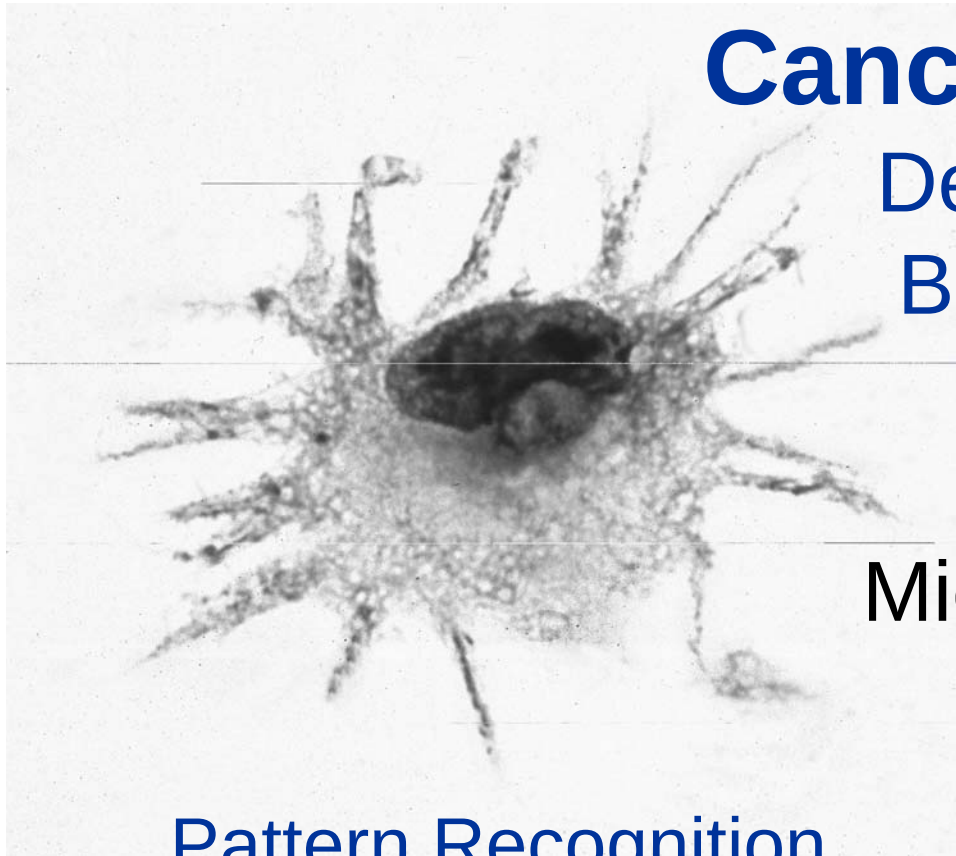




Cancer Biometrics

Development of Biomarker and Surrogates

Pattern Recognition

Michael T. Lotze
Molecular
Medicine
Institute

University of Pittsburgh

November 4, 2004

Where's the rub? Really useful biomarkers in cancer

SPECIAL INVESTIGATION

How to Win the War on Cancer

REAL ESTATE
Three Stocks,
Three Hot Markets

FORTUNE

WHY WE'RE
LOSING
THE WAR ON

CANCER

(AND HOW TO WIN IT)

By Clifton Leaf

FEBRUARY 23, 2004

BUSH'S
MILITARY RECORDS
IS DISNEY MOUSETRAPPED?



www.time.com AOL Keyword: TIME

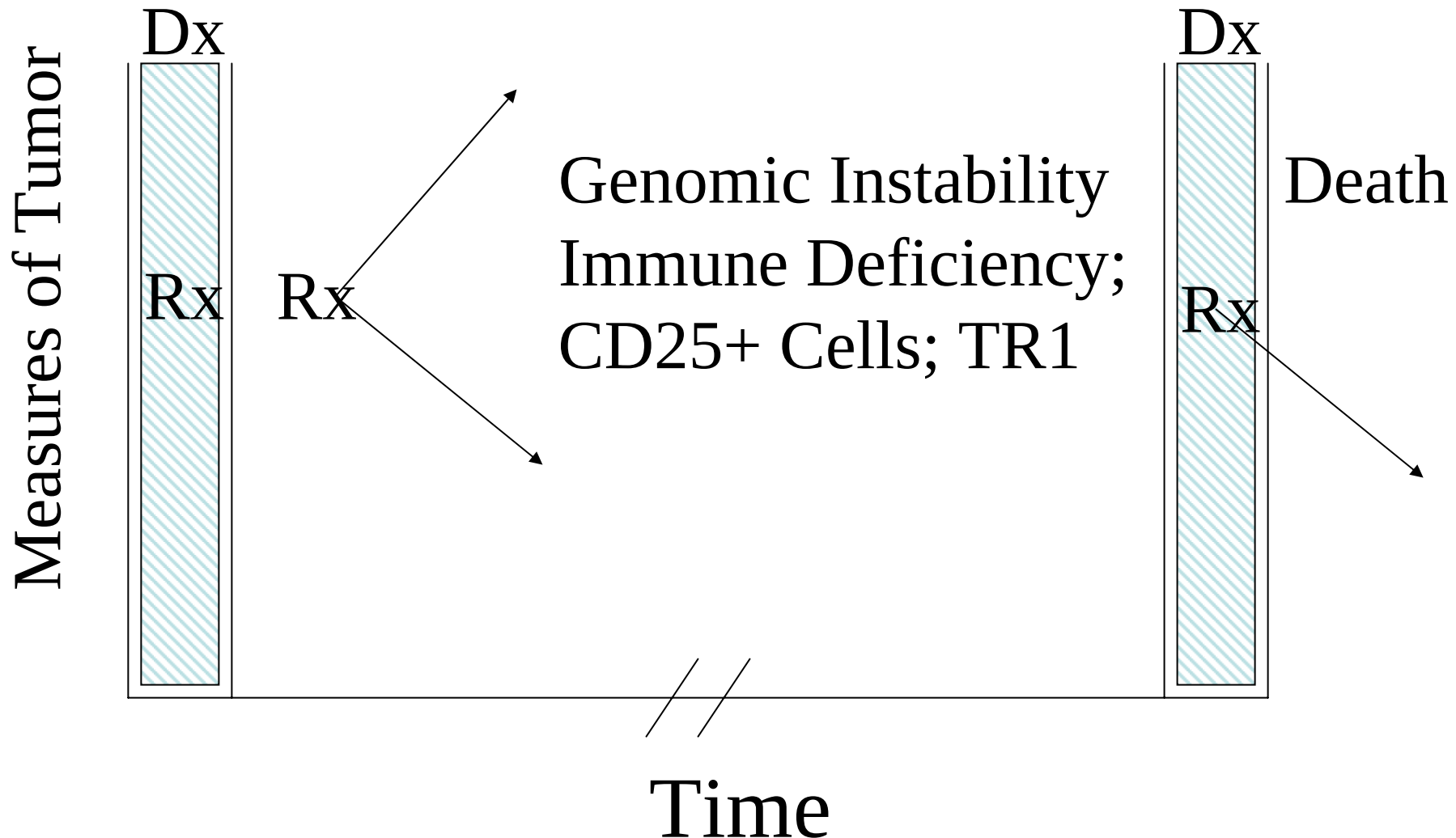
- A genetic disorder
- Disease in adults arises in the setting of inflammation
- Necrosis and necrotic factors drive tumor growth

DISPLAY UNTIL MARCH 29, 2004

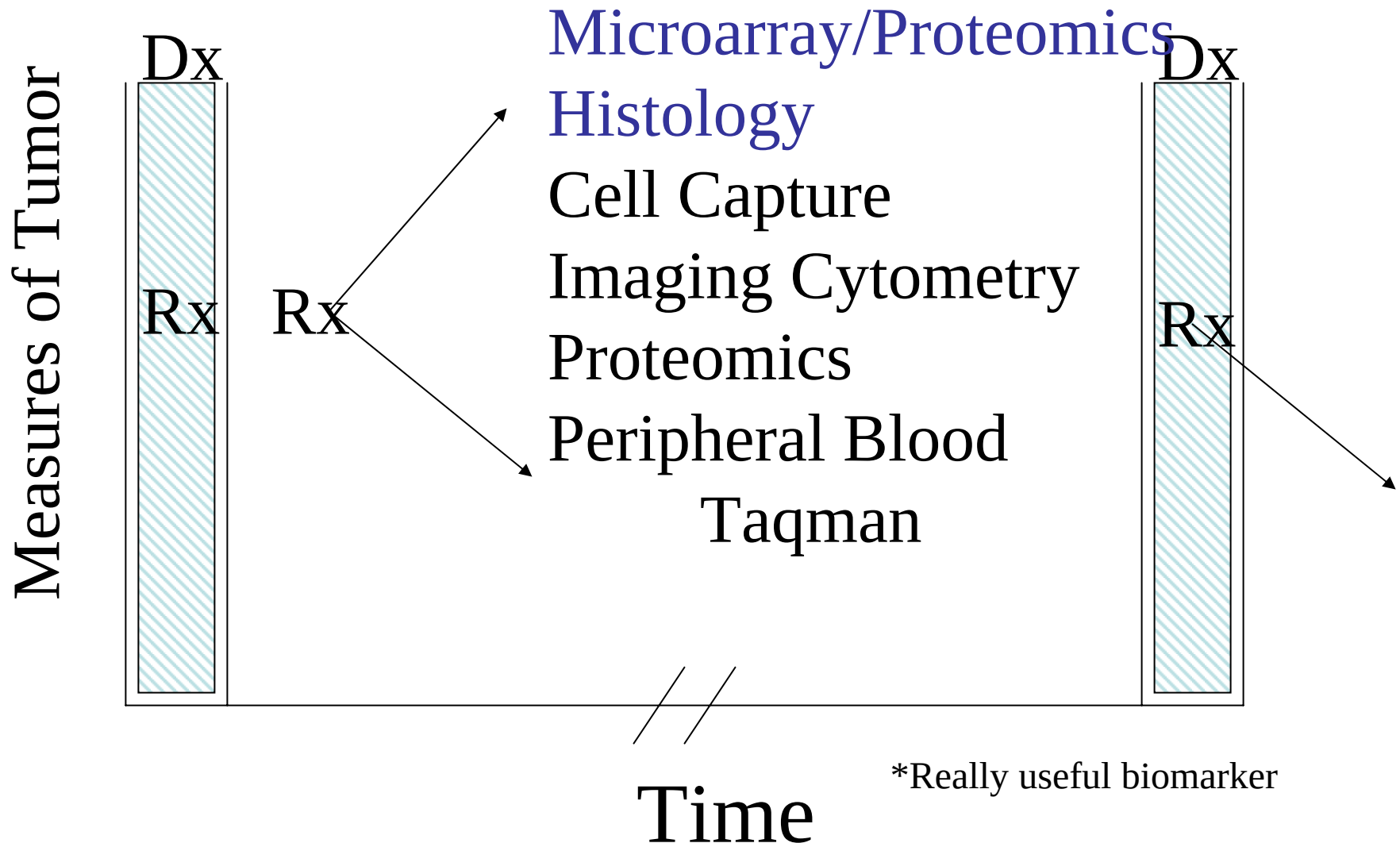


www.fortune.com (AOL Keyword: Fortune)

Cancer Diagnosis & Treatment Need for Vaccine Biomarkers & Surrogates – Cancer Biometrics



Where's the RUB*?



CANCER BIOMETRICS: Identifying Biomarkers and Surrogates For Tumor

Masur Auditorium
Thursday, October 30, 2003



National Institutes of Health





Cancer Biometrics

- 1] Genomic analysis**
- 2] Detection of molecular markers in peripheral blood and lymph node by tumor capture and RT-PCR**
- 3] Serum, plasma, and tumor proteomics**
- 4] Immune polymorphisms**
- 5] High content screening using flow and imaging cytometry**
- 6] Immunohistochemistry and tissue microarrays**
- 7] Assessment of immune infiltrate and necrosis in tumors.**

**Report from the International Society for the
Biologic Therapy of Cancer
Workshop on Cancer Biometrics:
Identifying Biomarkers and Surrogates
of Tumors in Patients
A meeting held at the Masur Auditorium,
National Institutes of Health**

Michael T. Lotze¹, Ena Wang², Francesco M. Marincola²,
Nabil Hanna³, Peter J Bugelski⁴, Christine A. Burns⁵,
George Coukos⁶, Nitin Damle⁷, Tony A. Godfrey^{8, 9}, W.
Martin Howell¹⁰, Monica C. Panelli², Michael A. Perricone¹¹,
Emanuel F. Petricoin¹², Guido Sauter¹³, Carmen
Scheibenbogen¹⁴, Steven C. Shivers¹⁵, D. Lansing
Taylor¹⁶, John N. Weinstein¹⁷, and Theresa L. Whiteside⁸

Two Sources from Blood

- Serum/protein - SELDI-TOF mass spectrometry [CIPHERGEN, Q-STAR]
Known proteins CBA, Luminex
- Cells – Microarray;
Proteomics; Imaging and Flow Cytometry



Clinical Applications Of Proteomic Technologies



"If it were not for the great variability among individuals,
Medicine might be a science not an art. (Sir William Osler, The
Principles and Practice of Medicine 1892)

Emanuel Petricoin CBER, FDA



National Institutes of Health

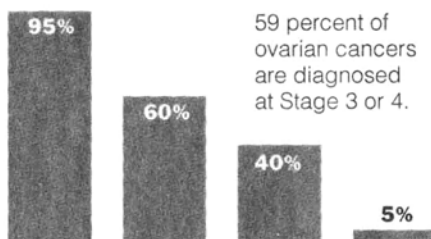


New York Times

Surviving Ovarian Cancer

Percentage of patients living five years or more after diagnosis.

SEVERITY OF CANCER AT DIAGNOSIS:
STAGE 1 2 3 4



Source: Dr. Timothy Veenstra,
SAIC-Frederick, Inc.

The New York Times

New Cancer Test Stirs Hope and Concern

By ANDREW POLLACK

Jill Doimer's mother died in 2002 from ovarian cancer, detected too late to be effectively treated.

So Ms. Doimer is eagerly awaiting the introduction of a new test that holds the promise of detecting early-stage ovarian cancer far more accurately than any test available now, using only blood from a finger prick.

Not only does she plan to be tested, but an advocacy group she helped found, Ovarian Awareness of Kentucky, also intends to

spread the word to women and doctors.

"If it's going to happen to me or anyone I know, I want it to be caught at an early stage," said Ms. Doimer, who lives in Louisville.

The new test, expected to be available in the next few months, could have a big effect on public health if it works as advertised. That is because when ovarian cancer is caught early, when it is treatable by surgery, more than 90 percent of women live five years or longer. But right now, about three-quarters of cases are detected after the cancer has advanced, and then only 35 percent of women survive five years.

The test is also the first to use a new technology that some believers say could revolutionize diagnostics. It looks not for a single telltale protein — like the prostate-specific antigen, or P.S.A., used to diagnose prostate cancer — but rather for a complex fingerprint formed by all the proteins in the blood. Similar tests are being developed for prostate, pancreatic, breast and other cancers. The technique may work for other diseases as well.

"I've been in cancer research for 40 years and I think it's the most important breakthrough in those years," said Dr.

Continued on Page 6

1. In the Nucleus

- Bends DNA
- Binds to distorted DNA
- Modulates the interaction of regulatory factors with their targets



2. Cell Migration Metastasis

3. To the Nucleus

NF- κ B
Kinases

Receptors

Plasminogen

RAGE
TLR2, TLR4

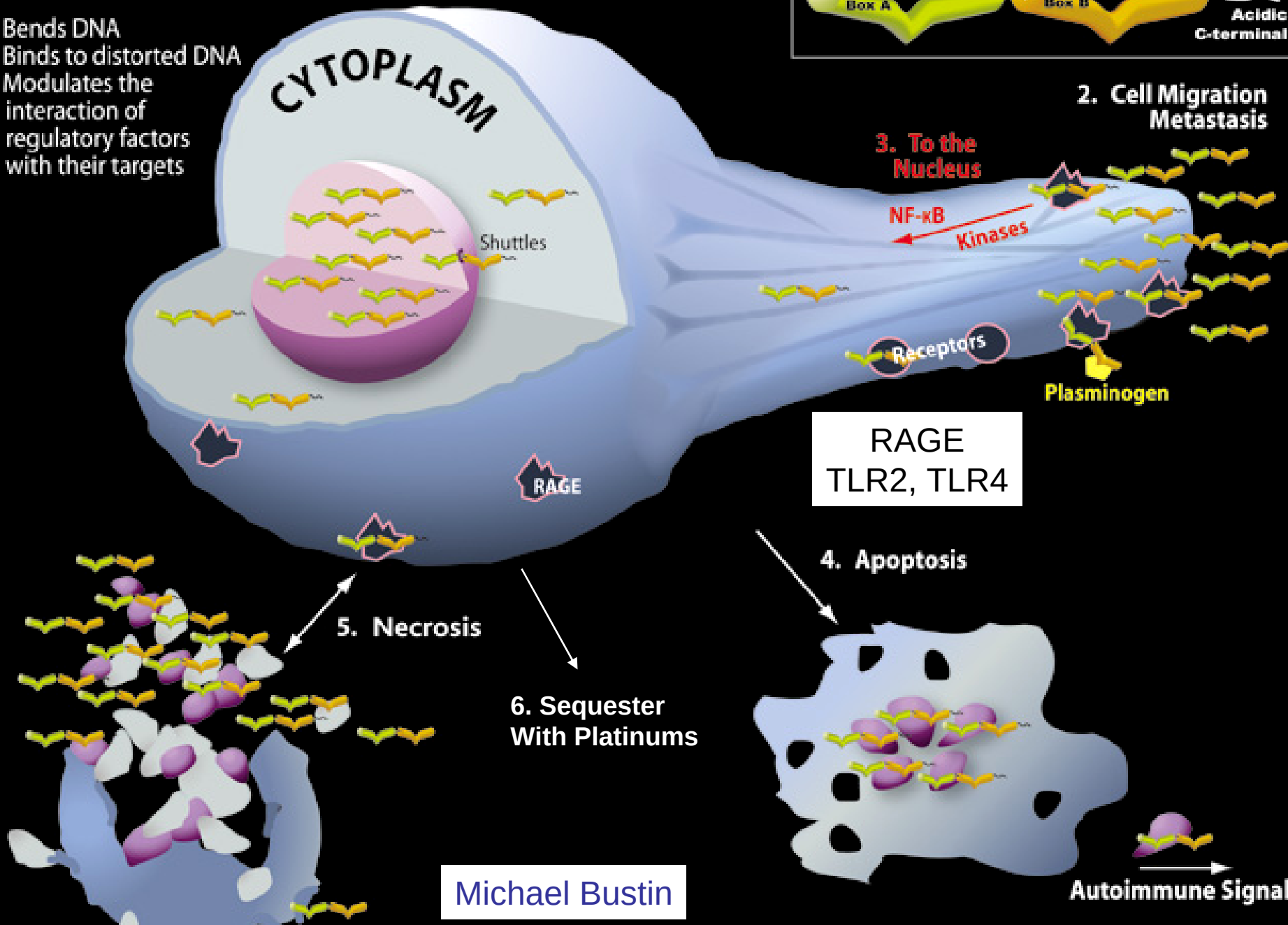
4. Apoptosis

5. Necrosis

6. Sequester With Platinums

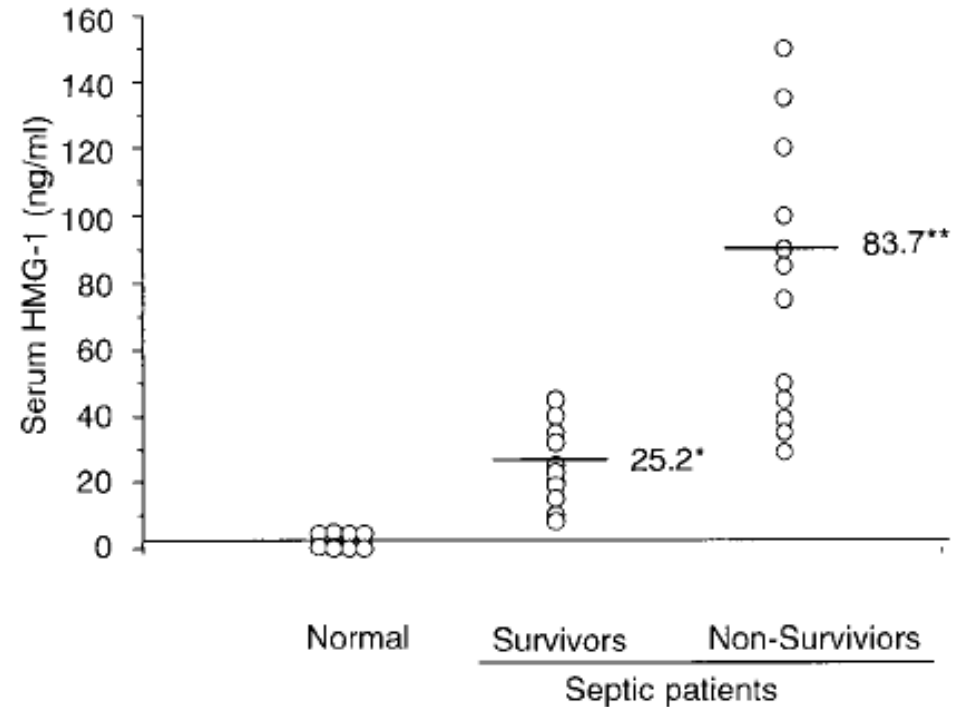
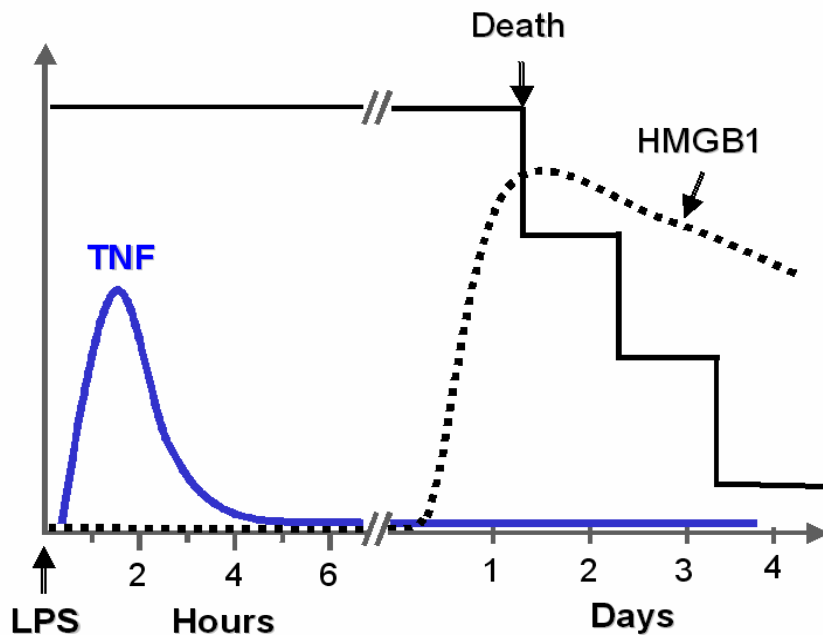
Michael Bustin

Autoimmune Signal

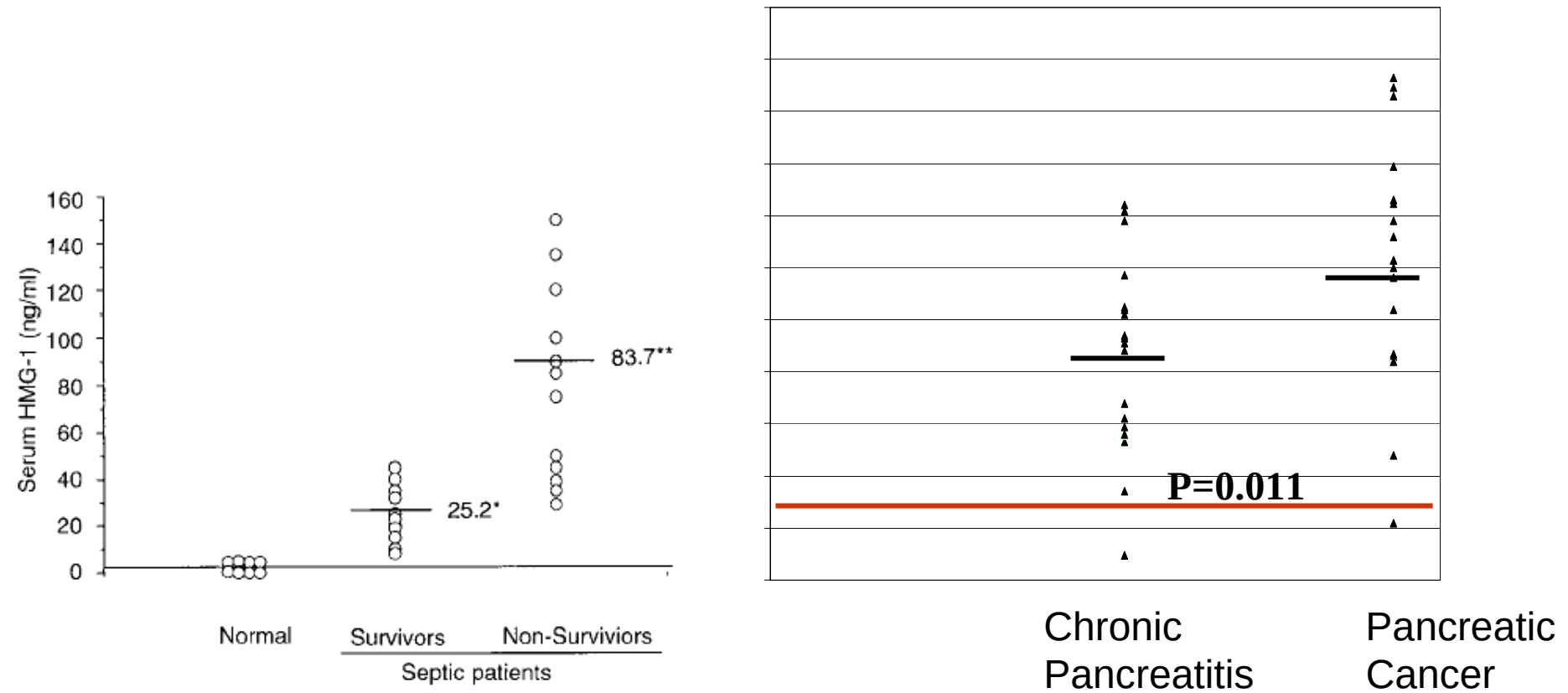


Serum Levels of HMGB1 Appear Prior to Death From Sepsis

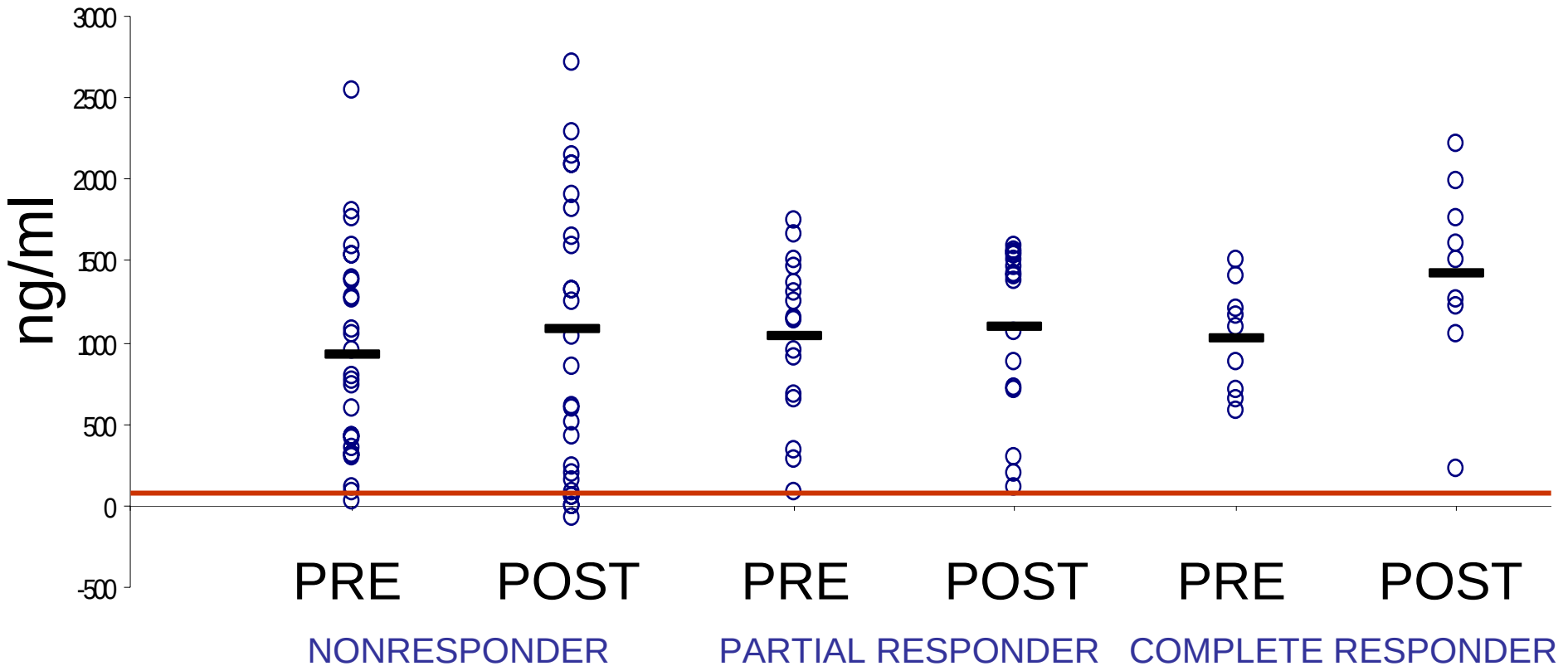
Kevin Tracy / Mitch Fink



HMGB1 is elevated in serum of patients with pancreatic cancer



Elevated Serum Levels of HMGB1 in Advanced Melanoma Pts Rx Hi-dose IL-2



Margot Gallowitsch

Contributors

- Bill Bigbee, Jim Lyons-Weiler, Anna Lokshin
- Herb Zeh; Dave Bartlett; Chas Brown; Yong Lee
- Pawel Kalinski, Per Basse, Ron Herberman, Theresa Whiteside
- Richard DeMarco; Jukka Vakkila; David Montag
- Mitchell Fink
- Marco Bianchi
- Kevin Tracey
- Ann Marie Schmidt
- Steven Rosenberg/John Wunderlich

University of Pittsburgh Molecular Medicine Institute



Recommendations

- 1] Minimum Information About a Microarray Experiment (MIAME) should be used [to standardize array data and metadata presentation;
- 2] In the process of developing high-throughput technologies promote assay standardization;
- 3] Promote automation technologies that will reduce the amount of sample manipulation that reduces inter-operator variability and produce more consistent analyses between individual clinical labs;

Recommendations

- 4] NIH/FDA/Biotech Cooperative Grants (non-SBIR) be funded to accelerate clinical applications;
- 5] NIH/FDA/Pharmaceutical companies should provide training/upgrades to staff involved in applying these new technologies;

Recommendations

- 6] Develop core facilities with array of advanced instruments/technologies available;
- 7] Enable sharing of results with development of open access multi-institutional website similar to NCI WEB site;
- 8] Develop continuous upgrades of Bioinformatics tools;

Recommendations

- 9] Implement training and subsequent testing systems on assays (normal vs disease) with large data bases;
- 10] As each new patient is validated through pathological diagnosis using retrospective or prospective data add its input to the expanding training set;
- 11] Establish database of normal ranges from various demographic populations to allow valid comparisons to disease states;

Recommendations

- 12] Create a national repository for serum/plasma as well as definition of the best practices to use for serum/plasma collection;
- 13] Standardize serum/plasma analysis, storage, and good laboratory practice through a combined effort of interested groups including the NCI, FDA, WHO, Red Cross, etc.;

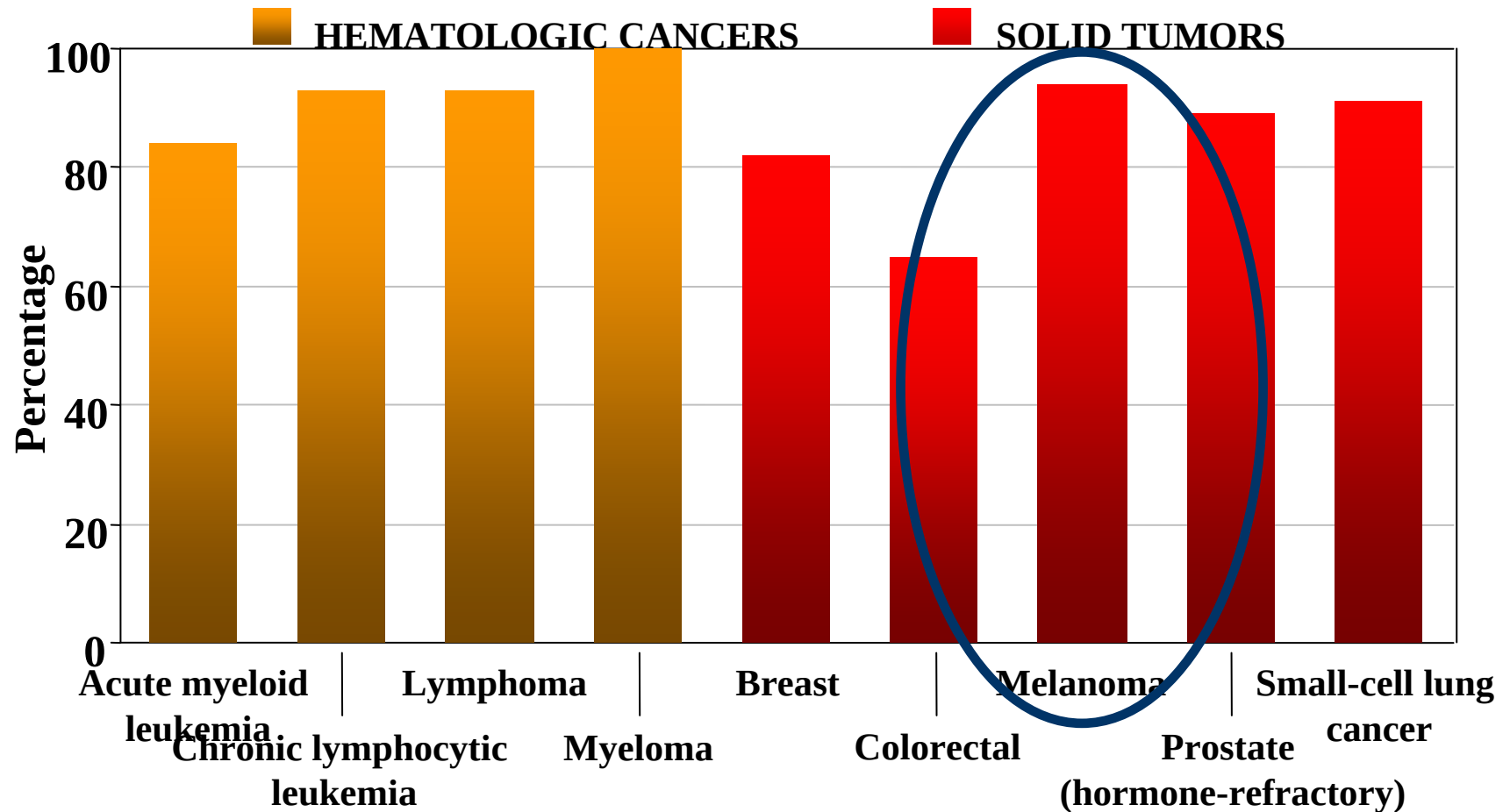
Recommendations

- 14] Fund and perform a definitive study of selected immune response gene polymorphisms in selected cancers such as cutaneous malignant melanoma, breast cancer and/or childhood leukaemia;
- 15] Insist that all patients in biotherapy studies have assessed at baseline and following therapy T cell counts (total, CD4, CD8) and T cell receptor ζ -chain expression by flow cytometry;

Recommendations

- 16] Develop integrated strategies to enhance antigen detection with immunohistochemistry strategies;
- 17] Coordinate with academic pathology groups to make standard of practice tumor biopsy assessment of intratumoral immune cells [T/NK/DC/B; neutrophils, eosinophils, and mast cells] and enumeration in all pathologic evaluations of all tumors in humans of micro- and macronecrosis.

Bcl-2: Produced At A High Level In Cancer



(Cerroni et al, 1995; Chen et al, 1997; Jiang et al, 1995; Karakas et al, 1998; Lanzafame et al, 1998; Lazaridou et al, 2000; Puthier et al, 1999; Sullivan et al, 1998; Yang et al, 1999)

Why Women Live Longer Than Men

