Cancer Biometrics
Development of Biomarker and Surrogates

Pattern Recognition

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Where’s the rub? Really useful biomarkers in cancer
• A genetic disorder
• Disease in adults arises in the setting of inflammation
• Necrosis and necrotic factors drive tumor growth
Cancer Diagnosis & Treatment
Need for Vaccine Biomarkers & Surrogates – Cancer Biometrics

Measures of Tumor

Dx

Rx

Genomic Instability
Immune Deficiency;
CD25+ Cells; TR1

Rx

Dx

Death

Rx

Time
Where’s the RUB*?

Microarray/Proteomics
Histology
Cell Capture
Imaging Cytometry
Proteomics
Peripheral Blood
Taqman

*Really useful biomarker
CANCER BIOMETRICS: Identifying Biomarkers and Surrogates For Tumor

Masur Auditorium
Thursday, October 30, 2003
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
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. Godfrey8, 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 spectometry [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
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.

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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

4. Apoptosis

5. Necrosis

6. Sequester With Platinums

RAGE
TLR2, TLR4
Serum Levels of HMGB1 Appear Prior to Death From Sepsis

Kevin Tracy / Mitch Fink

[Graph showing TNF and HMGB1 levels over time, with LPS injection and death as markers.]
HMGB1 is elevated in serum of patients with pancreatic cancer

Chronic Pancreatitis
Pancreatic Cancer

Herb Zeh/ Margot Gallowitsch
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
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
