The new post-genomic field of science

- Proteins are the primary target for most therapeutics
- New biomarkers for disease, toxicity and treatment
- Determine product potency, purity and consistency
- Endpoints and release specifications for drug products
- Molecular targeted therapy and patient tailored therapy - *Recent examples: GLEEVEC, HERCEPTIN. These drugs target activated and disregulated proteins, not genes.*

Regulatory Impact

- Vaccine assessment/potency
- Surrogate endpoints - efficacy/toxicity
- Quality control/quality assurance for product production
- New bioassays
- Biomarkers for early detection
- Toxicity detection and prediction

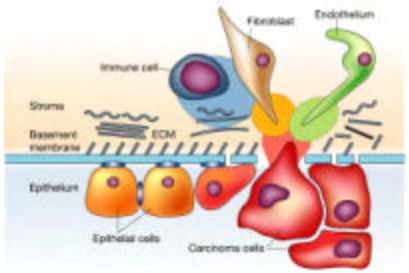
Regulatory Impact (cont.)

- Discovery of new therapeutic targets
- Risk of disease recurrence
- Patient-tailored therapy. Prospective selection
- New paradigm in disease classification/characterization
- Proteomic-based epidemiology

FDA views on proteomics:

- Critical component of safe and effective drug development
- Basis for new drug discovery, biomarkers and surrogate endpoints for toxicity and efficacy monitoring
- Means to detect and assess chemical and biological terrorist agents

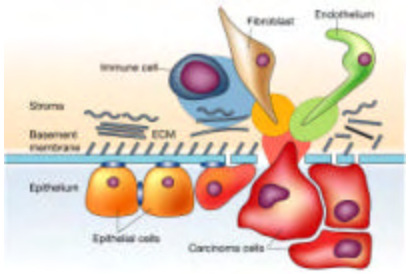
TISSUE MICROENVIRONMENT



NATURE 2001

- **Proteomic networks exist within the cell and outside the cell at the tumor-host interface**
- **Cancer is a proteomic disease at the functional level.**
- **The state of protein networks is dictated by the tissue context of the cell, and the local cell-cell or cell-matrix interactions**
- **Cell culture models may not accurately represent the fluctuating protein expression pattern and the state of protein interactions in the native tissue microenvironment**

PROTEOMIC INFORMATION



JAMA 2002

- **State of protein circuits within the cell and outside the cell at the tumor-host interface: Pathogenic role of dominant or deranged signal pathways**

- **Proteomic information content of circulating blood: Patterns of LMW proteins and peptides reflect organ pathologic states**

Keys to Cancer:

- **Early Detection-**

Development of new artificial intelligence-based bioinformatics tools for diagnostic proteomic pattern discovery

- **Molecular Diagnostics**

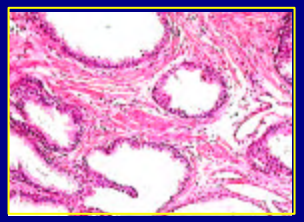
New Target Discovery (2D-PAGE)
Signal Pathway Profiling (Protein Arrays)
Phosphoproteomics (Protein Arrays/ 2D-PAGE)

- **Molecular Targeted Therapeutics**

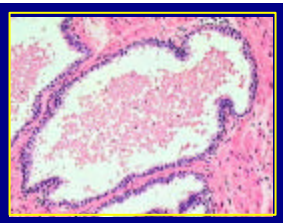
Implementation of proteomics to ongoing NCI-based clinical trials

PROTEOMIC ANALYSIS IN THE CONTEXT OF THE TISSUE MICROENVIRONMENT

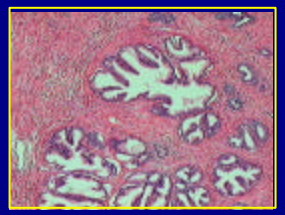
Human Prostate



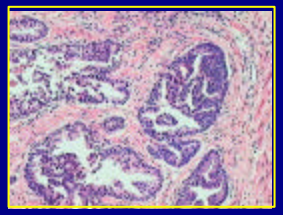
Low-grade PIN



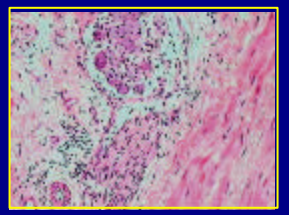
Normal



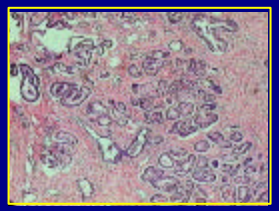
Hyperplasia



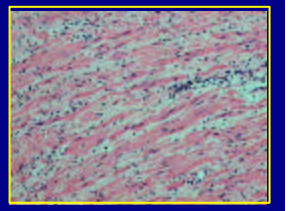
High-grade PIN



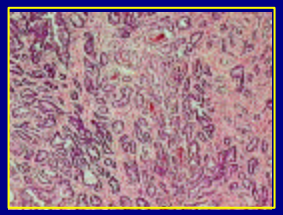
Nerve



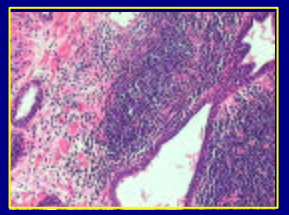
Well-differentiated carcinoma



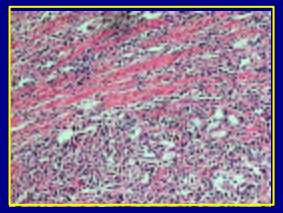
Stroma



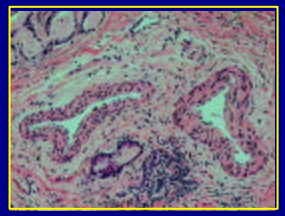
Moderately-differentiated carcinoma



Inflammation



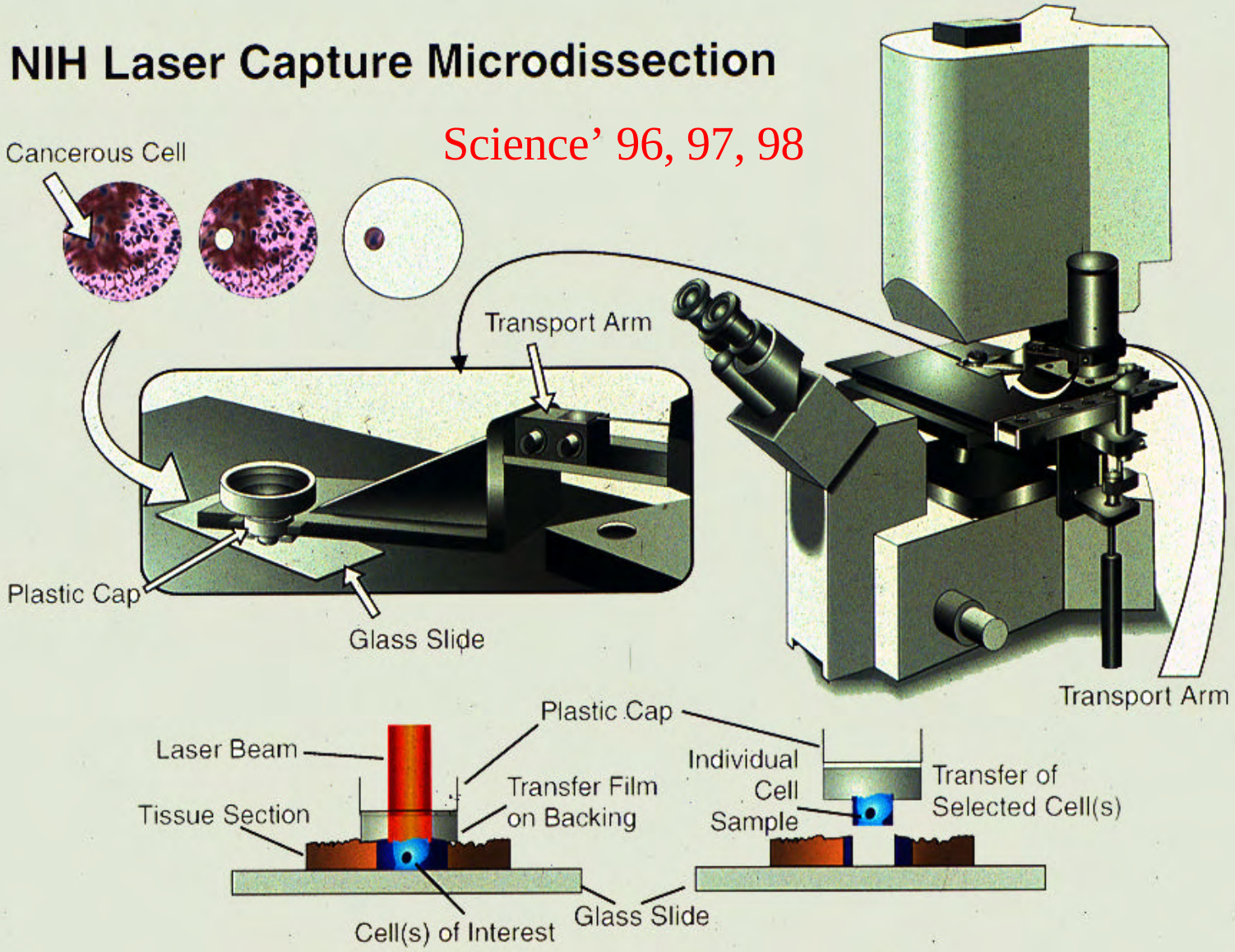
Poorly-differentiated carcinoma



Neovessels

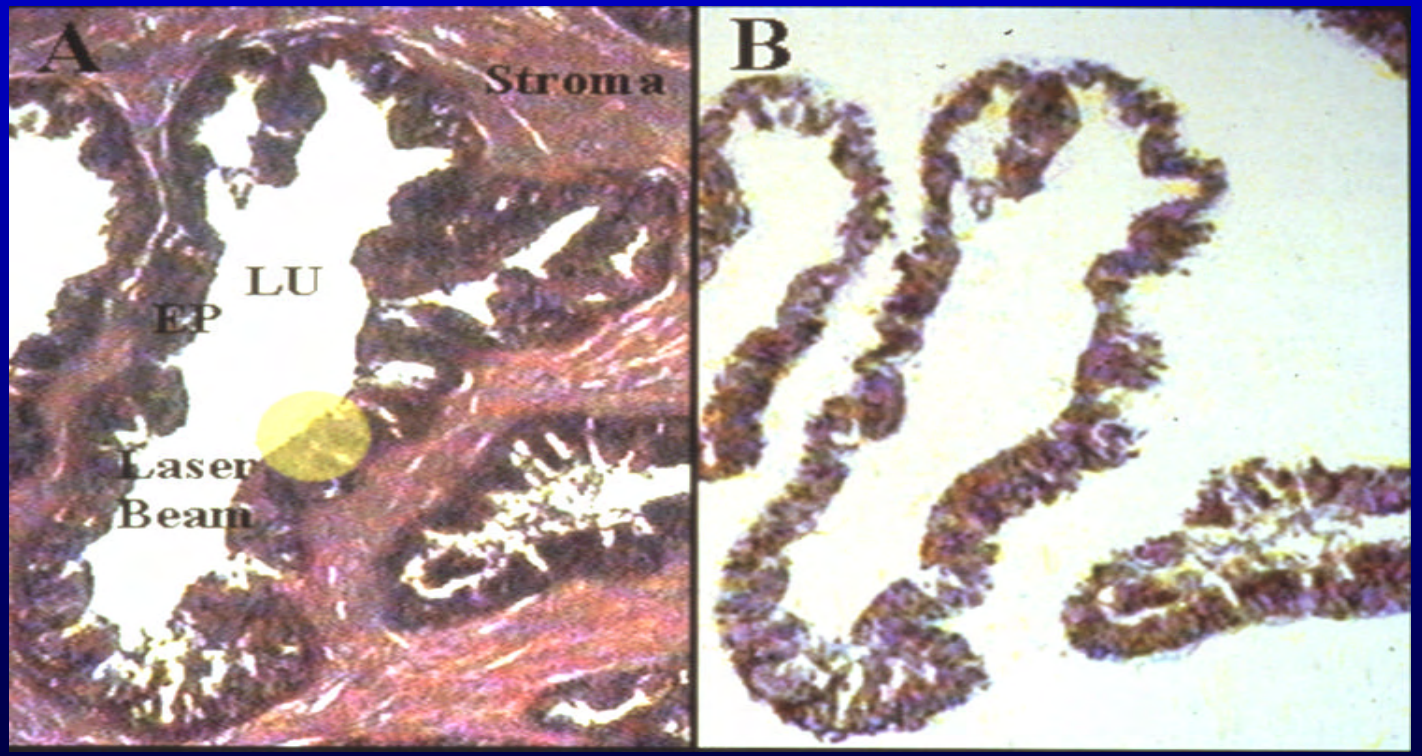
NIH Laser Capture Microdissection

Science' 96, 97, 98



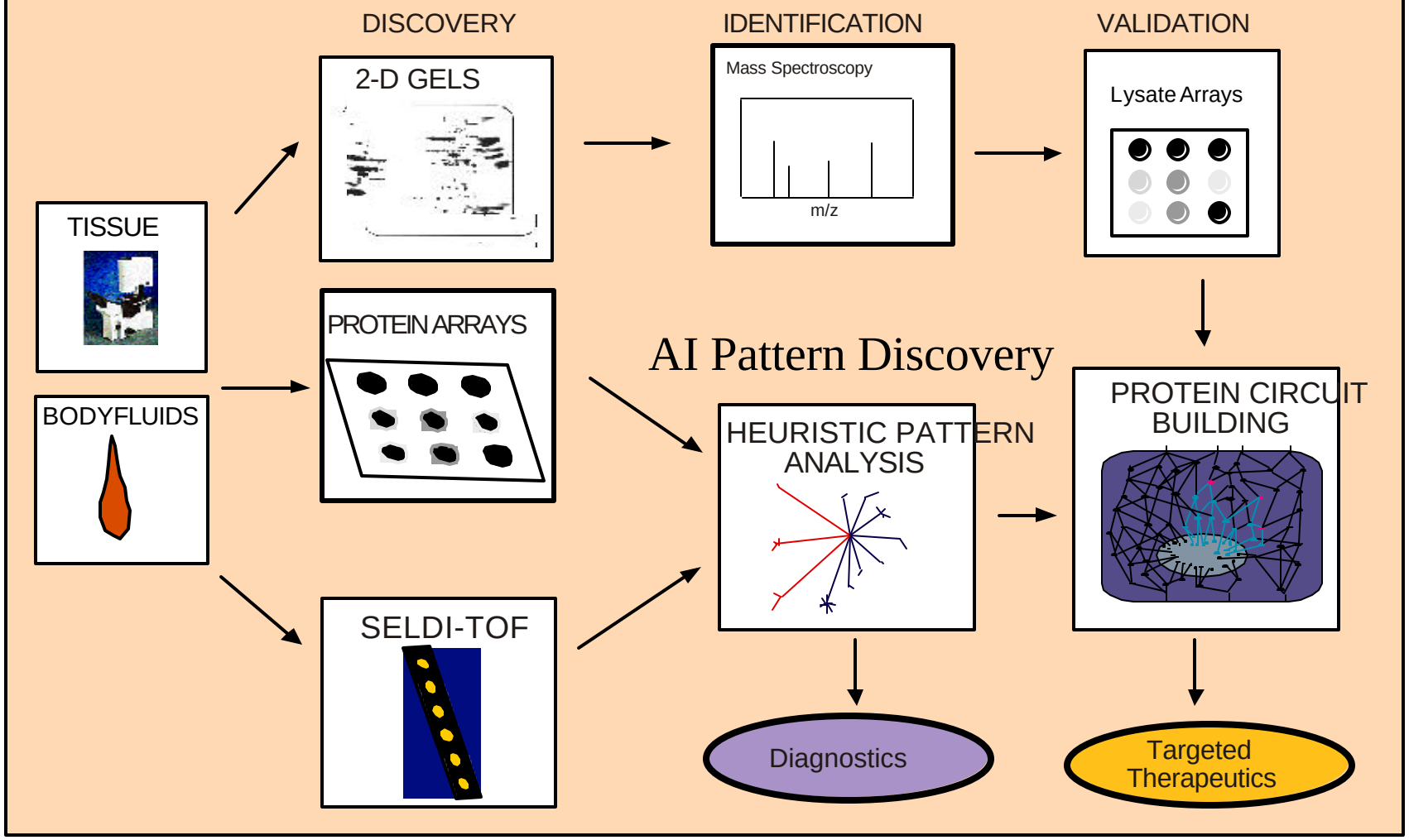
Before LCM

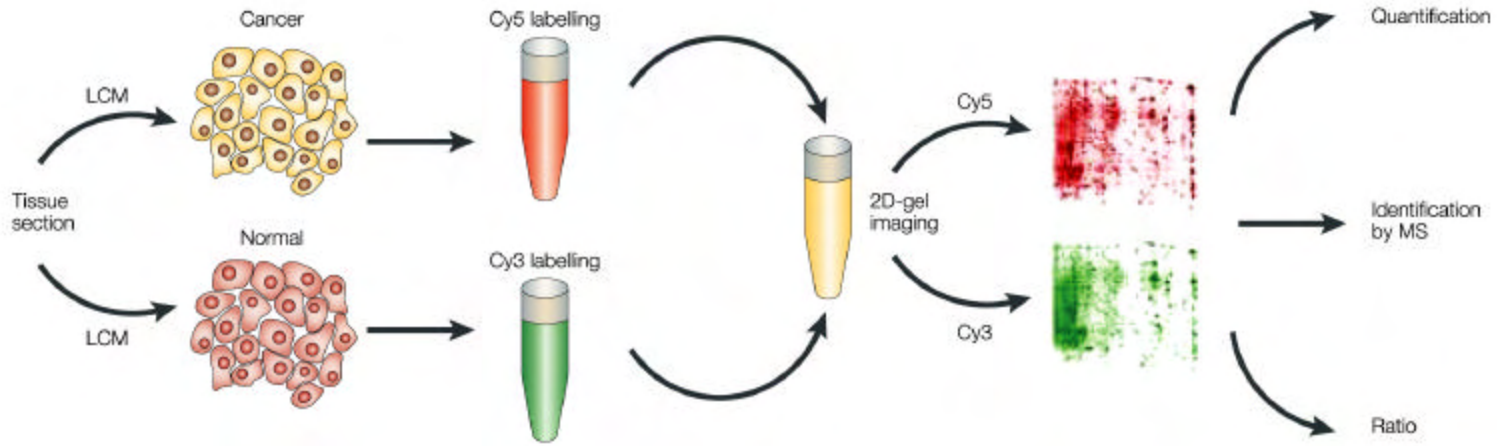
After LCM



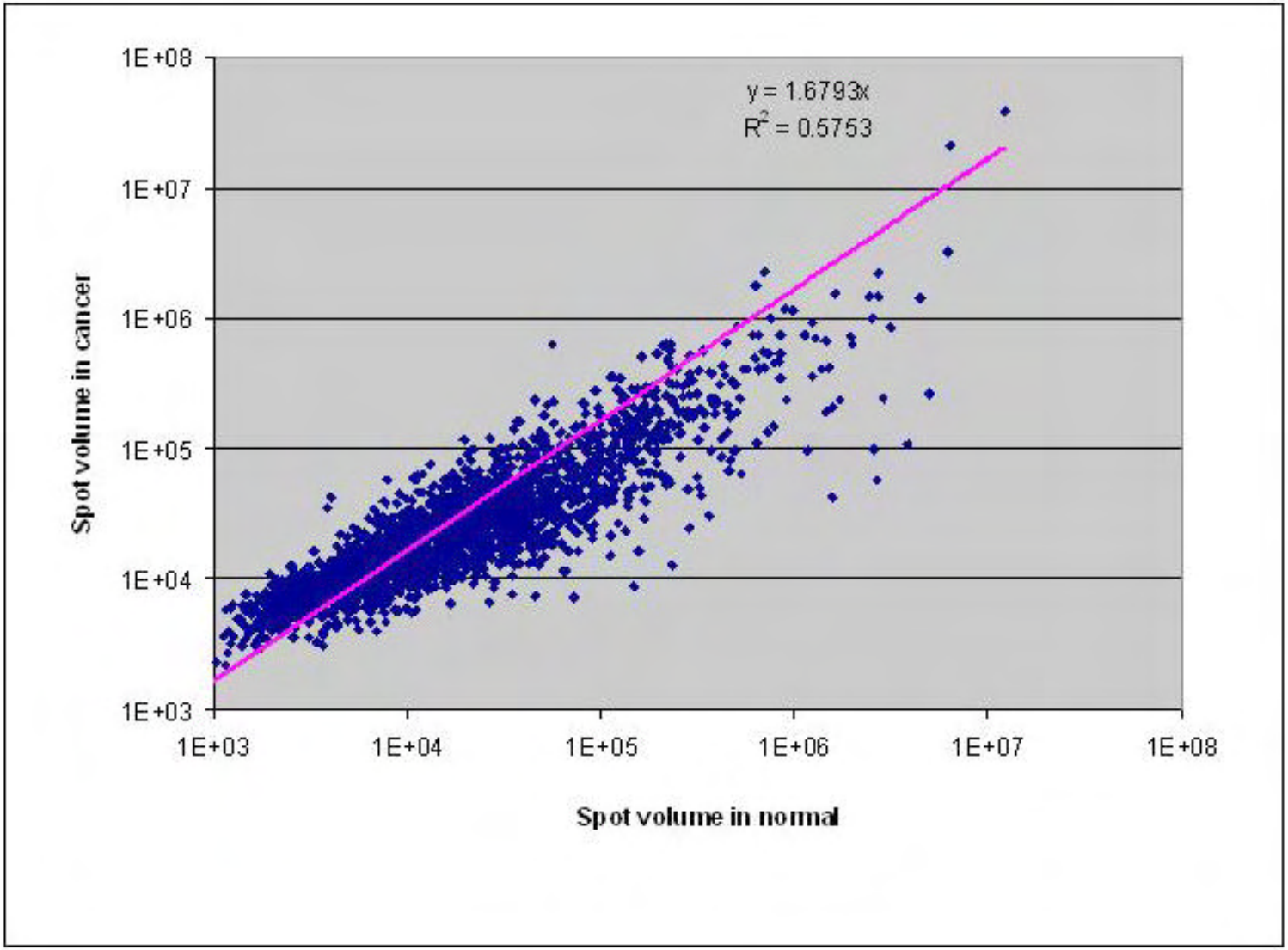
Case study: Prostate normal epithelium (human)

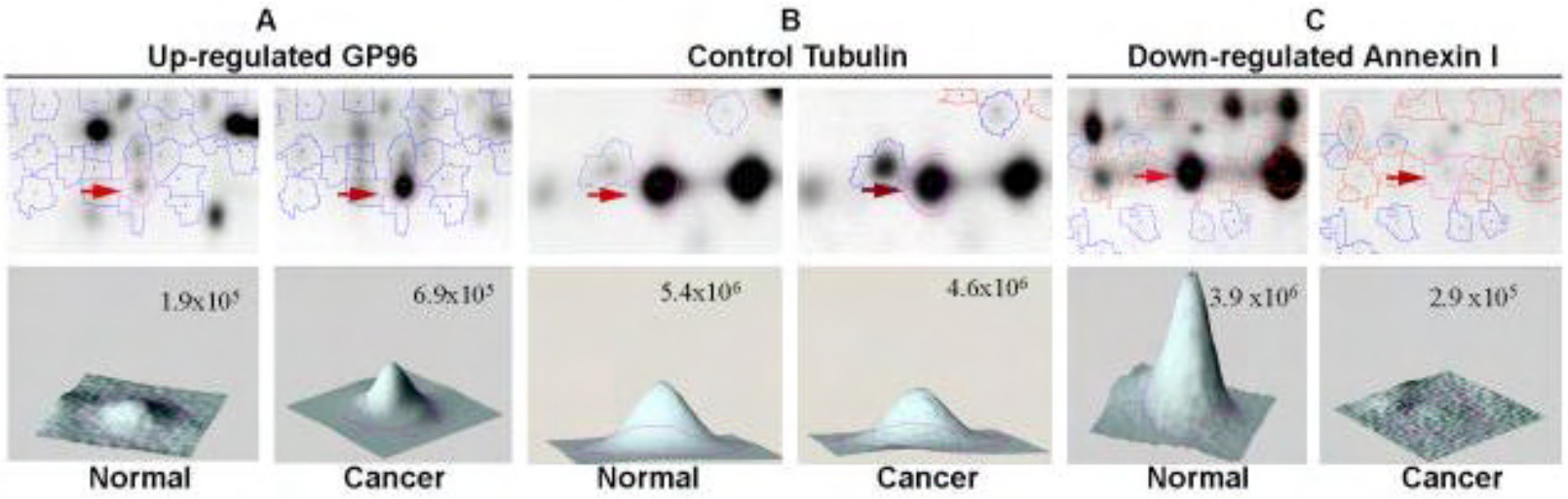
NCI - CBER/FDA CLINICAL PROTEOMICS PROGRAM- Began 2000





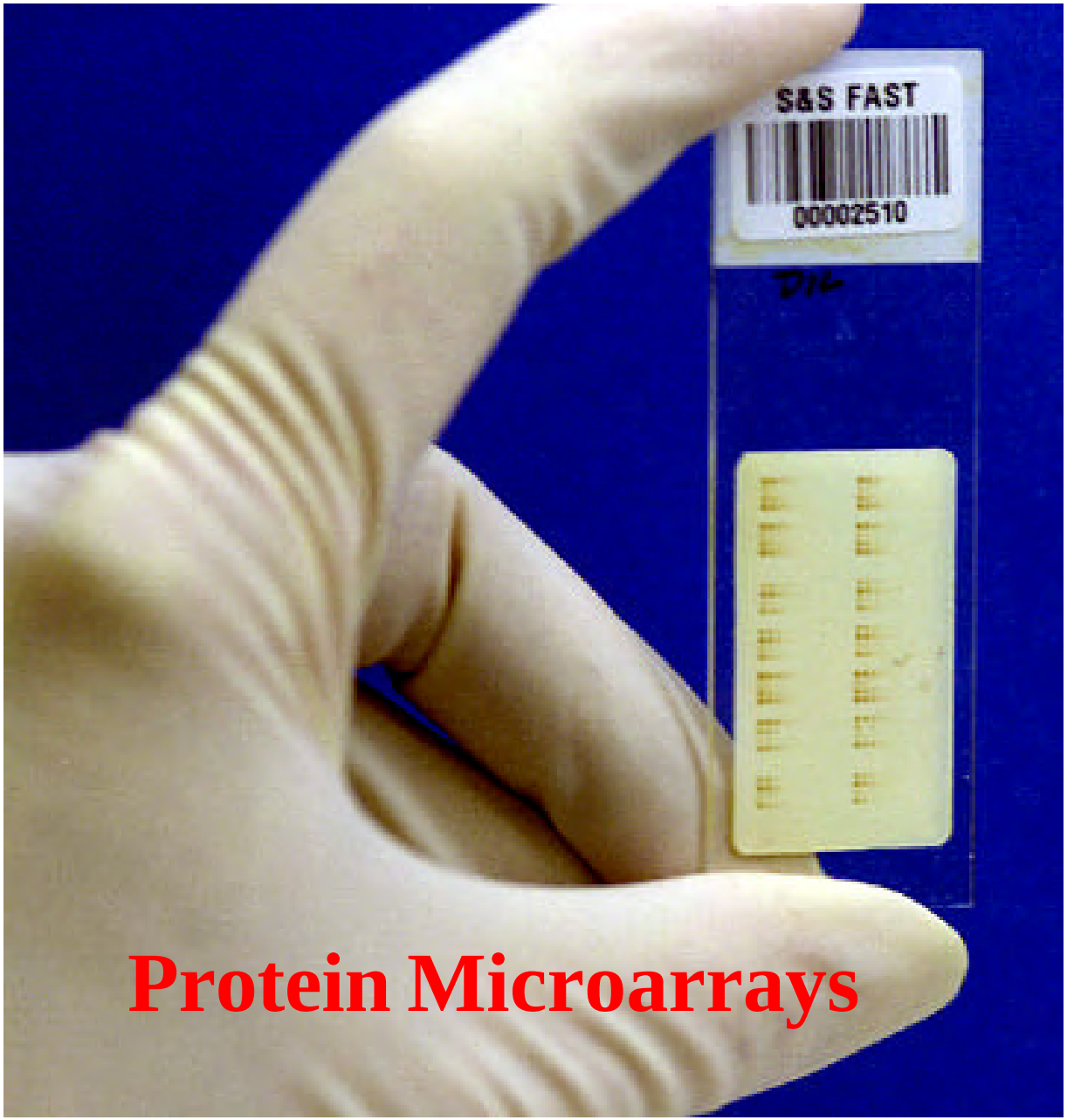
Nature Reviews | Drug Discovery


y = 1.6793x
R2 = 0.5753
1E+08
1E+07
1E+06
1E+05
1E+04
1E+03
Spot volume in cancer
1E+03
1E+04
1E+05
1E+06
1E+07
1E+08
Spot volume in normal

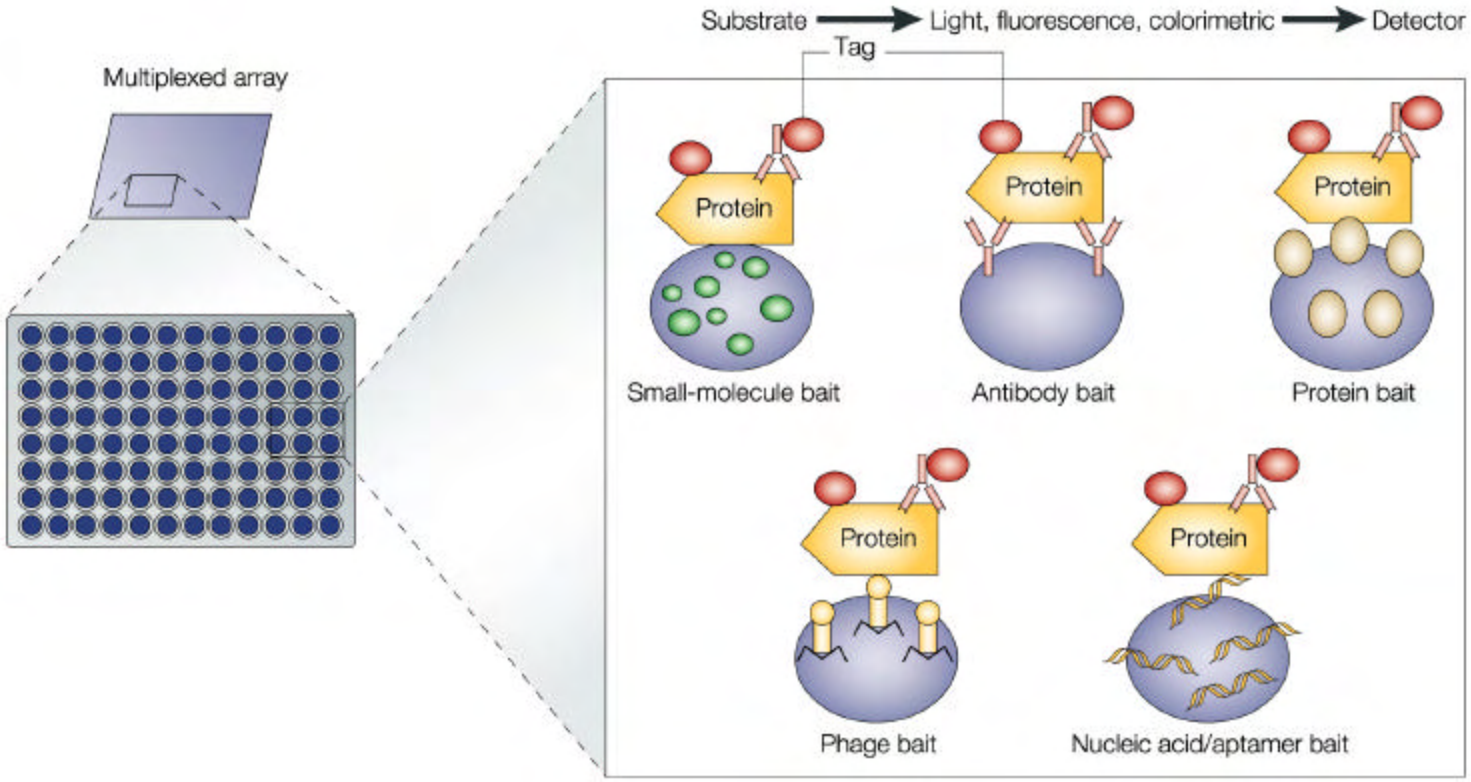


Differentially expressed proteins identified to date: >400

Breast, Prostate, Ovary, and Esophageal Cancer



Protein Microarrays


Substrate
Light, fluorescence, colorimetric
Detector
Tag
Multiplexed array
Protein
Protein
Protein
Small-molecule bait
Antibody bait
Protein bait
Protein
Protein
Phage bait
Nucleic acid/aptamer bait

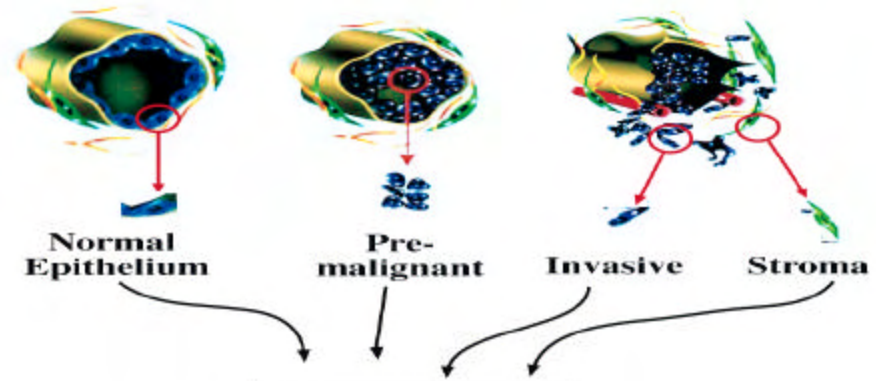
A New Protein Array Technology: Reverse Phase Protein Array

Oncogene 2001

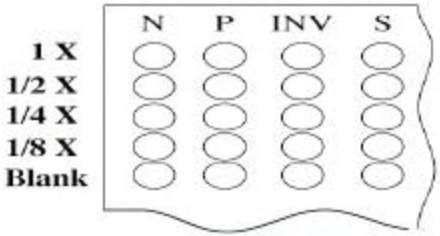
Coupling Laser Capture Microdissection
With High Throughput Protein Arrays

Patient biopsy tissue cells are microdissected:

2000 cells = 100 arrays



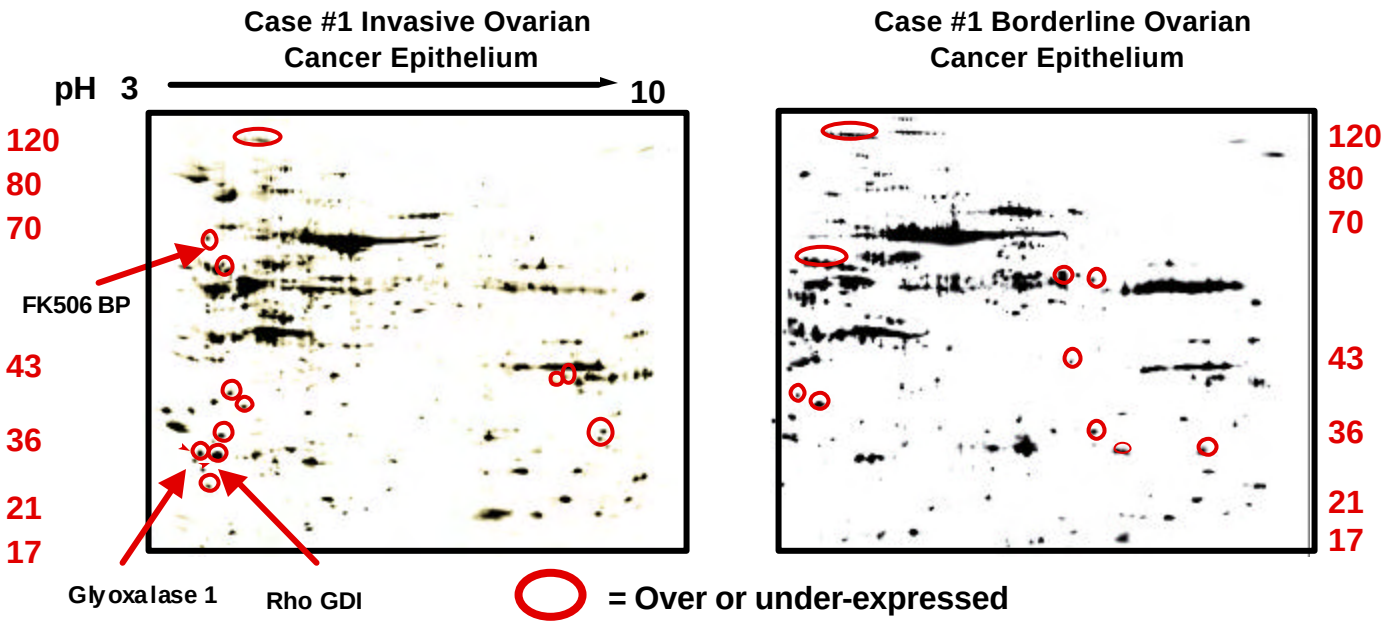
Each patient sample is arrayed in a miniature dilution curve:
Always in linear dynamic range of any antibody/ analyte pair

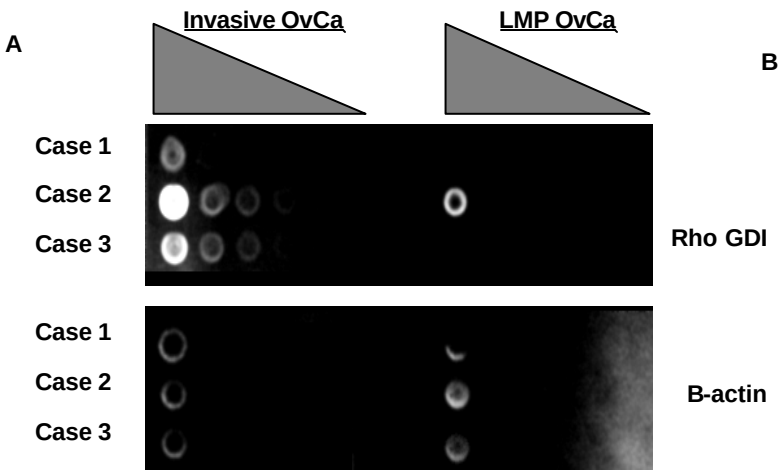


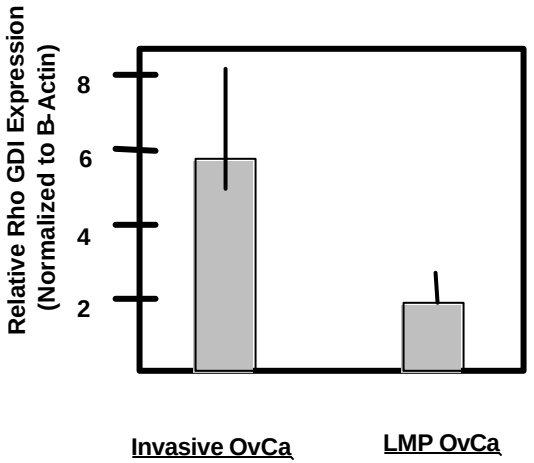
Arrays probed with labeled amplified antibody:

e.g. prostate cancer progression From one patient probed with Phospho-ERK antibody

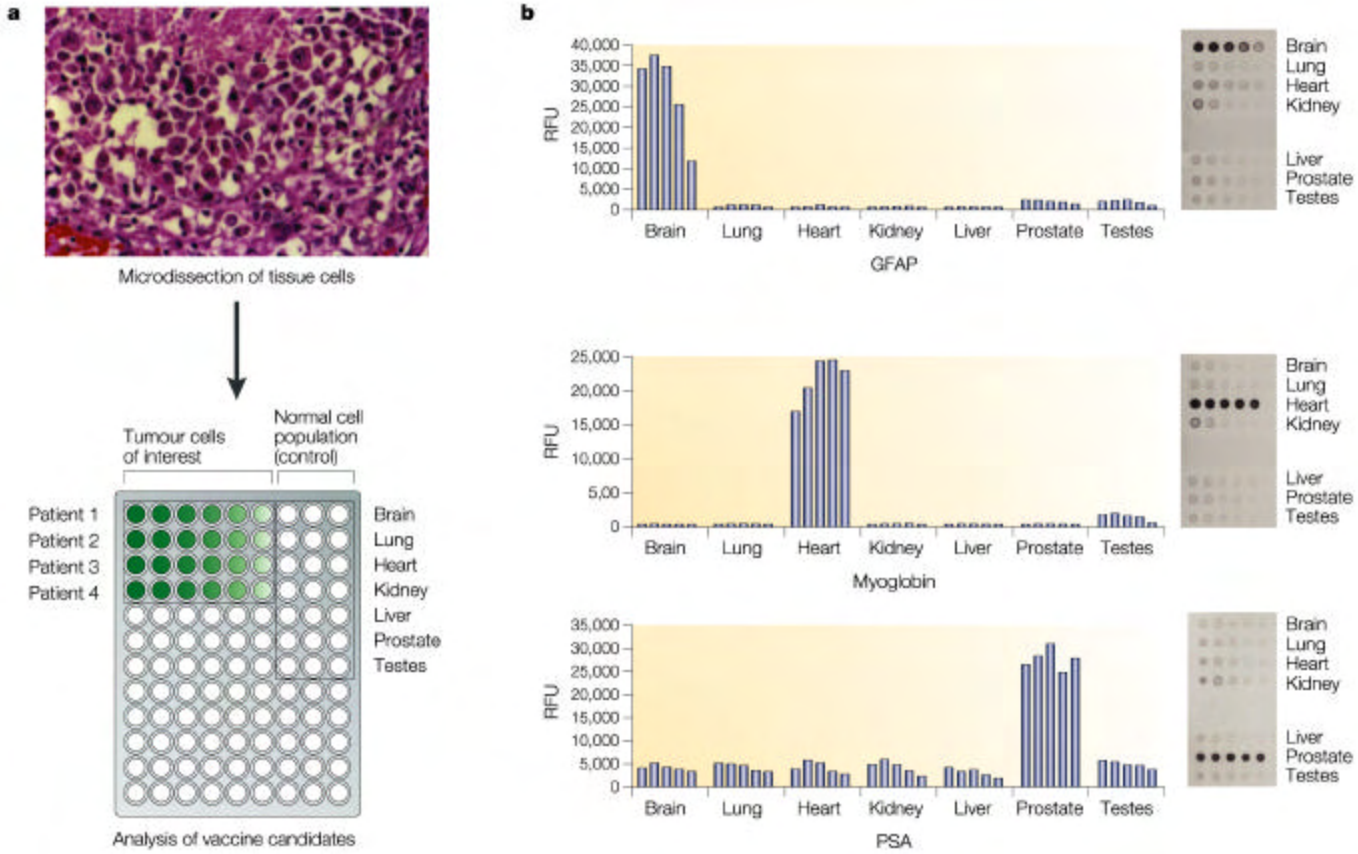
Protein Microarrays for High-throughput Target Validation



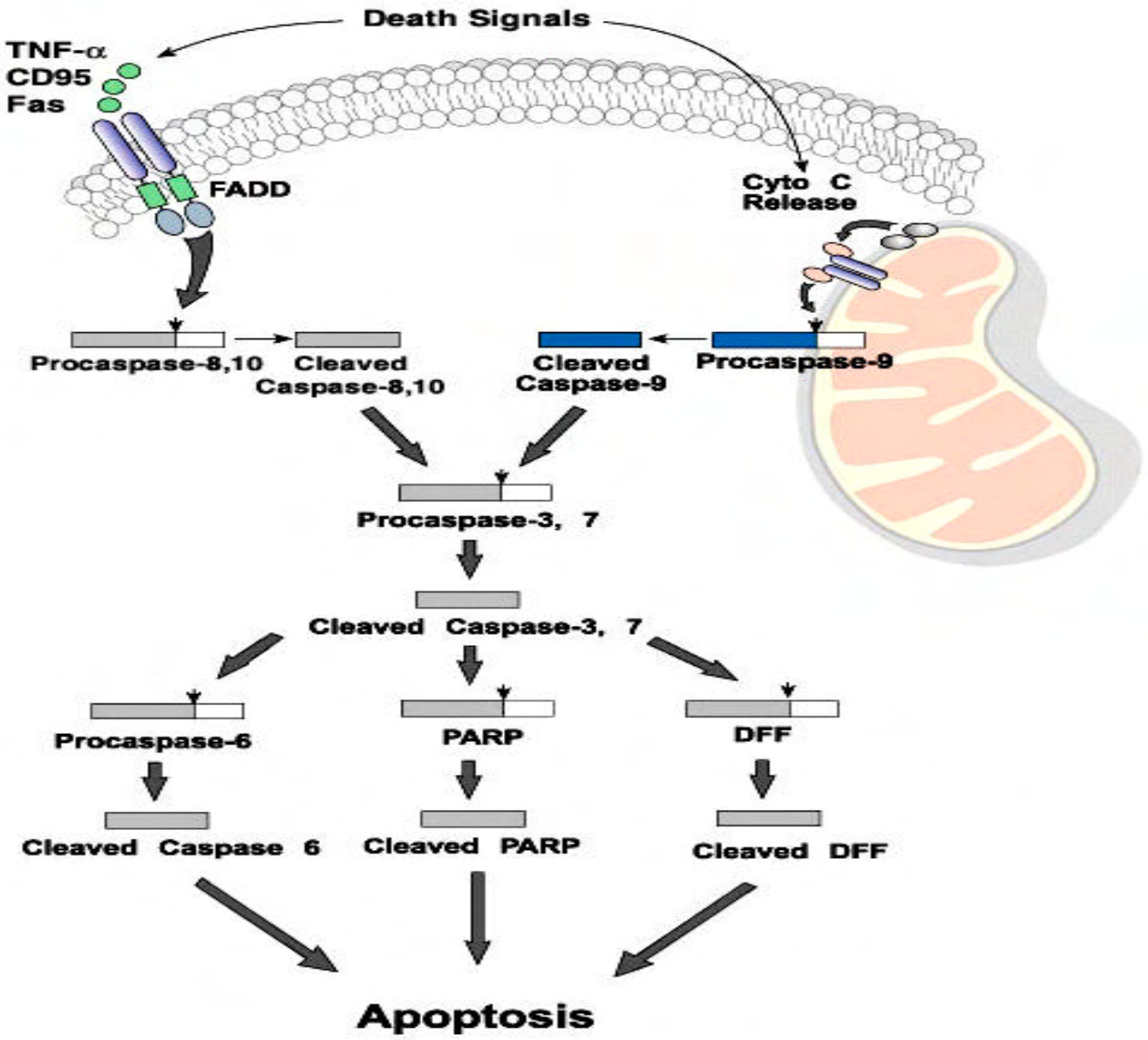




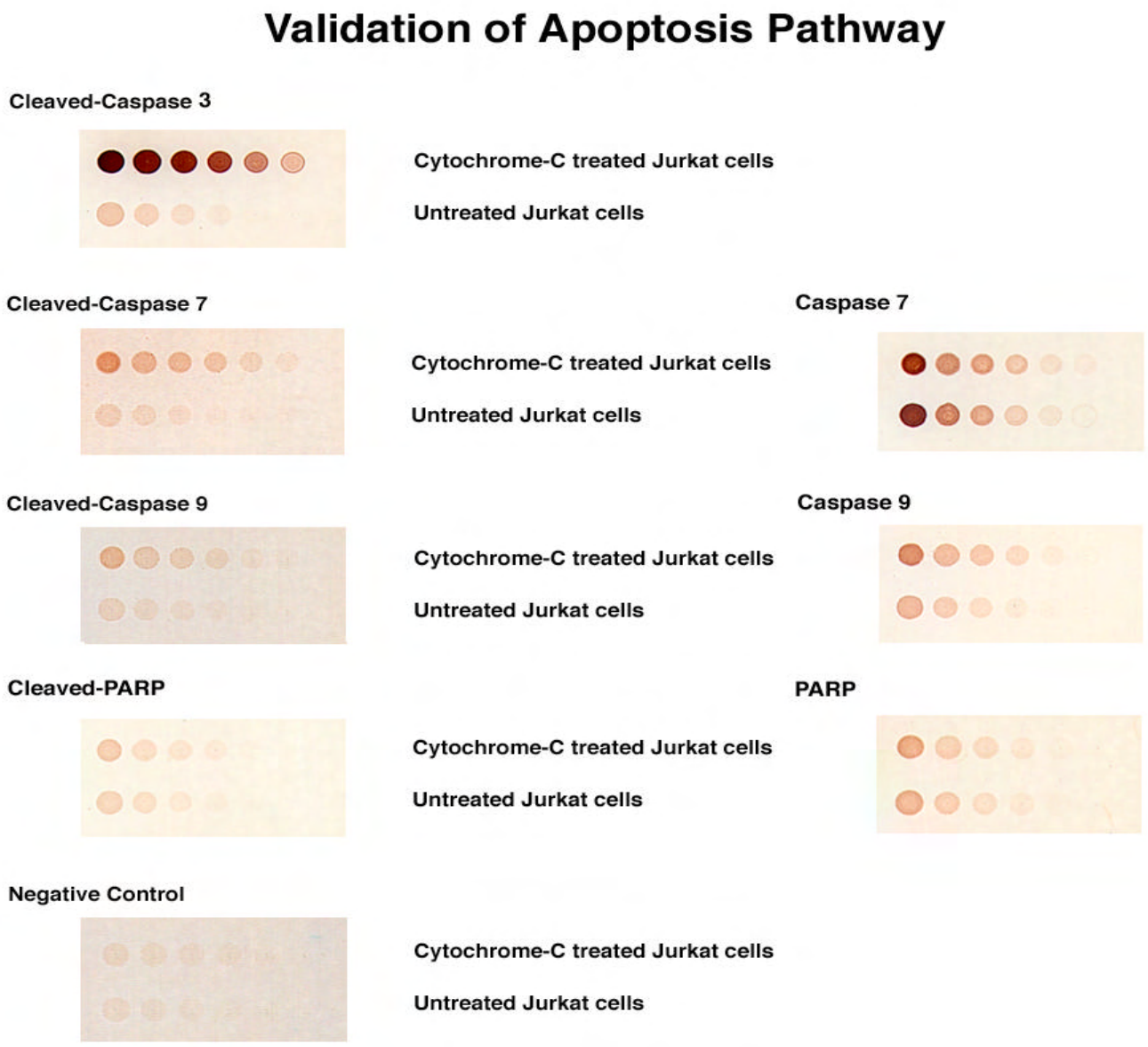
Brown et al, Proteomics, Jan. 2002


a
Microdissection of tissue cells
Tumour cells of interest
Normal cell population (control)
Patient 1
Patient 2
Patient 3
Patient 4
Brain
Lung
Heart
Kidney
Liver
Prostate
Testes
Analysis of vaccine candidates
b
RFU
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
Brain
Lung
Heart
Kidney
Liver
Prostate
Testes
GFAP
Myoglobin
PSA

Cell Survival Pathways



Protein Microarrays

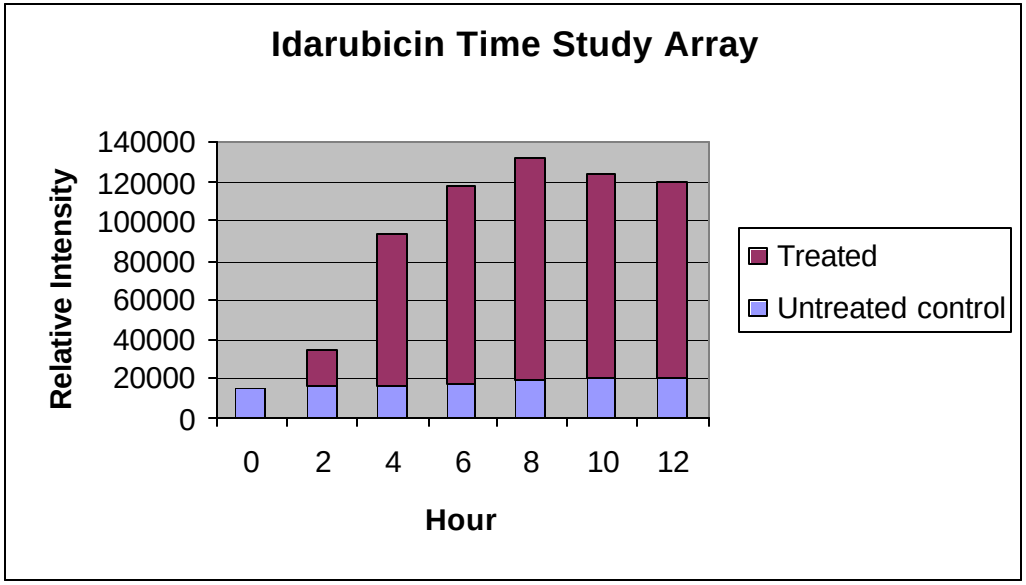


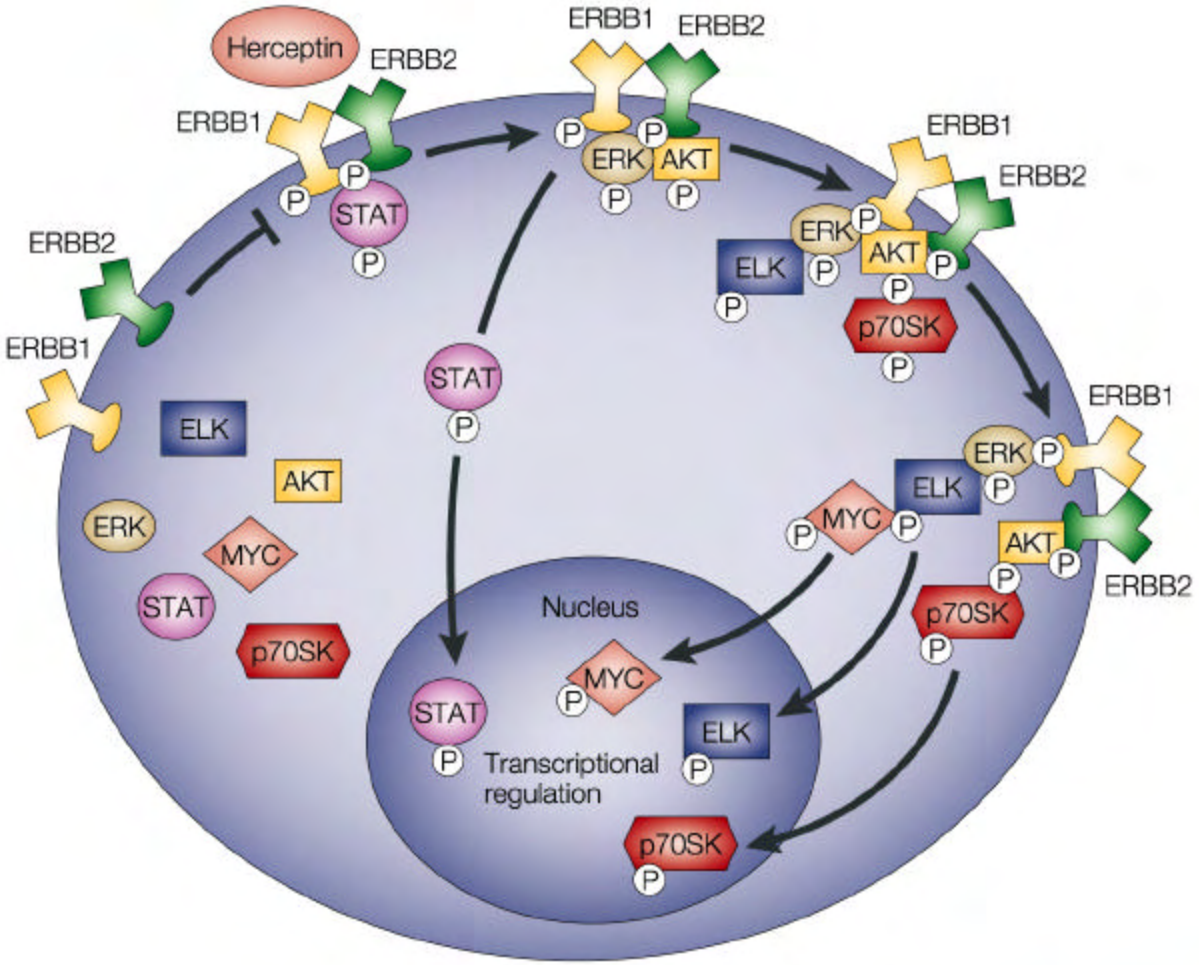
Human B Lymphoma Apoptosis Pathway Protein Microarrays

Cleaved Caspase 3

Time Course

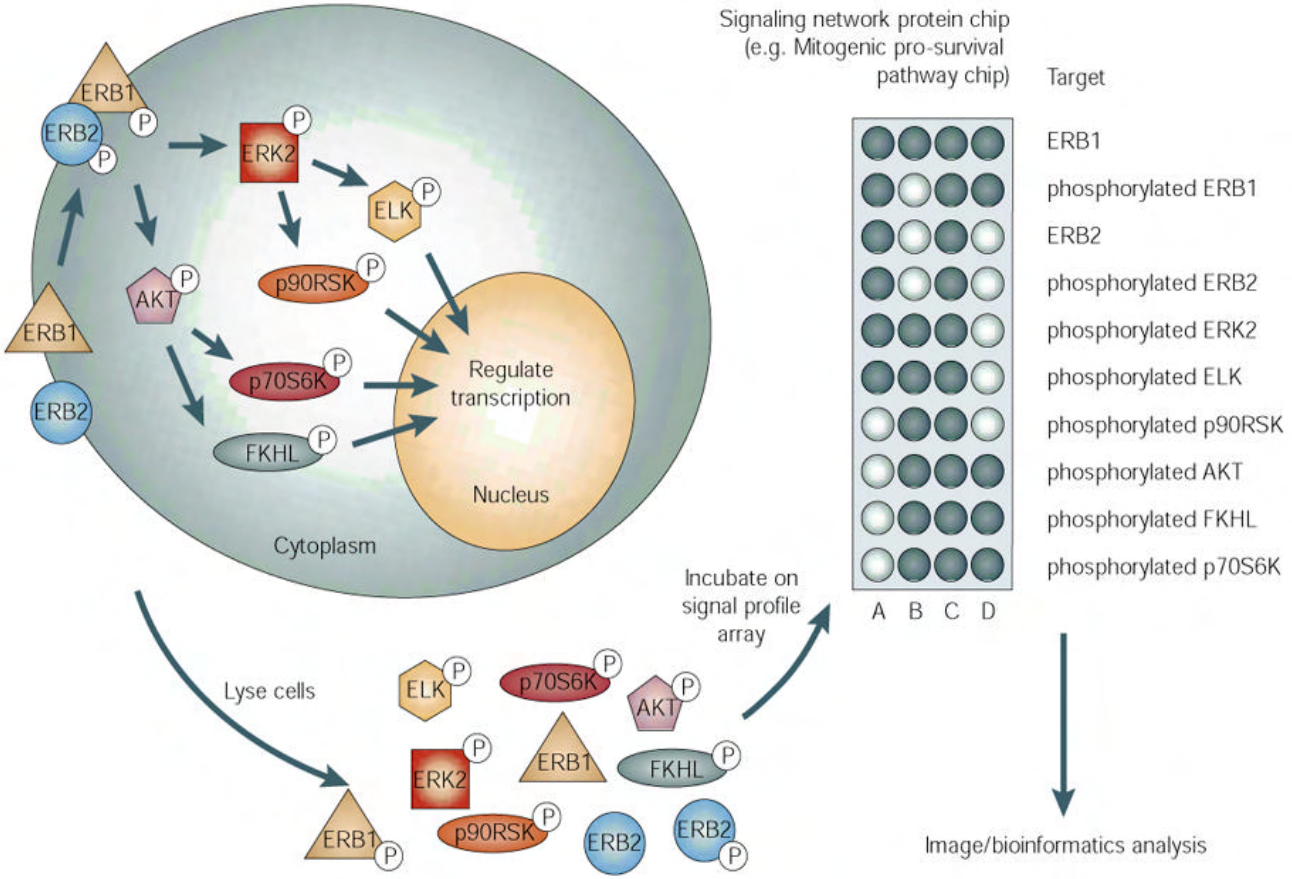
Untreated Treated





Nature Reviews | Drug Discovery

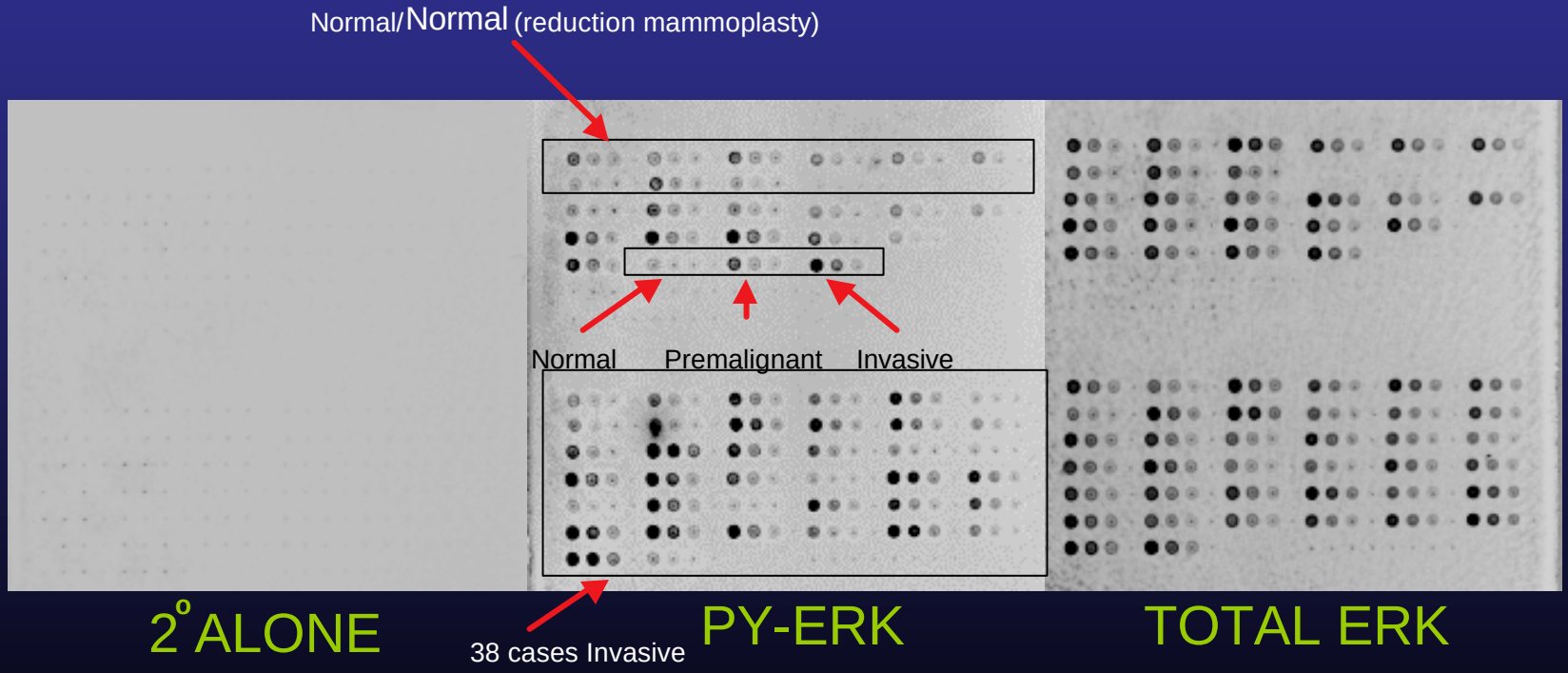
Signal Transduction Pathway Profiling



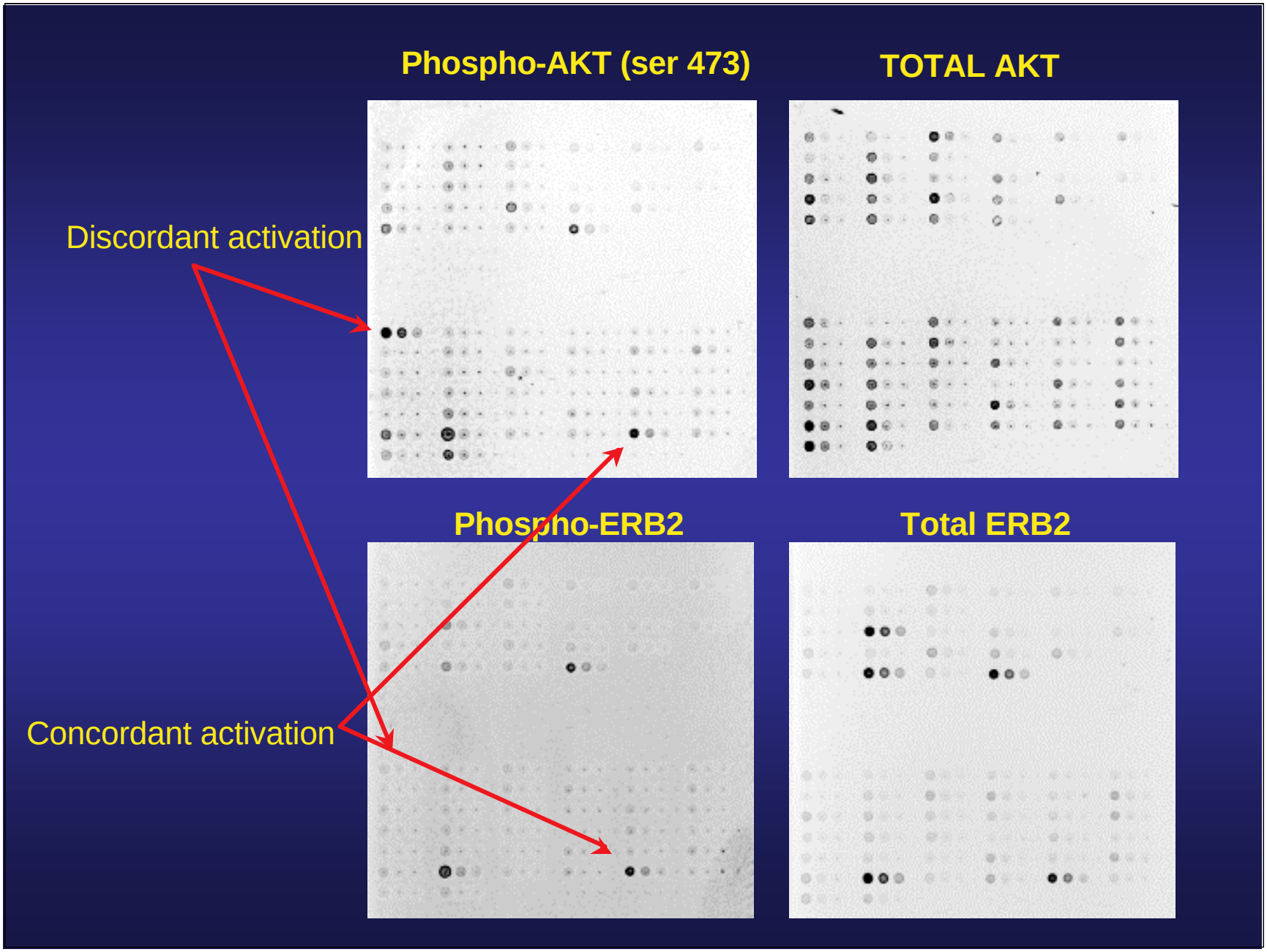
Nature Reviews | Genetics | October 2000

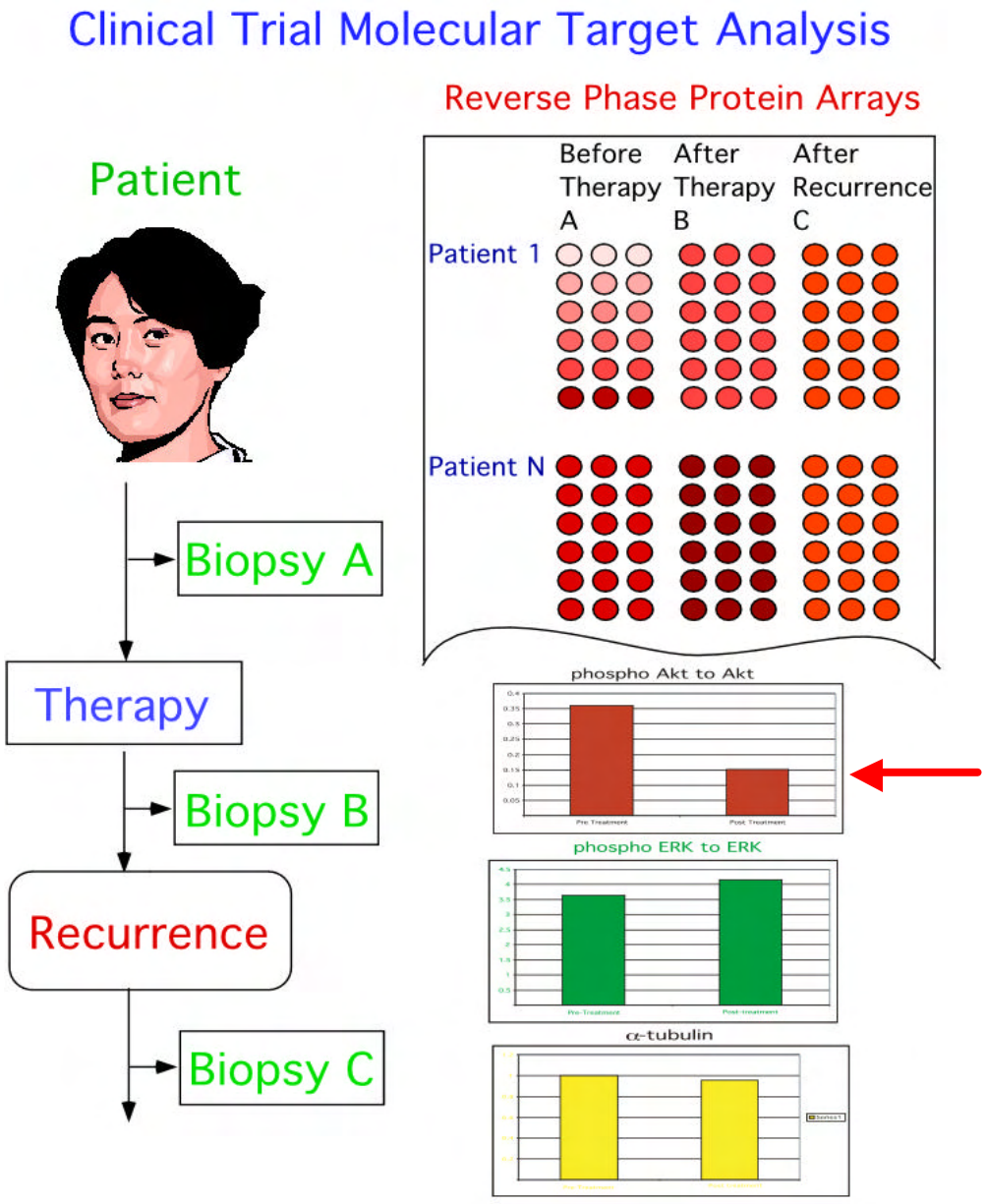
Use of Novel Protein Array Technology: Signal Pathway Profiling in Human Breast Cancer Biopsy Specimens

Coupling Laser Capture Microdissection With True Signal Pathway Profiling



Ongoing work: cluster analysis with 135 phospho-specific endpoints, all normalized to the self protein for true signal pathway profiling


Phospho-AKT (ser 473)
TOTAL AKT
Discordant activation
Phospho-ERB2
Total ERB2
Concordant activation



Clinical Trial:

•Herceptin followed by Taxol

•Metastatic Breast and Ovarian Ca

•Findings to date

HERCEPTIN REDUCES P-Akt PROSURVIVAL PATHWAY

HYPOTHESIS:

•Increased Sensitivity to apoptosis inducing therapy(e.g. Taxol)

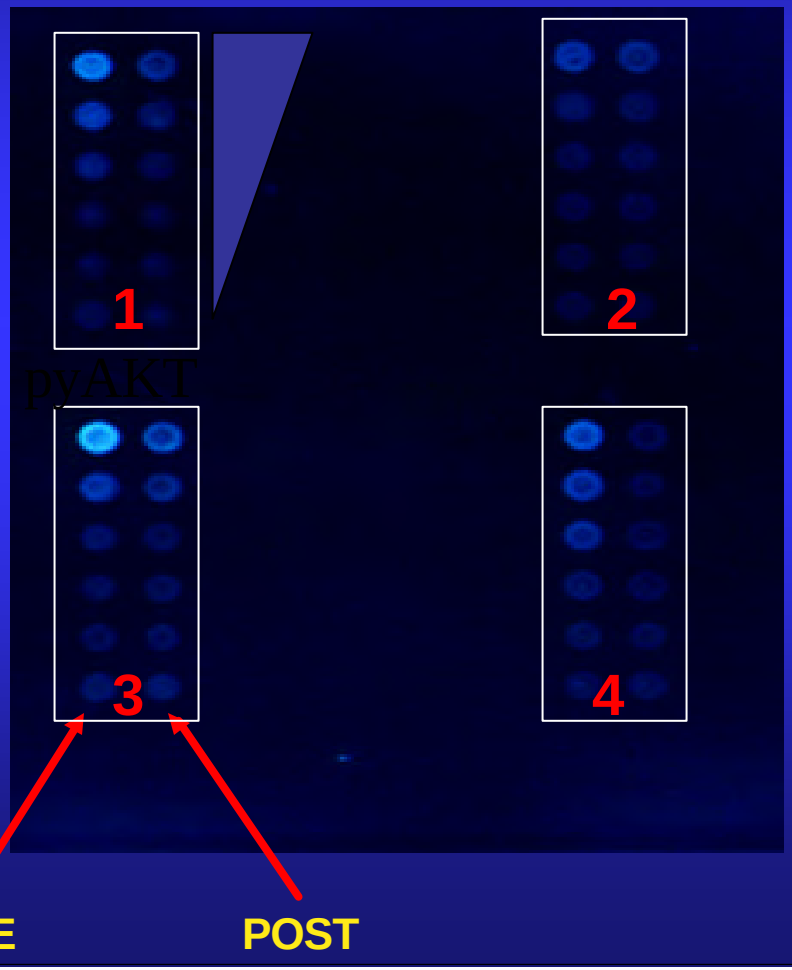
•Suppression of growth through de-repression of p21(Cip1/WAF)

Proteomic Endpoints from Clinical Trial Biopsies: Use of Protein Arrays

Pre and Post HERCEPTIN (1 Month)

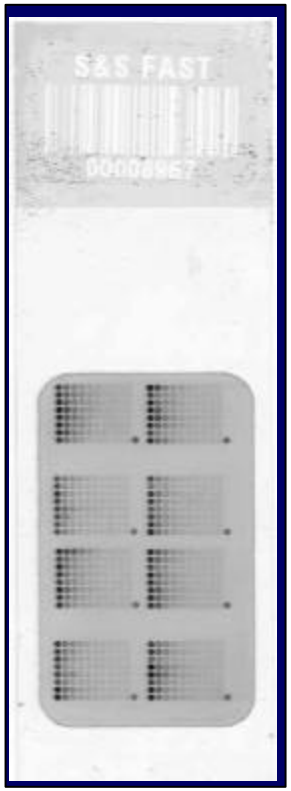
- **Phospho-AKT Endpoint**
- **500 microdissected cells**
- **Pre and Post Treatment Studies**

Responders: 1,3,4
Non-Responder: 2

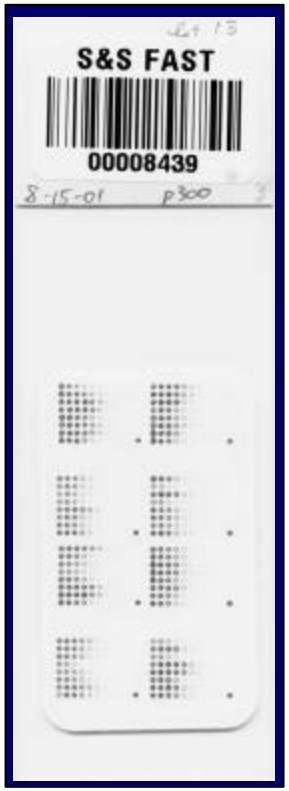


Protein array specification

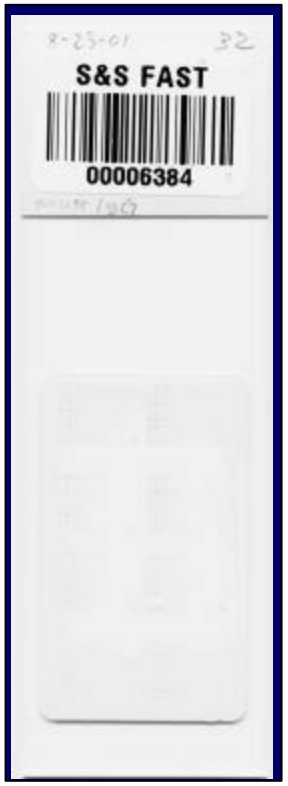
- Schleicher & Schuell (www.s-and-s.com) FAST slide (glass slide embedded 21 x 35 mm nitrocellulose membrane) was used.
- Total number of spots is 648.
- Spot all NCI60 cell lysates and 4 pools on a single slide.
- Each cell line has 10 different concentration spots.
- Achieved more than 1000-fold dynamic range.
- Requires total protein and negative control stains for a protein expression measurement.
- Takes 5 hours for making 20 full arrays.



Total protein (stained by SYPRO RUBY)



Protein of interest (p300)



Negative control (mouse IgG)

Raw pixel data generation by P-SCAN

P-SCAN (Peak quantification using Statistical Comparative ANalysis) is available at http://abs.cit.nih.gov/pscan/

1

Apply an image (TIFF) and select the area of array.

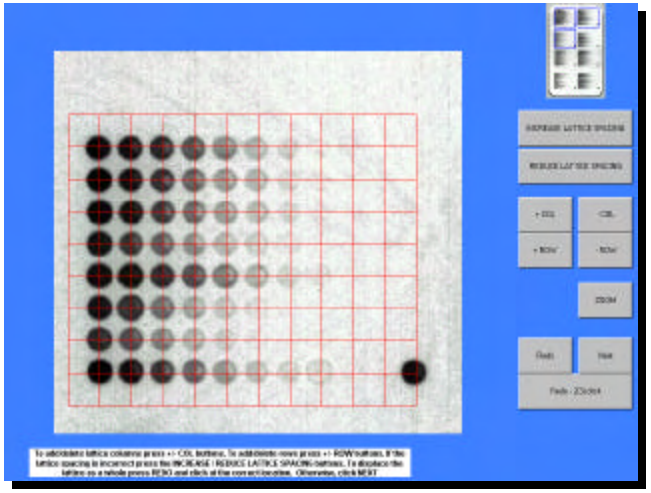
2

The array has been selected.

3

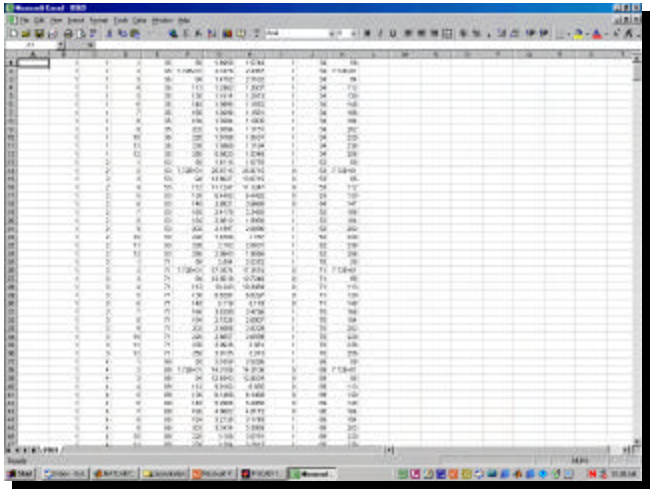
Set up the field. Intensity reading will be carried out by each field. There are 2 x 4 = 8 fields above.

4



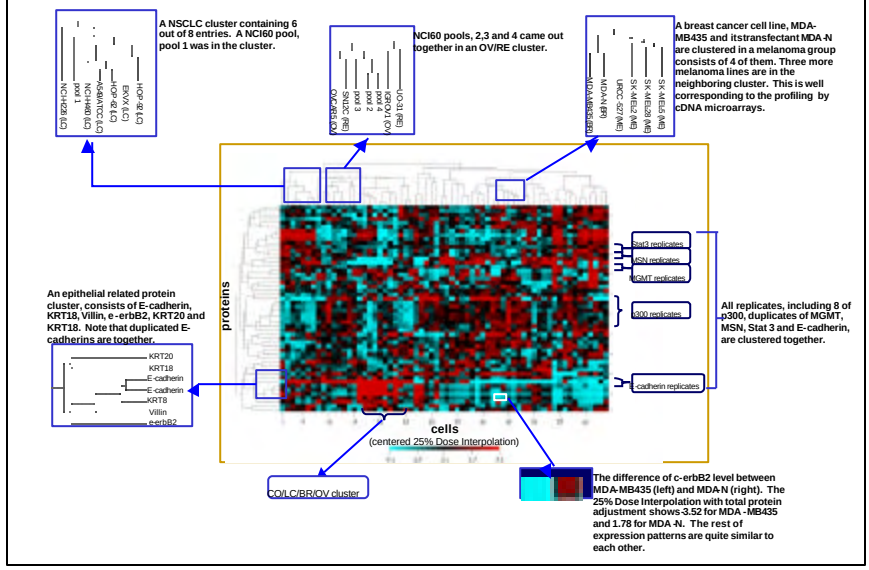
Align the lattice. A total of 120 intersections will set in a field and generates intensity number per spot. The right bottom dark spot is for control the alignment.

5

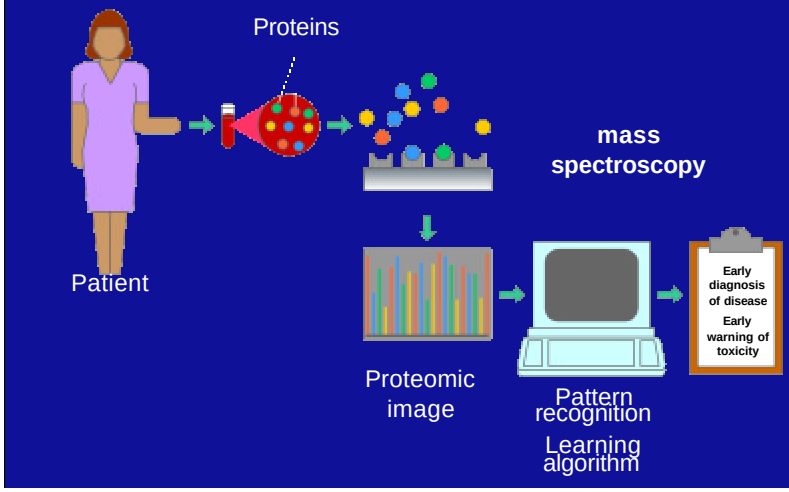


Raw pixel intensity data is exported onto an Excel worksheet along with its address on the array.

Cluster analysis of protein expression (1)

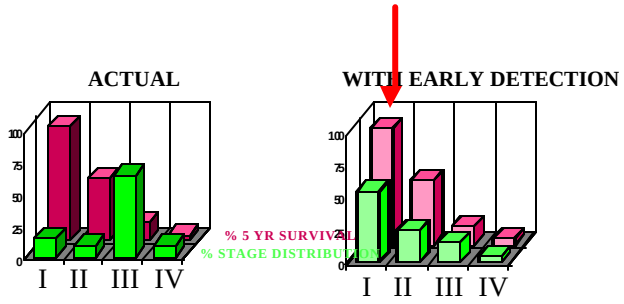


Serum Protein Pattern Diagnostics



PROTEOME SNAPSHOT PATTERN ANALY
APPLICATION TO EARLY DETECTION OF OVA

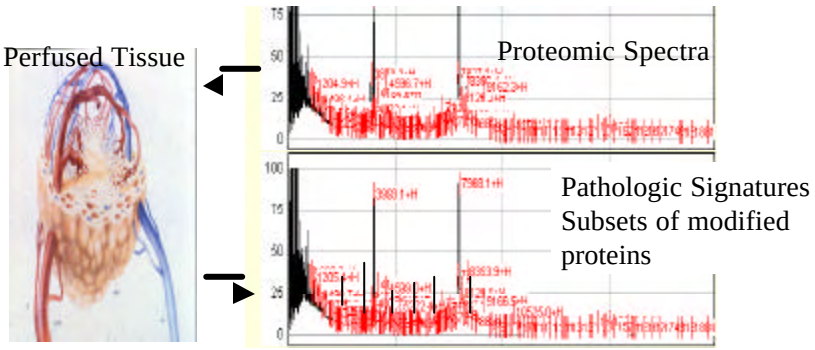
CAN PROTEIN PROFILING IDENTIFY A PROTEIN EXPRESSION
DIAGNOSTIC OF INVASIVE EPITHELIAL OVARIAN CA



A SHIFT IN NUMBER OF EARLY STAGE PATIENTS WILL EFF

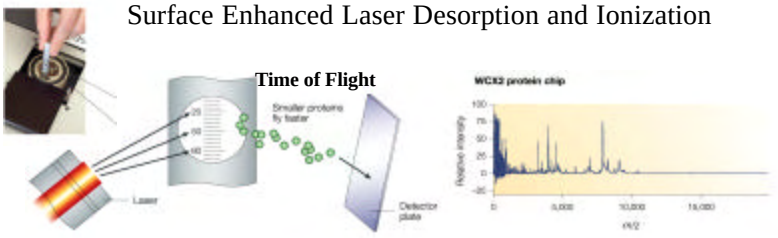
AND OVERALL SURVIVAL IN ABSENCE OF TREATMENT CO

PATTERNS OF PROTEOMIC INFORMATION IN SERUM

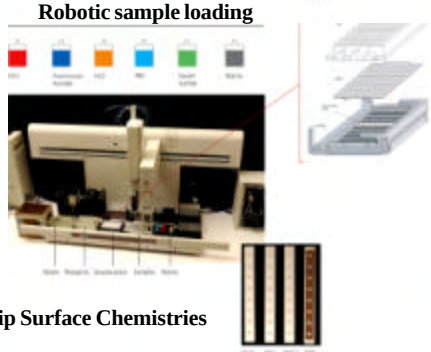


•How can we discover diagnostic proteomic patterns even without knowing the identity of the proteins ahead of time?

Surface Enhanced Laser Desorption and Ionization



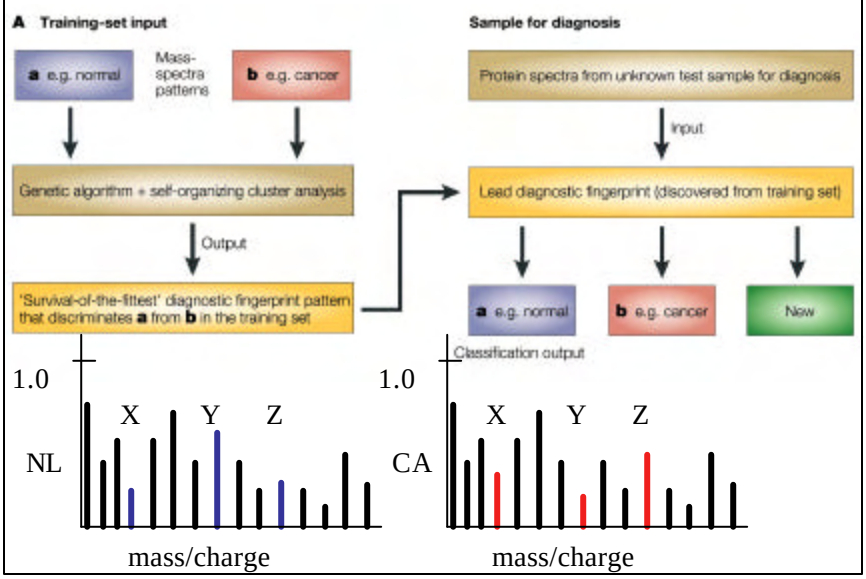
Robotic sample loading



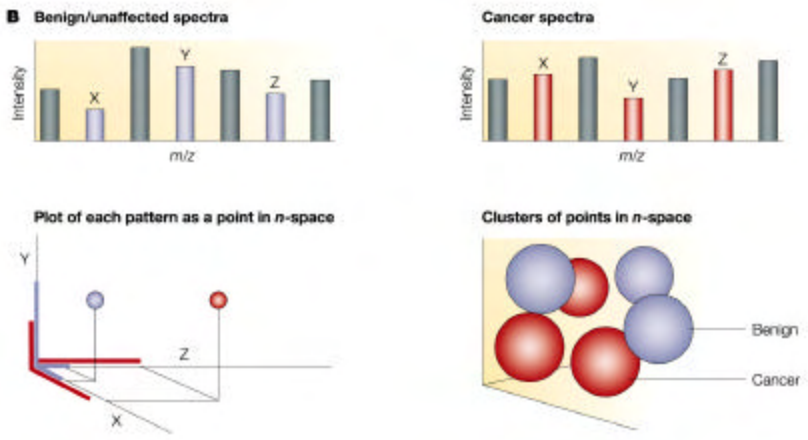
Chip Surface Chemistries

- Sample: Small volume non fractionated serum
- On-chip separation of proteins
- High throughput: 300 samples per day in batches of 100

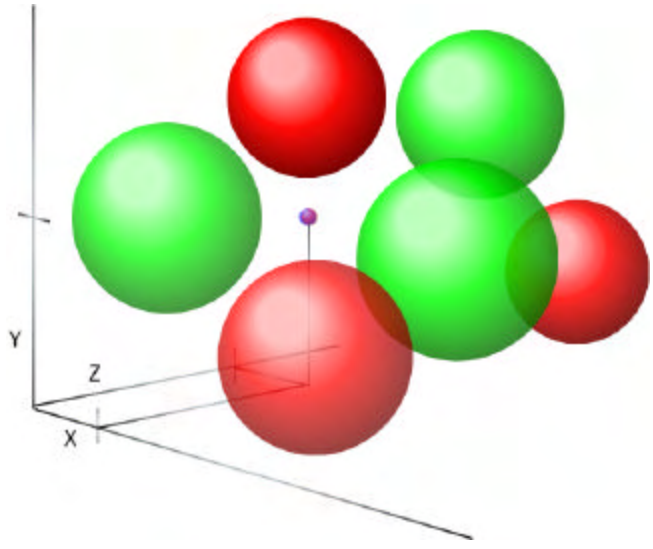
Bioinformatics Discovery Tool



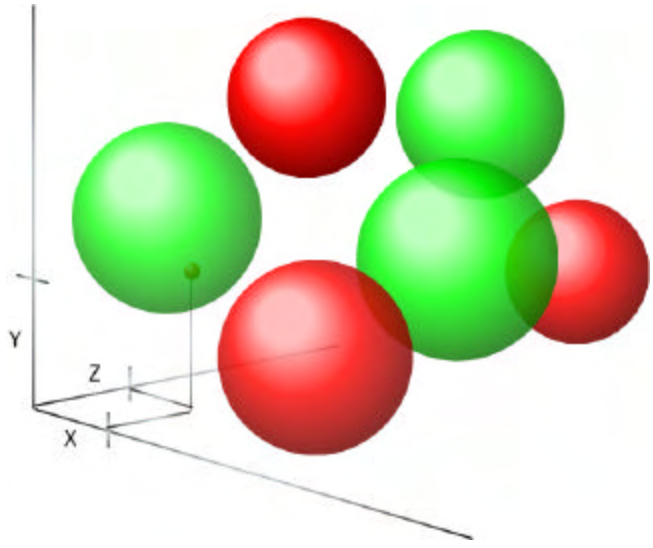
Proteomic Pattern Clustering in n-Space



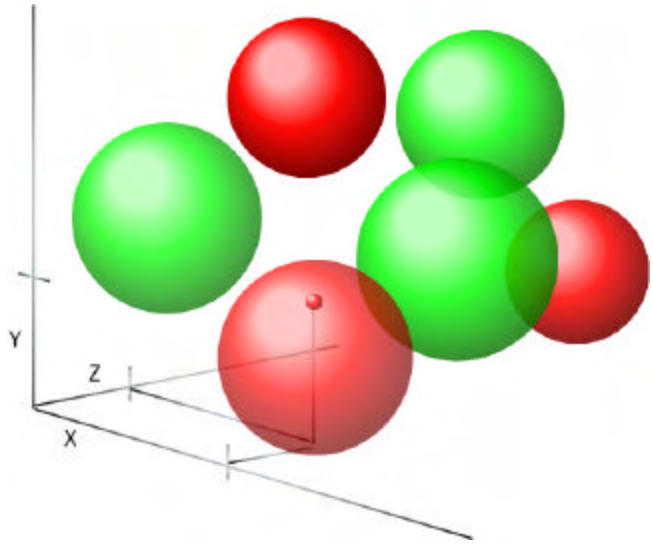
Classification of Unknown: NO MATCH



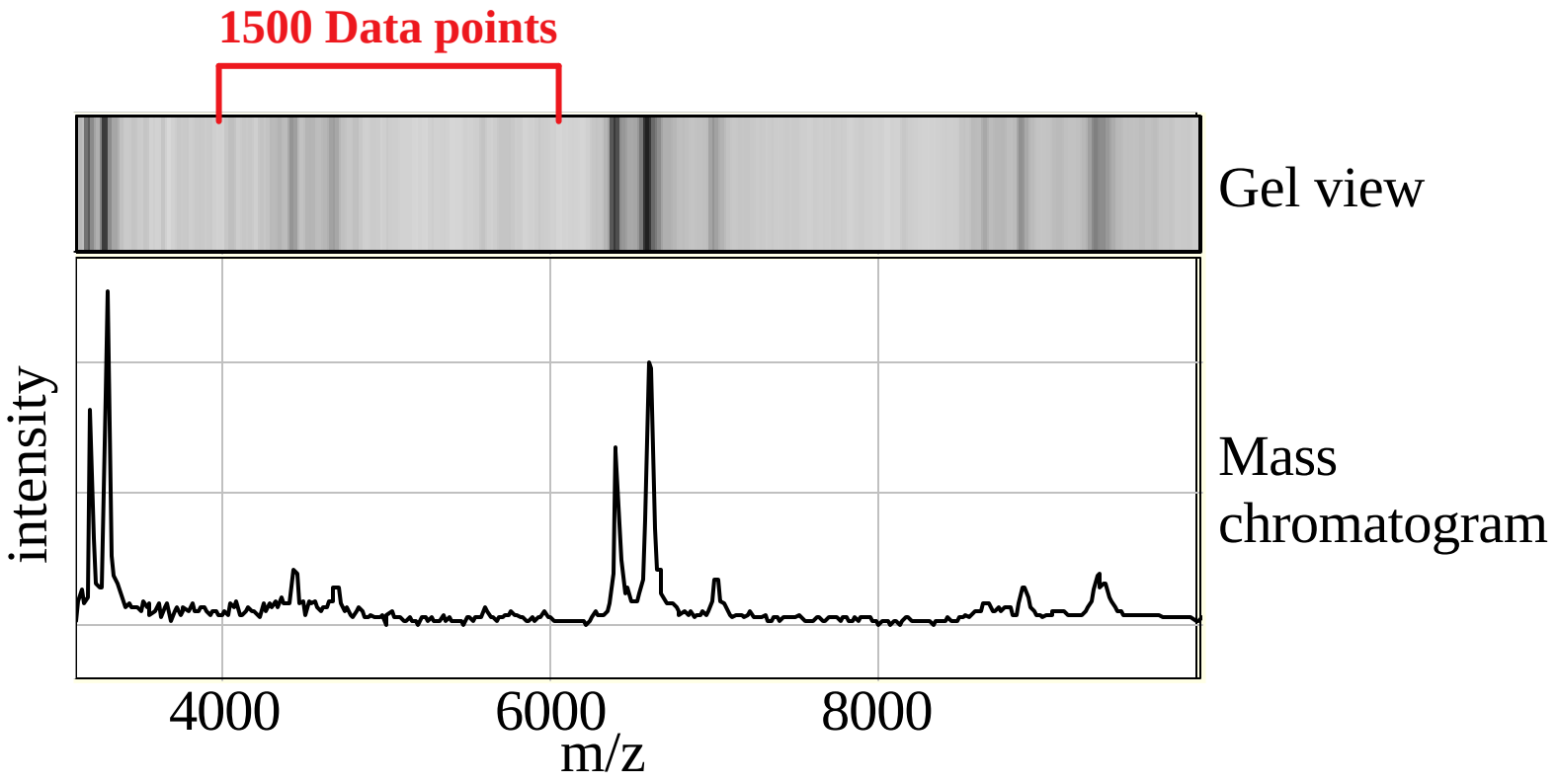
Classification of Unknown: BENIGN MATCH



Classification of Unknown: CANCER MATCH



Typical serum profile from SELDI analysis



Data analysis window: 0-20,000 Daltons = 15,500 data points

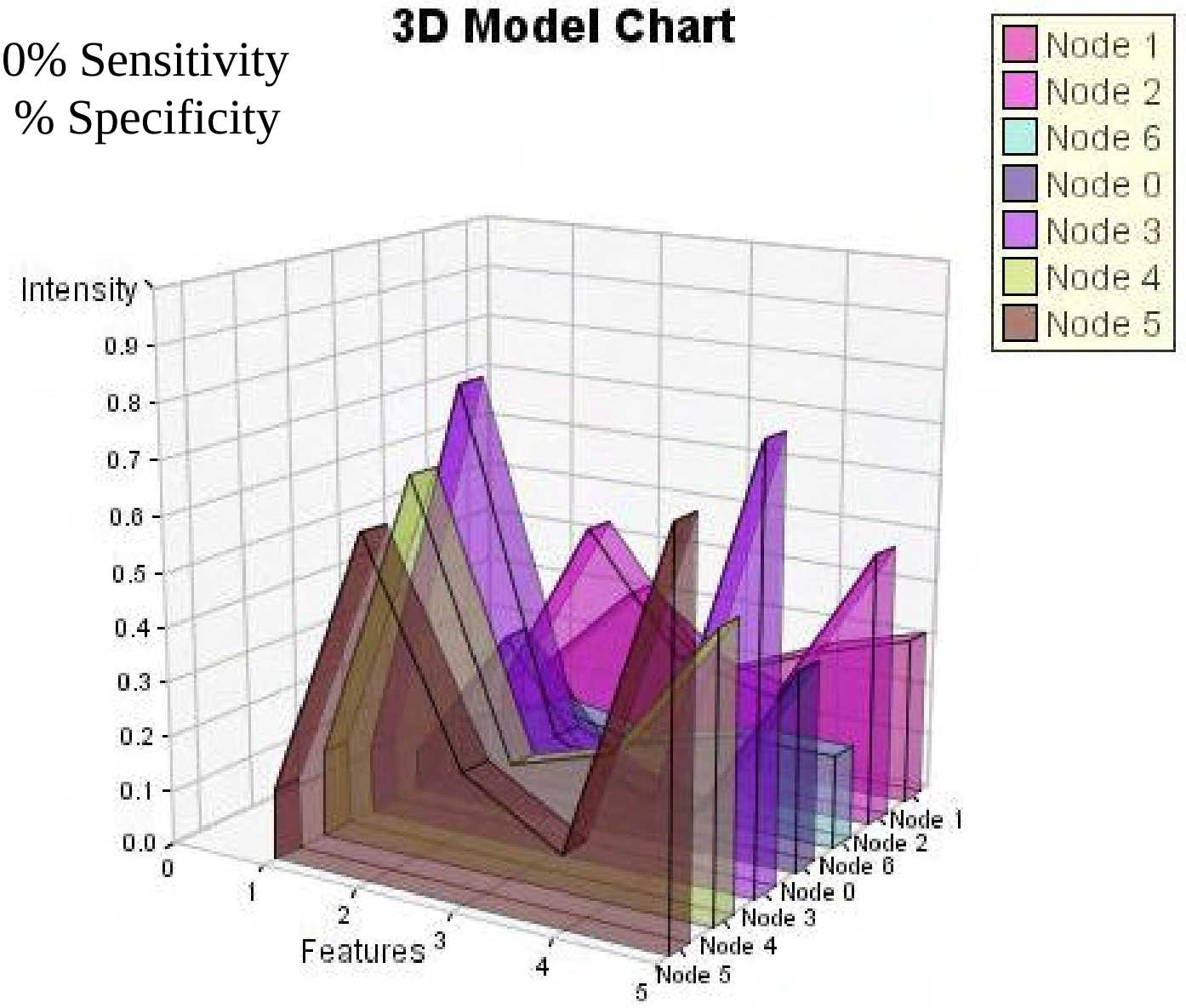
OVARY UNAFFECTED TRAINING SET [a]	
DISEASE STATUS	**N**
No Evidence of Ovarian Cysts	37
Benign Ovarian Cysts < 2.5 cm	11
Benign Ovarian Cysts > 2.5 cm	2
TOTAL	**50**

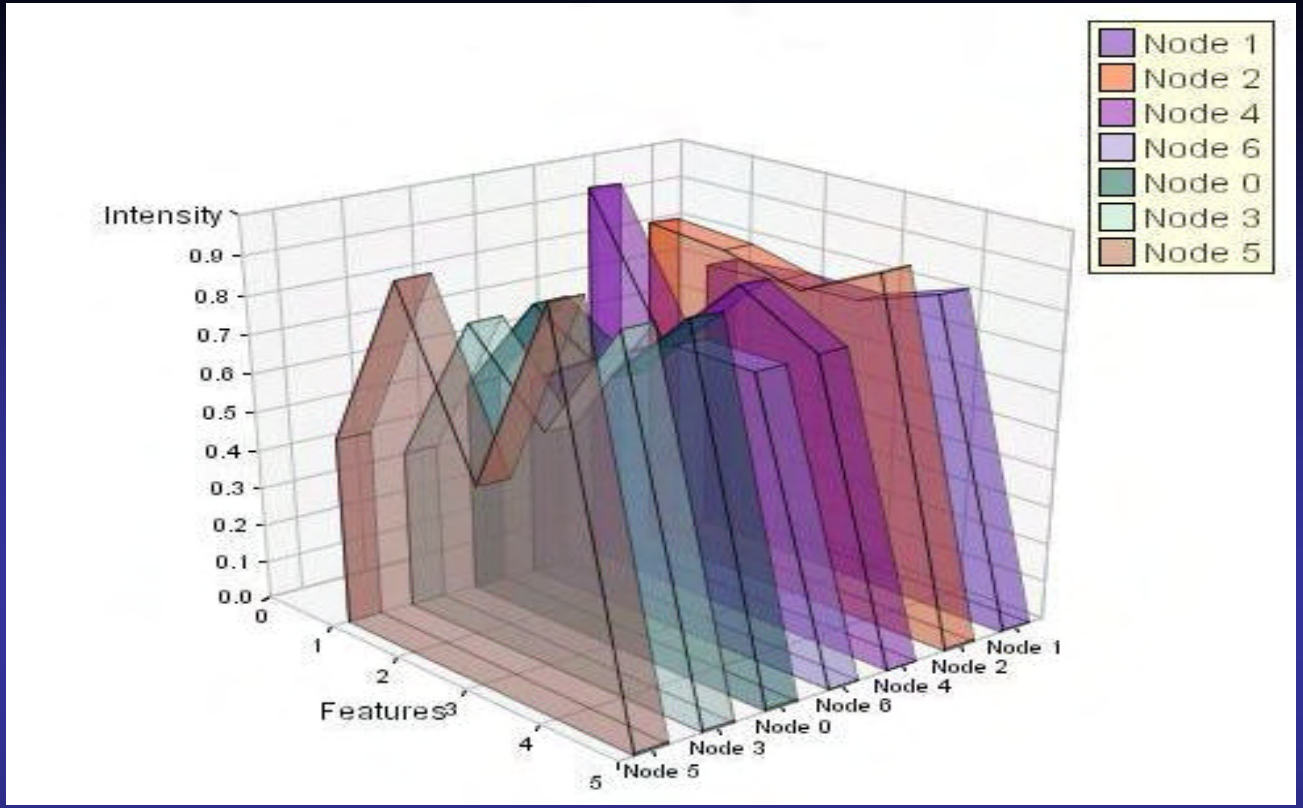
OVARY CANCER TRAINING SET [b]	
DISEASE STATUS	**N**
Surgically Staged Ovarian Cancer **Stage II, III, IV**	44
Surgically Staged Ovarian Cancer **Stage I**	6
TOTAL	**50**

a = Sera donated before 3-dimensional color Doppler flow ultrasound confirmation of benign cysts. All patients followed 5 years after sera collection.

b = Sera donated before surgical staging and diagnosis.

100% Sensitivity
95 % Specificity





NEW MODEL:

BLINDED TEST RESULTS:

100% Specificity and Sensitivity

50/50 Cancers, 63/63 Unaffected or Benign

Artificial Intelligence-Based Proteomic Pattern Diagnostics
Ovarian Cancer Results

BLINDED TEST DATA (N= 116 PATIENTS)

NED (5 Year follow up)	**22/24 (92%)**
Benign gynecologic and non-gyn inflammatory (cysts, fibroids) (RA, colitis, sinusitis)	**41/42 (98%)**

TOTAL SPECIFICITY: 63/66 = 95%

Ovarian cancer Stage II, III, IV	**32/32 (100%)**
Ovarian cancer Stage I	**18/18 (100%)**

TOTAL SENSITIVITY: 50/50 = 100%

POSITIVE PREDICTIVE VALUE: 95% VS. 20% FOR CA125

SERUM PROTEOMIC PATTERN DIAGNOSTICS

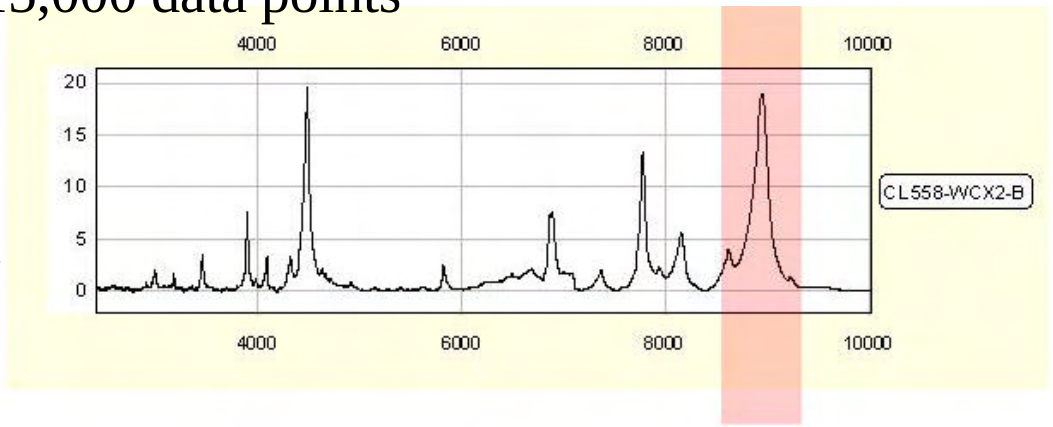
BLINDED TEST RESULTS: PROSTATE CANCER

N= 266

		Predicted Diagnosis by Proteomic Pattern Analysis	
Actual Diagnosis (serum PSA ng/ml)	**N**	**CANCER (% total)**	**BENIGN (% total)**
Prostate Cancer (> 4.0)	**38**	**36 (95%)**	**2 (5%)**
Benign (< 4.0)	**75**	**5 (7%)**	**70 (93%)**
Benign (>4.0)	**153**	**46 (30%)**	**117 (70%)**

Ciphergen

15,000 data points

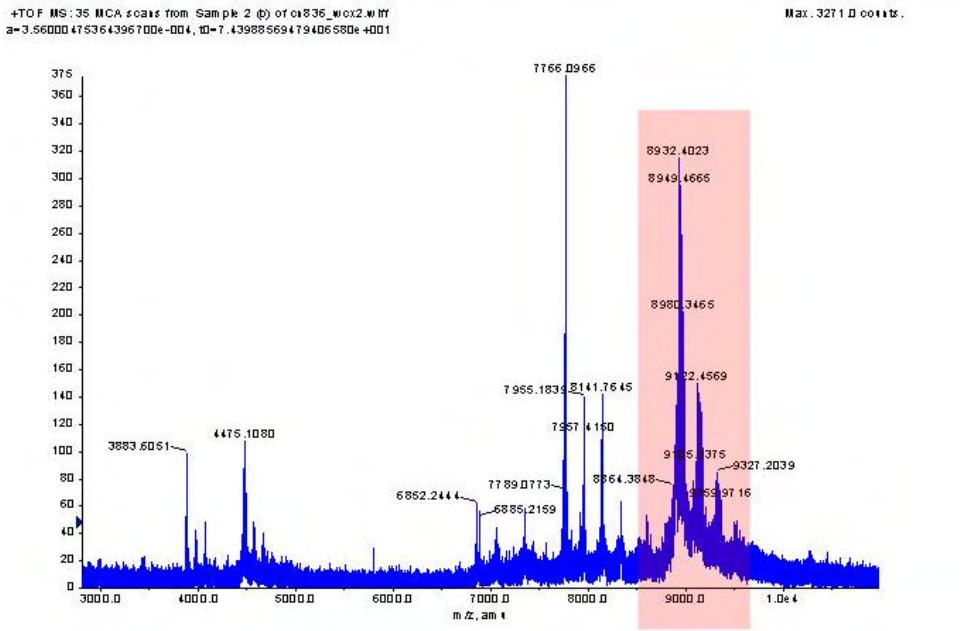


- Low Resolution
- No protein peak ID
- MALDI-TOF ions do not necessarily reflect relative abundance in sera

The ABI QSTAR® Pulsar Hybrid LC/MS/MS System is a high performance hybrid quadrupole time-of-flight mass spectrometer

ABI QSTAR

900,000 data points



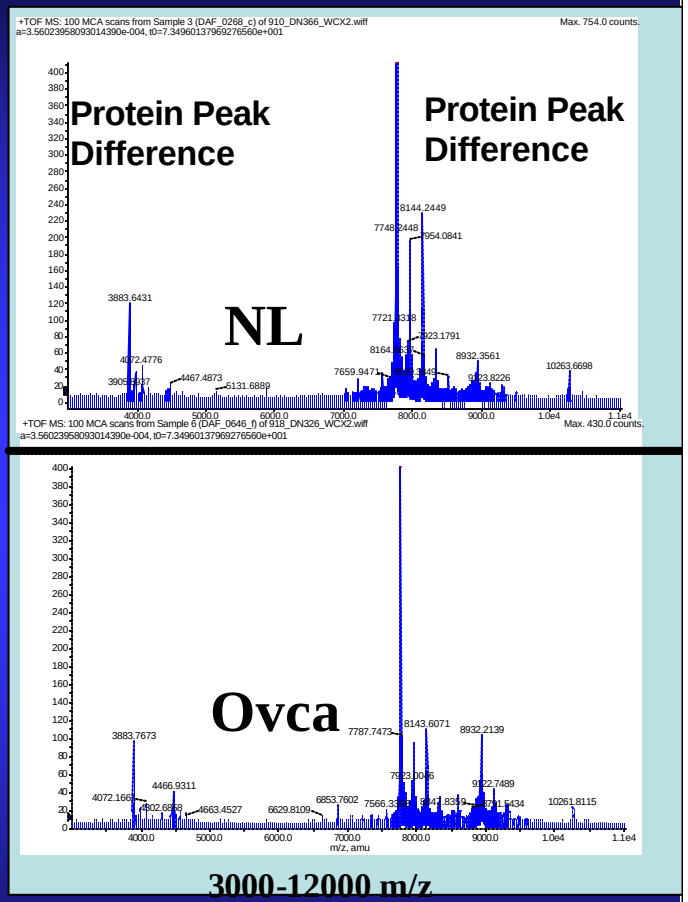
ABI QqTof Qstar Ovarian Results:

100% Sensitive and Specific

- **Q-STAR VALIDATION : Direct comparison to Cipheregen PBS II using the same WCX chips**
- **Independent analysis by Dr. Tim Veenstra and Dr. Thomas Conrads (Director, NCI Biomedical Proteomics Program)**
- **Serum sample: National Ovarian Cancer Early Detection Program (NOCEDP), Northwestern University; Director: Dr. David Fishman**
- **Total Number of samples:**
  Unaffected = 95, Ovarian Cancer = 153

Samples were divided into 3 groups:

A. 84 training samples (28 Unaffected and 56 Ovarian Cancer)
B. 87 testing samples (30 Unaffected and 57 Cancer)
C. 87 blind validation samples (37 Unaffected and 40 Cancer)



Results:

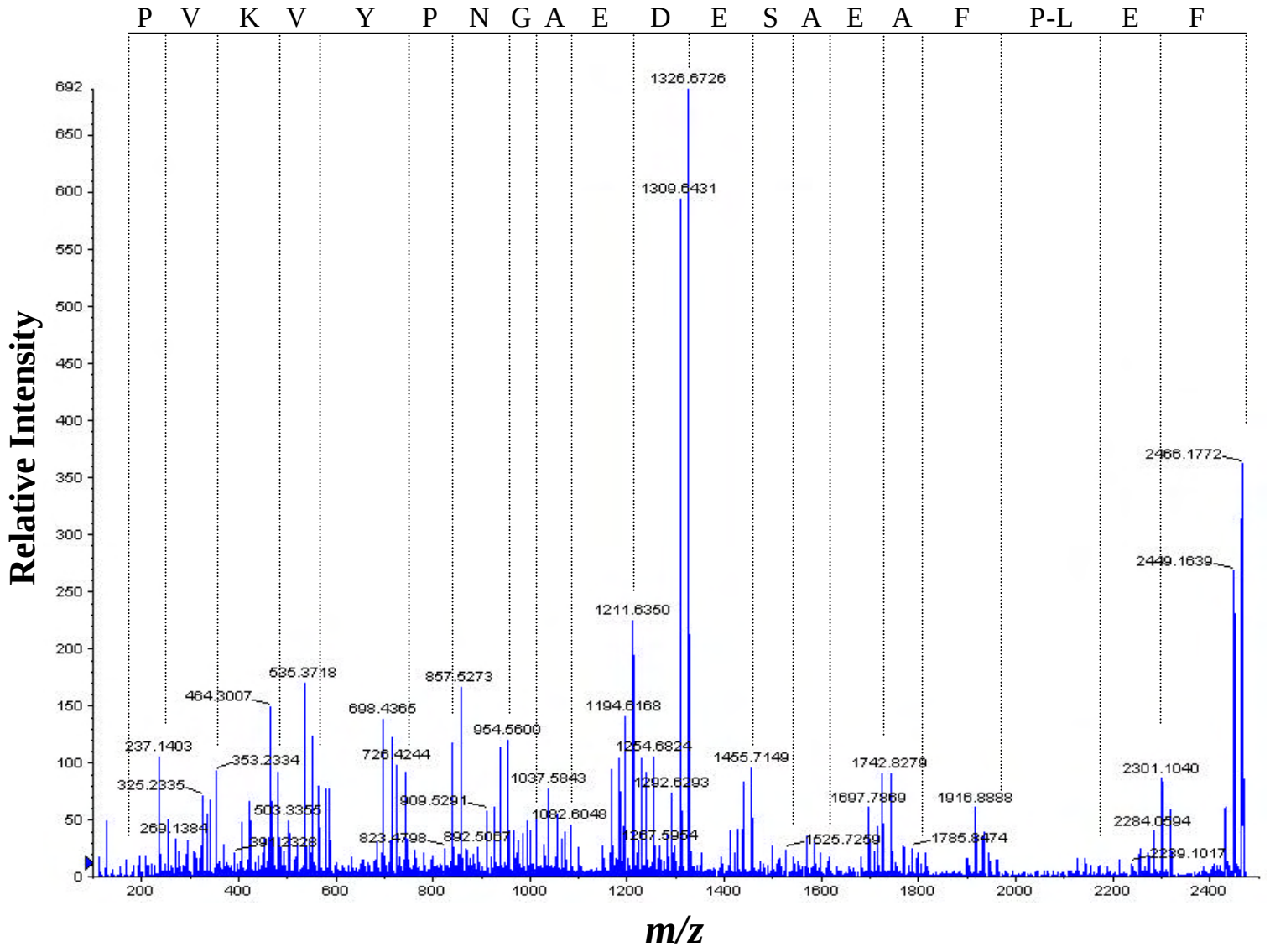
- **Two different models generated 100% sensitivity and specificity.**
- **These same model correctly classified 100% of the blinded samples.**

Key Ions (m/z) values from one model:

1276.8612	2374.2444	4292.900	7060.1210	8605.678	8706.065	9870.9375

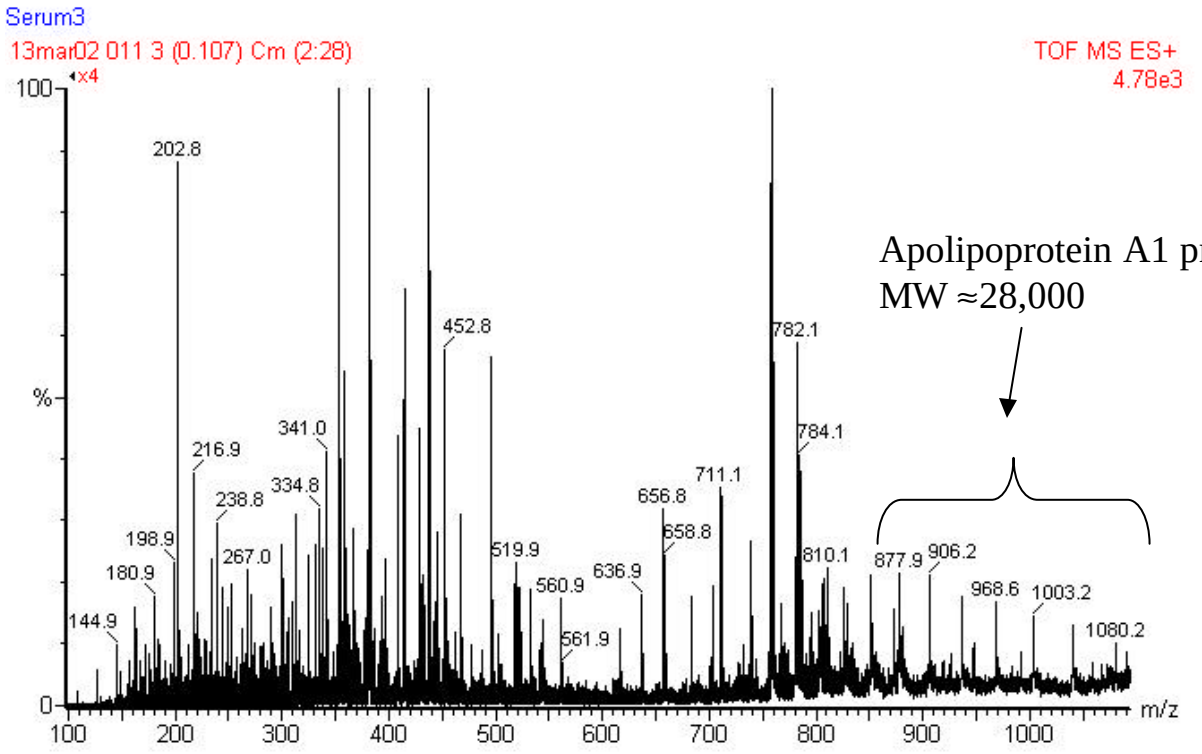
Protein Peptide ID directly from complex Q-Star Spectra

Adrenocorticotropic hormone 2 clip 18-39 tandem MS spectrum



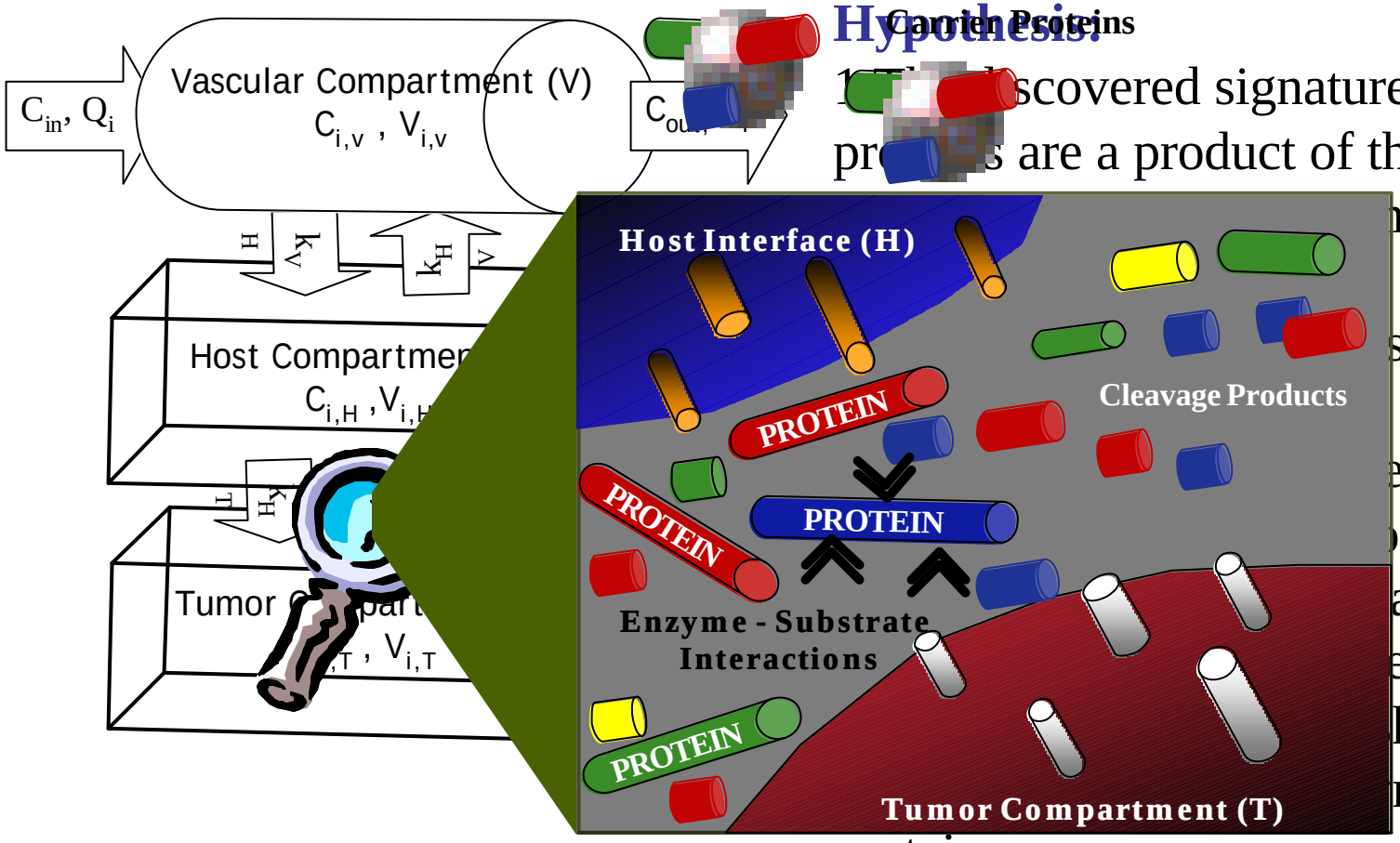
Human serum - Micromass LCT and ESI-Chip

500 x diluted in 1:1 ACN:H20, 0.2% formic acid



Apolipoprotein A1 precursor ?
MW ≈28,000

Source of Ions Comprising Diagnostic Signature Subset



Hypothesis:

1. The discovered signature proteins are a product of the ment,
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proteins

Nth Dimensional Proteomic Pattern Analysis:

A New Paradigm for Diagnostics

- **Requires less than 1 microliter of raw unfractionated serum**
- **MALDI-TOF profiles obtained in less than 5 minutes**
- **High throughput: Capacity to analyze more than 400 samples/day**
- **Nth-Dimensional analysis virtually instantaneous once training sets are defined**
- **Validated sera added into an ever-expanding training population: models get better and better as more data is analyzed**
- **Analysis compatible with web-centric platforms**

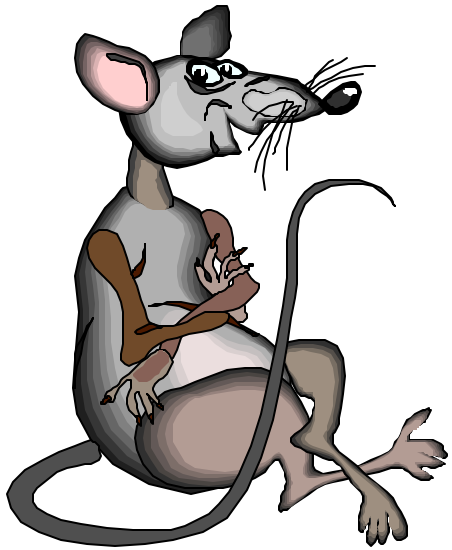
Sistare Vasculitis Results 8-5-02

Vasculitis Samples
Negative = 21 samples
Positive = 16 samples

37 Total samples
19 Testing set (10 Negative and 9 Positive)
18 Training set (11 Negative and 7 Positive)
100% specificity and sensitivity

Validation with Renal Positive and Negative
Classified 15/15 (100%) Renal Negative as negative
Classified 8/11 (72.7%) Renal Positive as negative

Model:



Node	Count	State	StateSum	Error		475.495	875.625	1067.490	980.226	9551.137	2527.856	11683.457	6266.976	17988.113	4037.875
0	11	0	2	2	0.997	0.806	0.756	0.843	0.024	0.241	0.016	0.102	0.000	0.156
1	6	1	5	1	1.000	0.719	0.656	0.710	0.018	0.192	0.013	0.083	0.000	0.117
2	1	0	0	0	0.840	0.652	0.675	1.000	0.017	0.191	0.012	0.072	0.000	0.119

Sistare Renal Results 8-5-02

Renal Samples
Negative = 15 samples
Renal = 11 samples

26 Total samples
10 Testing set (6 Negative and 4 Renal)
16 Training set (7 Negative and 7 Renal)
100% specificity and sensitivity

Validation with Vasculitis Positive and Negative
Classified 21/21 (100%) Vasculitis Negative as negative
Classified 16/16 (100%) Vasculitis Positive as positive

Model:

Node	Count	State	StateSum	Error							
	4183.515	12346.710	5396.381	10426.889	3605.287	14183.555	10286.063	3772.441			
0	6	0	0	0	0.896	0.039	0.512	0.077	1.000	0.000	0.152	0.915
1	7	1	7	0	0.938	0.001	0.648	0.028	0.994	0.008	0.045	0.988
2	3	0	0	0	1.000	0.000	0.338	0.010	0.602	0.018	0.021	0.672

Sistare Dox Results 8-5-02

Dox Samples
Negative = 79 samples
Positive = 19 samples

98 Total samples
50 Testing set (39 Negative and 11Positive)
48 Training set (40 Negative and 8 Positive)
100% specificity and sensitivity

Validation with 46 unknown samples
Predicted 18/46 Positive
Predicted 28/46 Negative

Model:

Node	Count	State	StateSum	Error	14003.968	5136.478	2971.389	3631.956	8408.127	2639.668	2700.797	3995.735	3919.051	3996.903
0	1	Dox Positive	1	0	0.000	0.250	0.386	0.349	0.345	0.486	0.468	1.000	0.415	0.957
1	4	Dox Positive	3	1	0.000	0.283	0.543	0.446	1.000	0.695	0.666	0.568	0.443	0.561
4	1	Dox Positive	1	0	0.000	0.286	0.548	0.457	0.274	0.628	0.613	1.000	0.912	0.973
7	1	Dox Positive	1	0	0.000	0.368	0.682	0.540	0.310	0.827	0.789	1.000	0.783	0.986
2	1	Negative	0	0	0.000	0.175	0.644	0.461	0.886	0.885	0.847	1.000	0.491	0.946
3	13	Negative	1	1	0.000	0.418	0.831	0.636	0.241	1.000	0.966	0.668	0.608	0.662
5	8	Negative	0	0	0.000	0.420	0.776	0.638	0.919	0.959	0.925	0.959	0.644	0.938
6	18	Negative	1	1	0.000	0.432	0.812	0.648	0.485	0.994	0.951	0.923	0.657	0.901
8	1	Negative	0	0	0.000	0.378	0.764	0.609	0.980	1.000	0.966	0.702	0.589	0.703

Sistare Cardiotoxicity Results 8-5-02

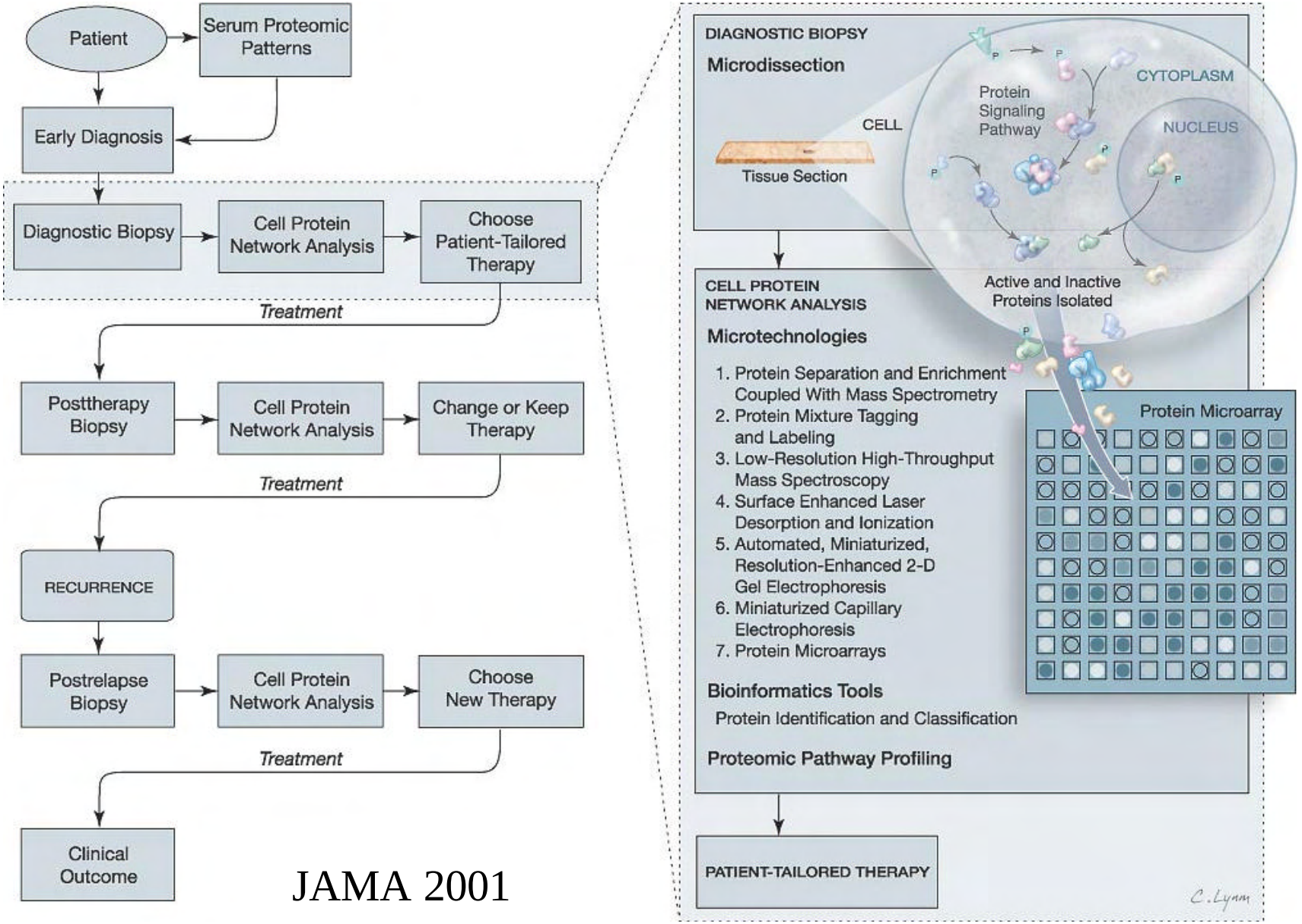
Cardiotoxicity Samples
Negative = 54 samples
Positive = 70 samples

124 Total samples
62 Testing set (29 Negative and 33 Positive)
62 Training set (25 Negative and 37 Positive)
91.6% specificity 81.5% sensitivity

Validation with 23 unknown samples
Predicted 7/23 Negative
Predicted 16/23 Positive

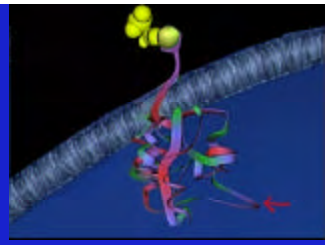
Model:

Node	Count	State	Error	493.592	984.298	6310.890	8526.993	577.758	577.758	7977.216	881.130	8865.985	16758.039
0	35	Cardiotox	10	0.976	0.735	0.096	0.041	0.980	0.980	0.048	0.886	0.045	0.000
1	30	Negative	6	1.000	0.574	0.101	0.059	0.753	0.753	0.083	0.661	0.087	0.000
2	45	Cardiotox	15	1.000	0.666	0.188	0.172	0.782	0.782	0.390	0.720	0.244	0.000
3	10	Cardiotox	2	1.000	0.456	0.133	0.141	0.566	0.566	0.331	0.501	0.185	0.000
4	4	Negative	1	1.000	0.807	0.251	0.274	0.897	0.897	0.667	0.858	0.351	0.000


Patient
Serum Proteomic Patterns
Early Diagnosis
Diagnostic Biopsy
Cell Protein Network Analysis
Choose Patient-Tailored Therapy
Treatment
Posttherapy Biopsy
Cell Protein Network Analysis
Change or Keep Therapy
Treatment
RECURRENCE
Postrelapse Biopsy
Cell Protein Network Analysis
Choose New Therapy
Treatment
Clinical Outcome
DIAGNOSTIC BIOPSY
Microdissection
Tissue Section
CELL
CYTOPLASM
Protein Signaling Pathway
NUCLEUS
Active and Inactive Proteins Isolated
CELL PROTEIN NETWORK ANALYSIS
Microtechnologies
1. Protein Separation and Enrichment Coupled With Mass Spectrometry
2. Protein Mixture Tagging and Labeling
3. Low-Resolution High-Throughput Mass Spectroscopy
4. Surface Enhanced Laser Desorption and Ionization
5. Automated, Miniaturized, Resolution-Enhanced 2-D Gel Electrophoresis
6. Miniaturized Capillary Electrophoresis
7. Protein Microarrays
Protein Microarray
Bioinformatics Tools
Protein Identification and Classification
Proteomic Pathway Profiling
PATIENT-TAILORED THERAPY
C. Lynn

JAMA 2001

Serum Proteomic Pattern Diagnostics



- TISSUE PATHOLOGIC STATES ARE REFLECTED IN HIDDEN SERUM PROTEOMIC PATTERNS UNCOVERED USING AN ARTIFICIAL BIOINFORMATICS TOOL THAT LEARNS THE MOST FIT SOLUTION

- WE HYPOTHESIZE THAT SERUM PROTEOMIC PATTERNS ARE PRODUCT OF THE UNIQUE TUMOR-HOST MICROENVIRONMENT AND REFLECT TUMOR AND HOST INTERACTION

CURRENT STRATEGY:

TWO INDEPENDENT TRACKS:

1. SCIENTIFIC INVESTIGATION INTO SPECIFIC SOURCE AND IDENTITY OF THE CLASSIFIERS

2. NCI-BASED NATIONAL CLINICAL TRIAL ON SERUM PROTEOMIC PATTERN DIAGNOSTICS WHERE IDENTITY IS NOT NEEDED

CCR NCI Clinical Proteomics Reference Laboratory

- **Phase One:** Quality assurance, sensitivity, specificity, reproducibility, and exclusion of degraded samples, validation of initial results on larger retrospective study sets

- **Phase Two:**

A. Prospective longitudinal testing for ovarian cancer recurrence.

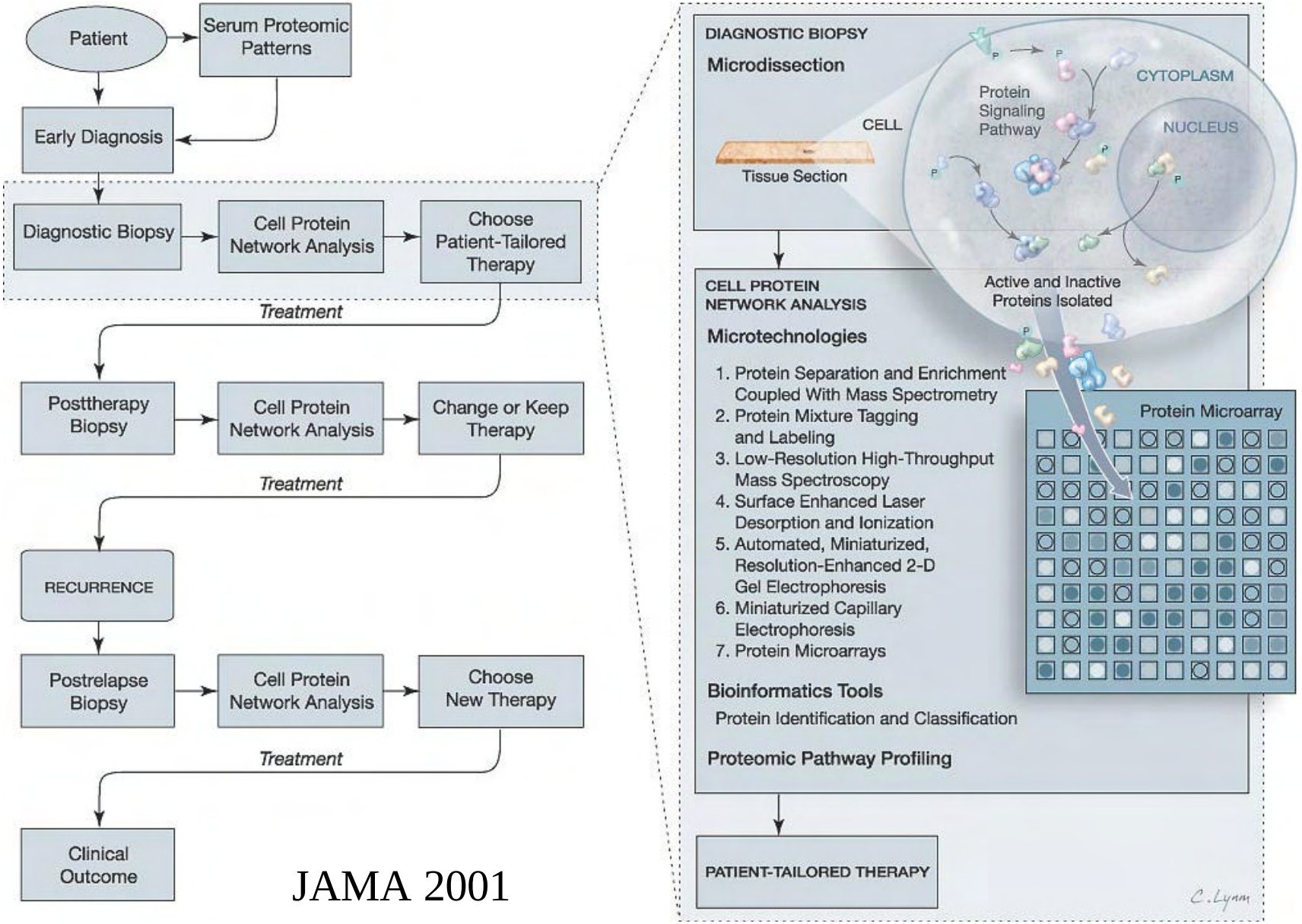
B. Classification of benign from malignant GYN disease in Women who have been diagnosed with a pelvic mass

C. High Risk Screening

- **Phase Three:** Extension to breast, prostate, lung, colon, and pancreatic cancer

Gynecologic Extramural Collaborators

- Northwestern Ovarian Cancer Early Detection Program, David Fishman
  Ovarian Cancer EDRN Consortium, David Fishman PI
- Pacific Ovarian Cancer Research Consortium, Marsha Rivken Center; Univ. Washington ovarian cancer SPORE, Nicole Urban, PI, Saul Rivken, Director
- University of Pennsylvania, George Coukos
- Memorial Sloan Kettering Cancer Center High Risk Screening Program, Ken Offit , PI
- Gynecologic Oncology Group clinical trial link newly diagnosed women, Elise Kohn PI
- Inter SPORE collaboration for screening study (ovarian cancer SPORES: U Wash, Urban confirmed; U Alabama, Partridge confirmed; Fox Chase Cancer Center, Hamilton/Daly) link for pelvic mass trial (protocol and formal SPORE collaboration mechanism in development)
- St. Bartholomew's Hospital, Ovarian Cancer Screening Program, Ian Jacobs, PI, Steve Skates, statistician
- Cancer Gene Network High Risk Women Pilot Program, through Steven Skates and CGN Steering Committee
- University of Alabama SPORE, support reference laboratory development, W. Grizzle
- Stonybrook and Long Island Jewish Hospital Consortium


Patient
Serum Proteomic Patterns
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Choose Patient-Tailored Therapy
Treatment
Posttherapy Biopsy
Cell Protein Network Analysis
Change or Keep Therapy
Treatment
RECURRENCE
Postrelapse Biopsy
Cell Protein Network Analysis
Choose New Therapy
Treatment
Clinical Outcome
DIAGNOSTIC BIOPSY
Microdissection
Tissue Section
CELL
CYTOPLASM
Protein Signaling Pathway
NUCLEUS
Active and Inactive Proteins Isolated
CELL PROTEIN NETWORK ANALYSIS
Microtechnologies
1. Protein Separation and Enrichment Coupled With Mass Spectrometry
2. Protein Mixture Tagging and Labeling
3. Low-Resolution High-Throughput Mass Spectroscopy
4. Surface Enhanced Laser Desorption and Ionization
5. Automated, Miniaturized, Resolution-Enhanced 2-D Gel Electrophoresis
6. Miniaturized Capillary Electrophoresis
7. Protein Microarrays
Protein Microarray
Bioinformatics Tools
Protein Identification and Classification
Proteomic Pathway Profiling
PATIENT-TAILORED THERAPY
C. Lynn

JAMA 2001

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