investigations.

For the prospects of clinical translation, the major challenge is to move the field in a cost effective manner. Thus, the NCI Cancer Imaging Program, together with extramural and intramural staff across other institutes of NIH (NIDDK, NHLBI, NIBIB, and NCRR), challenged the academic investigators to generate a consensus publication (whitepaper) that outlines the current status of HP-$^{13}C/^{15}N$ MRS/MRSI methods and identifies the scientific challenges and translational barriers for implementing this technology in clinical trials and/or applying it in clinical settings. This challenge led to the publication in the Feb 2011 issue of ***Neoplasia*** entitled "*Analysis of Cancer Metabolism by Imaging Hyperpolarized Nuclei: Prospects for Translation to Clinical Research*". The consensus effort leading to this whitepaper was first initiated in the fall of 2009 with the creation of a draft document and the organization of an international workshop at the ISMRM meeting in May 2010 to review this draft. The workshop was attended by over 40 scientists from academia, industry, pharmaceutical companies and federal agencies from the US and internationally. The whitepaper was also reviewed by correspondence with a total of over 60 scientists both nationally and internationally. This workshop/whitepaper has impacted the progress of the field as reflected in related presentations at the 2011 ISMRM meeting. This work was presented at a recent international workshop (Canada CIHR, CR UK and NCI) where the goals are to leverage resources to support imaging methods and their correlation with genomics and proteomics methods (London UK, June 30th-July 1st 2011). This poster presents an overall review of the current research status, challenges and barriers.

Unmet need for tumor biology imaging in the cancer genomics era

The advances in cancer genomics are enabling the discovery of somatic mutations and novel disease genes, therefore establishing a framework for comprehensive studies of cancer biology. Integrated studies of genome, epigenome, transcriptome, interactome, metabonome, and proteome reveal mechanisms of tumorigenesis at multiple biologic levels and may enable personalized medicine strategies. These developments create novel opportunities/challenges for cancer imaging, which has long been applied in cancer & treatment through assessing anatomy, functions, cellularity and limited molecular events. Thus, there are gaps between cancer genomics and cancer imaging in the context of providing comparable information at the tumor biology level. The discovery of HP-$^{13}C/^{15}N$ MRSI appears to be the enabling technology to fill in and/or to reduce these gaps.

Why use HP-$^{13}C/^{15}N$ in MRSI?

Cancers are known to adapt to alterations in several metabolic pathways, including glycolysis, glutaminolysis and fatty acid synthesis. These metabolic pathways involve the uptake carbon/nitrogen from nutrients, then the conversion to carbohydrates, proteins, lipids and nucleic acids to support the growth and survival of cancer cells. $^{13}C/^{15}N$ NMR provide spectra with peaks well-separated by large chemical shifts (Fig 1a), thus can be used to differentiate/trace these metabolic alterations at molecular levels and provide molecular signatures for staging tumors and/or identifying tumor subtypes, i.e., distinguish breast tumors Luminal-like with basal-like (Fig 1b). The natural abundance of $^{13}C/^{15}N$ is low (1.1%/0.37%), so selective labeling can be used to trace specific pathways (Fig 1c). Since the sensitivity is much lower than that of ^{1}H MRS ($^{13}C/^{15}N$: 0.25/0.10), $^{13}C/^{15}N$ MRS is rarely used for *in vivo* imaging.

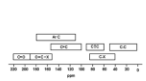


Fig 1a ^{13}C Chemical shift

Fig. 1c Major energetic metabolic pathway of cell associated with ^{13}C labeled pyruvate, *Gollman K, et al, Cancer Res, 66:10855 (2006)*

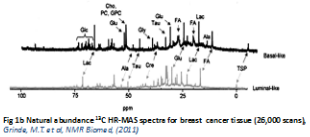


Fig 1b Natural abundance ^{13}C HR-MAS spectra for breast cancer tissue (26,000 scans), *Grinde, M.T et al, NMR Biomed, (2011)*

Hyperpolarization is a cutting-edge technology to increase the detecting S/N of $^{13}C/^{15}N$ MRS from 10,000 to 100,000 fold by temporally re-distributing nuclear spin population in the magnetic field(Fig 2a). There are three methodologies to achieve HP-$^{13}C/^{15}N$, namely dynamic nuclear polarization (DNP), parahydrogen induced polarization (PHIP), and signal amplification by reversible exchange (SABRE). As consequence, the S/N of 1 scan in DNP sample is substantially higher than that of 256 scans of a conventional sample (Fig 2b). The produced HP agents can be administrated via IV bolus injection or infusion. This advance makes it feasible to use $^{13}C/^{15}N$ MRS for *in vivo* imaging. Although the lifetime of HP-$^{13}C/^{15}N$ is as short as a few minutes, but this is not a major barrier in translation into clinic applications, as indicated by the whitepaper.

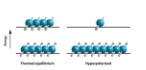


Fig 2a Spin distribution in normal and hyperpolarized nuclear spin, *Mannen S, et al, Eur Radiol, 18:57 (2008)*

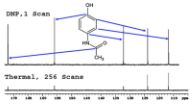


Fig 2b ^{13}C spectra in normal and hyperpolarized molecules

The enhancement effect of HP-$^{13}C/^{15}N$ is enabling us to: **(1)** perform real time imaging of substrate-inhibitors at temporal resolution of seconds to measure metabolic flux and/or chemical reaction rates for small molecules involved in fast pathways (Fig 3a); **(2)** use inherently biocompatible, non-radioactive molecular imaging probes, such as ^{13}C-labeled pyruvate, lactate and glutamine or ^{15}N-labeled choline, etc; **(3)** image multiple agents & functions simultaneously for comprehensive evaluation of tumors, such as pyruvate for metabolism, bicarbonate for pH, fumarate for necrosis, urea for vascularity, etc (Fig 3b); **(4)** image multiple metabolic intermediates, such as the metabolic intermediates in the process of converting ^{13}C-d$_5$-glu to lactate (Fig 3c); **(5)** image agents, metabolites & functions longitudinally with multiple sequential injections; **(6)** map individual agents, metabolites & functions with high spatial resolution and provide direct comparison of tumor with normal tissues (Fig 3d) without co-registration of images.

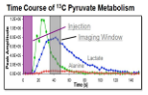


Fig 3a Time course of HP-13C pyr metabolism *Albers, M. J. et al, Cancer Res, 68: 8607(2008)*

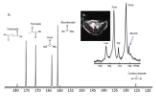


Fig 3b ^{13}C spectra of multi-compound polarization *in vitro* and in TRAMP mouse at 3T, *Wilson, DM, et al, JMR, 209: 141 (2010)*

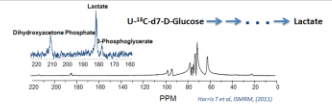


Fig 3c ^{13}C MRS for [U-^{13}C]-d7-glucose in breast cancer cells, *Harris T et al, ISMRM, (2011)*

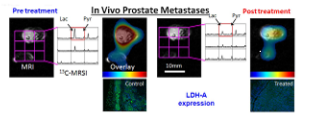


Fig 3d ^{13}C MRSI at 18 second post injection of [1-^{13}C] pyruvate in mice tumor model treated with imatinib-paditaxel, *Dafni, H. et al, Cancer Res, 70:7400(2010)*

Roles of HP-$^{13}C/^{15}N$ MRSI in cancer research

Metabolism as an important cancer hallmark was initially recognized as the **Warburg effect** and has been connected to most cancer hallmarks later (Fig 4a). Various molecular mechanisms of cancer-specific metabolic reprogramming have been discovered, leading us to identify many therapeutic targets (Fig 4b). Because the preclinical and clinical evaluation of metabolic therapy for cancer is in its infancy, research in this area becomes a niche application for HP-$^{13}C/^{15}N$ MRSI. The abnormal metabolic phenotypes are early and sensitive biomarkers of cancer, but complexity arises from spontaneous alterations caused by various tumor environmental or microenvironmental stresses, such as hypoxia, pH, nutrients, and autophagy (Fig 4c). HP-$^{13}C/^{15}N$ MRSI as an imaging tool can detect the alternations in any of these scenarios occurring in living cells, perfused tissues, living animals, or human beings.

Fig 4a The seven hallmarks of cancer and their links to tumor metabolism, *Kroemer G, et al, Cancer Cell, 13:472 (2008)*

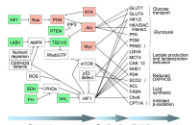


Fig 4b Molecular mechanisms of cancer-specific metabolic reprogramming, *Kroemer G, et al, Cancer Cell, 13:472 (2008)*

Fig 4c Determinants of the tumor metabolic phenotype, *Cairns R.A. et al, Nat Rev Cancer, 11: 85 (2011)*

The application of HP-$^{13}C/^{15}N$ MRSI in cancer research started in 2006. Many imaging probes have been identified, examples of which are [1, 2-^{13}C]pyruvate, [^{13}C]bicarbonate, [1, 4-^{13}C]fumarate , [1-^{13}C]lactate, [5-^{13}C] glutamine, [1,2-^{13}C] acetate, [2-^{13}C]-fructose, [1-^{13}C] succinate,[1-^{13}C] a-ketoisocaproate, [^{13}C]urea, [^{13}C] –choline, [^{15}N]-choline, and U-[^{13}C]-d$_7$-D-glucose. These probes have been used in imaging cancers and their microenvironments, such as Myc oncogene on/off, tumor pH, tumor cell necrosis/hypoxia, alteration in PDH flux, response to genotoxic treatment & cytotoxic treatment, prostate metastasis, and in evaluating therapeutic treatment such as PI3K inhibition by imatinib-paclitaxel, androgen deprivation therapy, brain tumor by temozolomide, lymphoma by etoposide, myc oncogene on/off by doxycycline, vascular disruption by combretastatin, breast tumor by doxorubicin, with the subjects ranging from living cells (Fig 5a), to animals (Fig 5b) and humans (Fig 5c). The first-in-human trial in prostate cancer patients started at UCSF in Oct, 2010 (Fig 5c).

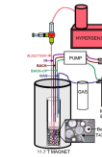


Fig 5a Cell perfusion system, *Harris T et al, PNAS, 106:18131 (2009)*

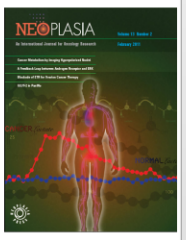


Fig 5c UCSF first-in-human trial, *Neoplasia, 2011*

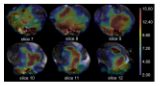


Fig 5b ^{13}C lactate heterogeneous distribution in a TRAMP mouse, *Lupu IM et al, Magn Reson Imag, 28: 153 (2010)*

How does cancer genomics benefit from HP-$^{13}C/^{15}N$ MRSI?

The advances of cancer genomics are enabling us to identify specific genes and their functions in driving cancer progression. Mutations are found in metabolic genes (IDH, SDH, FH, etc) (Fig 6a), and more often somatic mutations occur in oncogenes (PI3K, Myc, etc), and suppressor genes (p53, VHL etc) in the key pathways (Fig 4b), where these genes control the complicated interactions among pathways, networks & circuits (Fig 6b). HP-$^{13}C/^{15}N$ MRSI has the capability to simultaneously image multiple agents/functions. Thus, the effects of these alterations can be evaluated through using targeted specific probes or multiple probes to simultaneously examine several metabolic checkpoints qualitatively, semi-quantitatively and/or quantitatively. These strategies are also applicable to examine the influence of tumor microenvironments, inflammatory conditions and stressful environments.

Genetic instability leads to complexity in various progressions related to the diagnosis and treatment of cancer, i.e., evolution/metastasis of tumors, development of tumor heterogeneity, and development of therapeutic resistance. These processes are highly dynamic, heterogeneous and spatially distributed. Furthermore, the evolution of these processes may follow multi-clonal progression model (Fig 6c) in additional to the traditional, linear progression model. HP-$^{13}C/^{15}N$ MRSI has the capability to simultaneously image multiple agents/functions at real time and the capability of imaging longitudinally without radiation effects. It can thus be used to identify/quantify these alterations at the molecular level and locate/map them spatially and longitudinally.

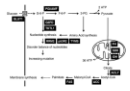


Fig 6a Metabolic genes in cancer, *Furuta E, et al, Biochimica Biophysica Acta. 1805:141 (2011)*

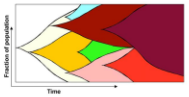


Fig 6c Multi-clonal model of tumor progression, *Merajver M, et al, Biochimica Biophysica Acta, 1805:105 (2011)*

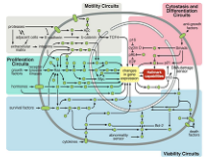


Fig 6b Intracellular signaling networks regulate the operation of the cancer cell, *Hanahan D, et al, Cell, 144:646 (2011)*

Roles of HP-$^{13}C/^{15}N$ MRSI in personalized medicine

- Detects early effects of oncogenes/suppressor genes
- Detects early effects of mutant metabolic genes
- Longitudinally traces genetic instability
- Detects metabolic adaptations to micro-environment *in vivo*
- Maps cancer genotypes/subtypes in primary and metastatic tumors
- Evaluates targeted metabolic therapy
- Evaluates combined/multi-drug metabolic therapy
- Evaluates strategies of re-programming metabolic pathways
- Etc, etc

Commercially available HP-products

On the market:

- ***HyperSense***™: Oxford instrument, DNP technology, *in vitro* & animals (Fig 7a)
- ***SpinLab***™: GE, DNP technology, animals & human (Fig 7b)
- ***$^{13}C/^{15}N$ probes***: Cambridge Isotope Inc, Isotec/Sigma-Aldrich Inc

To be on market:

- ***PASADENA/PHIP***: Spin dynamics
- ***SABRE***: Bruker

Fig 7a *HyperSense*™ (Oxford Instrument)

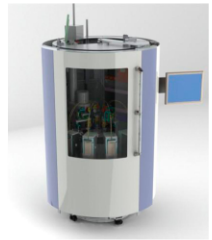


Fig 7b *SpinLab*™ (GE)

The whitepaper recommendations

1. Improve the existing technology to enhance the efficiency of rapidly and conveniently producing large volumes of highly polarized materials; understand correlations between enzyme-catalyzed reactions and malignancy,
2. Investigate technologies to preserve and store polarizations for prolonged periods,
3. Develop agents enriched with either ^{13}C or ^{15}N that combine two features: long T_1 of the hyperpolarized nucleus and rapid entry into meaningful biochemical pathways,
4. Develop consensus in the MR community for coherent strategies to standardize/harmonize methods for hyperpolarized MR data acquisition, platform-independent common protocols for quality assurance, calibration of administered doses, and software for data analysis,
5. Foster academic and industry collaborations around polarizers and large-animal systems at multiple research sites,
6. Develop a consensus on how to validate these emerging HP methods to help accelerate clinical research.

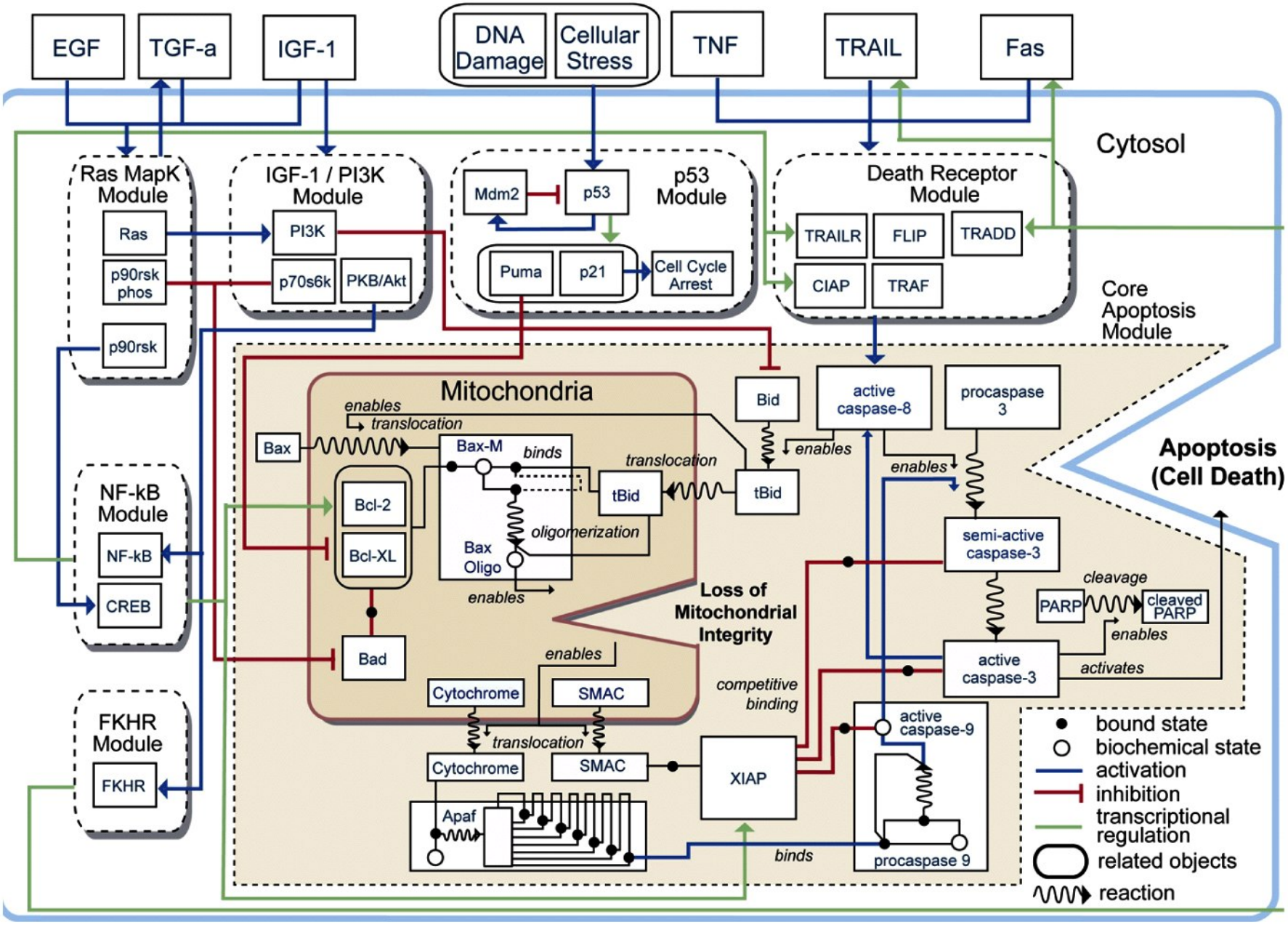


Figure 9.37 *The Biology of Cancer* (© Garland Science 2007)

How should AAPM move forward?

- Do we continue to focus in the sciences and practices of radiation physics, radiological imaging physics and nuclear medicine physics as they apply to humans?
- Do we expand the focus of AAPM to include a broader scope of science?
- What? Who? How?
  - ***Work Group on the Future of Research and Education***

My thoughts…

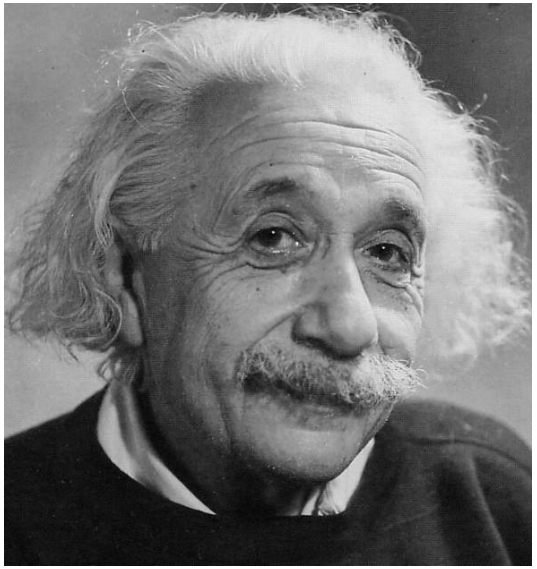
- Some reasonably obvious opportunities.
  - Quantitative imaging for therapy response assessment
  - Functional (metabolic and physiologic) imaging to understand and sample tumor phenotype
- Participation in team science to solve the “big problems” of the future.
  - We bring quantitative science skills that will enhance these teams.
- Organically develop new directions and scientific focus in areas of biomedical research expected to impact healthcare in the future.
- Partner with other organizations and groups to collectively advance the **impact** of medical physics research.

My thoughts…

- This will require us to refine our educational programs to meet the scientific needs for future in research medical physics.
  - Inclusion of non-traditional material in the curriculum of students intending to pursue a career in research.
- The AAPM's role is to provide a framework and infrastructure for addressing these challenges and opportunities, and to organize efforts to achieve our goals in research.
  - ***Symposium at 2014 AAPM meeting on PSOC related research?***

Imagination is more important than knowledge.

Albert Einstein



The enemy is cancer, not another lab or institution.

John Mendelsohn