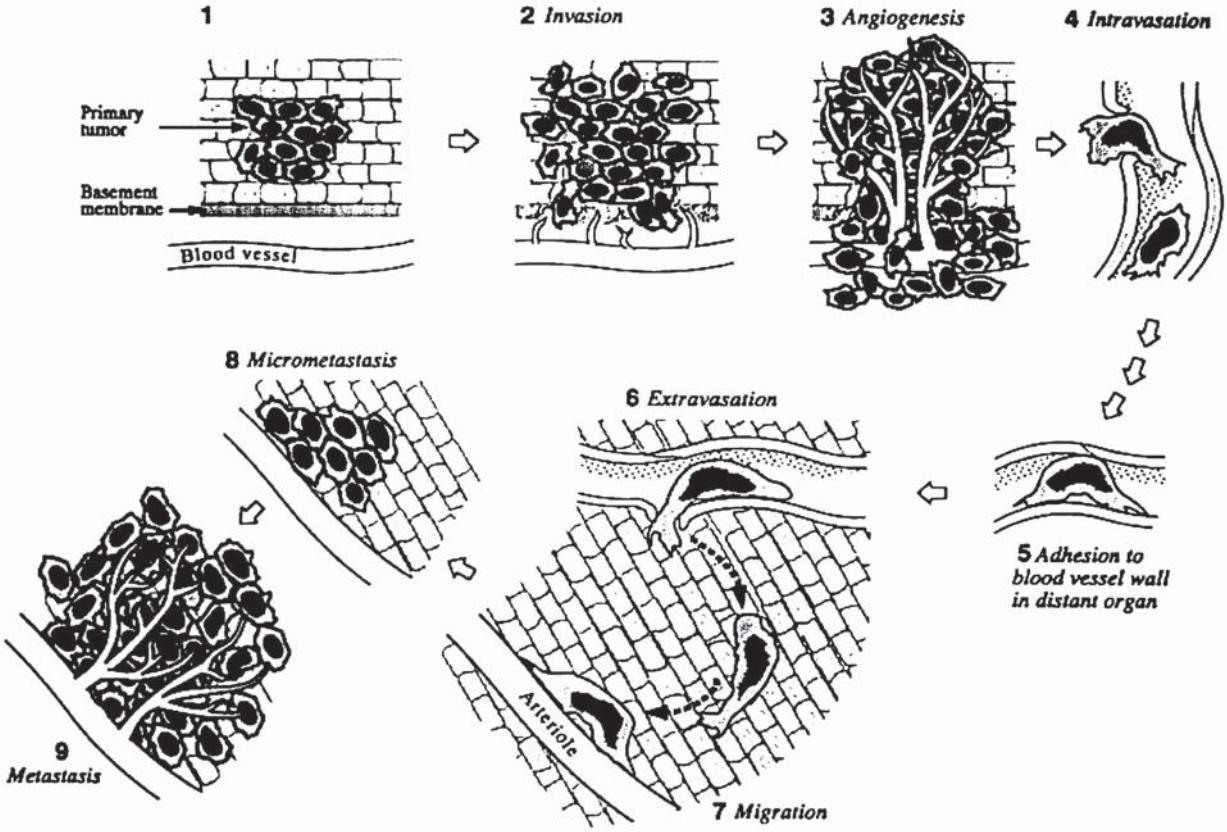
Regulation of Prostate Cancer Metastasis

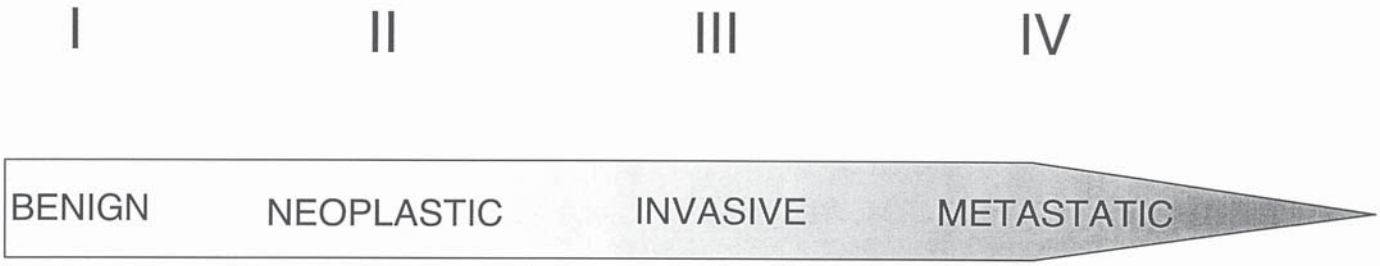
NCAB

February 12, 2003

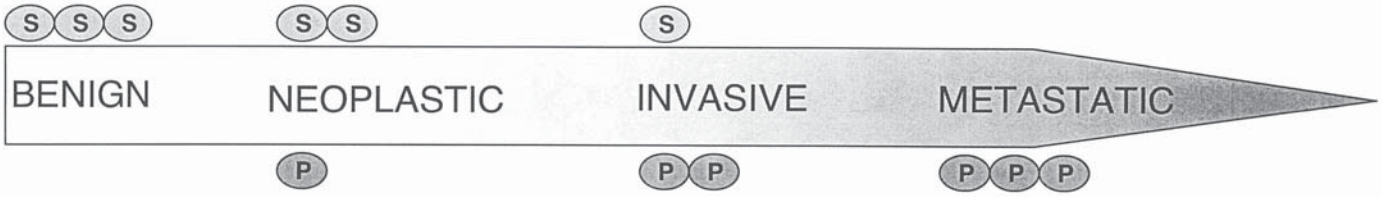
Bruce Zetter
Boston Children's Hospital

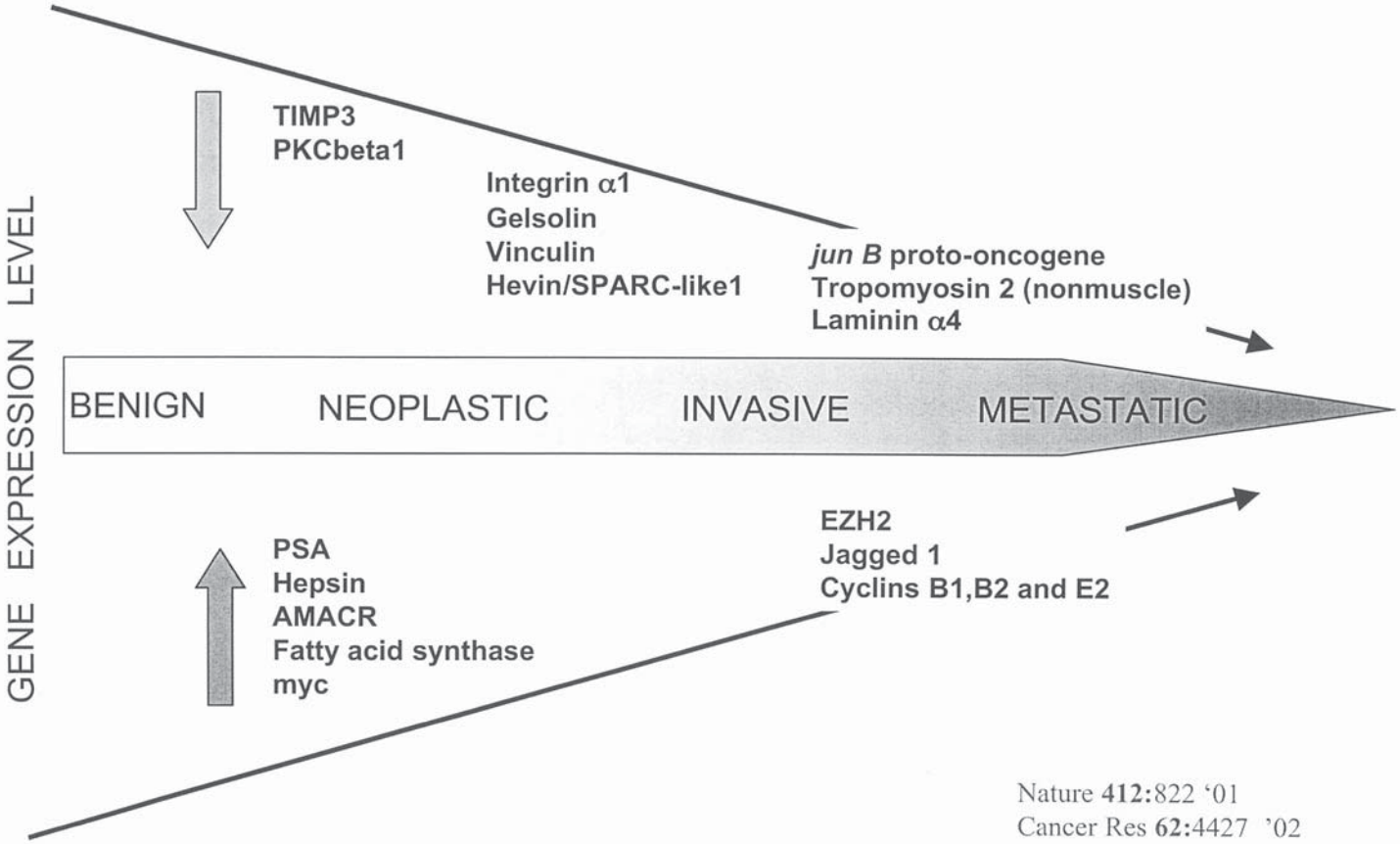

1
Primary tumor
Basement membrane
Blood vessel
2 Invasion
3 Angiogenesis
4 Intravasation
5 Adhesion to blood vessel wall in distant organ
6 Extravasation
Arteriole
7 Migration
8 Micrometastasis
9 Metastasis

TUMOR PROGRESSION

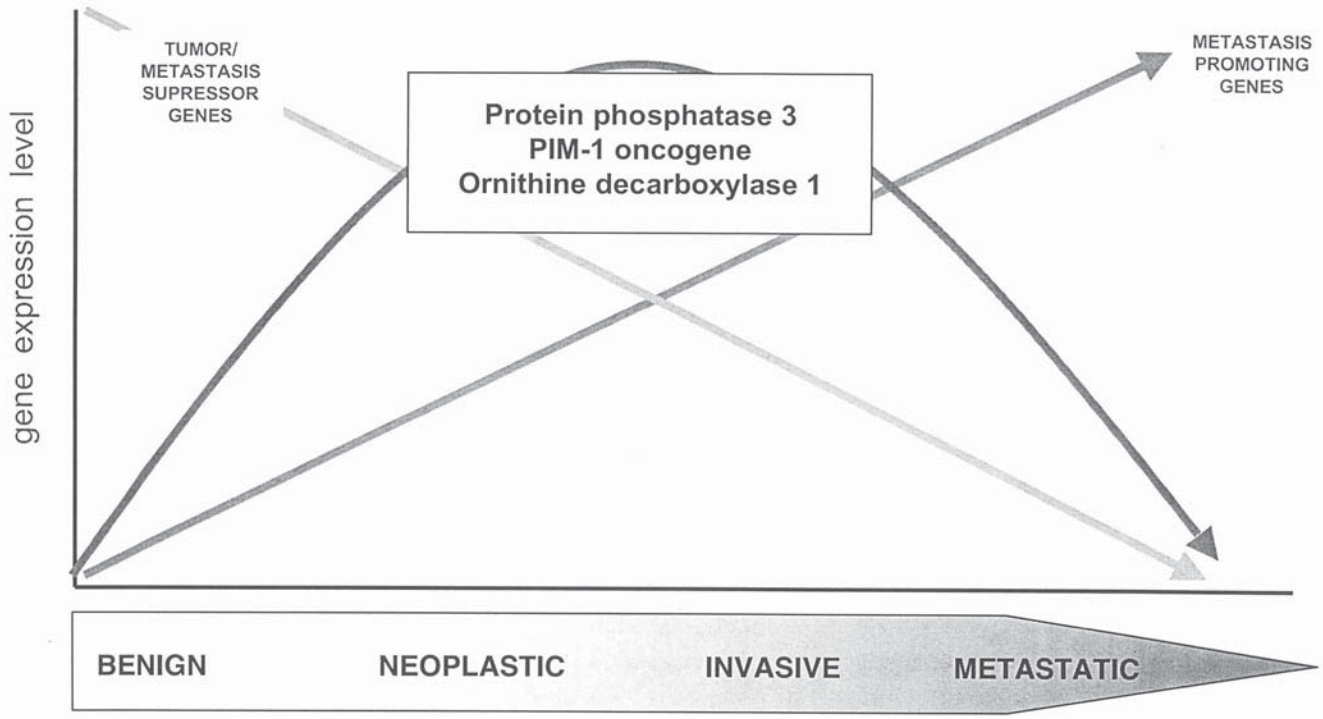


TUMOR PROGRESSION





Nature **412:**822 '01
Cancer Res **62:**4427 '02
Cancer Res **62:**4499 '02


TUMOR/
METASTASIS
SUPRESSOR
GENES
Protein phosphatase 3
PIM-1 oncogene
Ornithine decarboxylase 1
METASTASIS
PROMOTING
GENES
gene expression level
BENIGN
NEOPLASTIC
INVASIVE
METASTATIC

Leading Sites of New Cancer Cases and Deaths – 2003 Estimates*

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 220,900 (33%)	Breast 211,300 (32%)	Lung & bronchus 88,400 (31%)	Lung & bronchus 68,800 (25%)
Lung & bronchus 91,800 (14%)	Lung & bronchus 80,100 (12%)	Prostate 28,900 (10%)	Breast 39,800 (15%)
Colon & rectum 72,800 (11%)	Colon & rectum 74,700 (11%)	Colon & rectum 28,300 (10%)	Colon & rectum 28,800 (11%)
Urinary bladder 42,200 (6%)	Uterine corpus 40,100 (6%)	Pancreas 14,700 (5%)	Pancreas 15,300 (6%)
Melanoma of the skin 29,900 (4%)	Ovary 25,400 (4%)	Non-Hodgkin lymphoma 12,200 (4%)	Ovary 14,300 (5%)
Non-Hodgkin lymphoma 28,300 (4%)	Non-Hodgkin lymphoma 25,100 (4%)	Leukemia 12,100 (4%)	Non-Hodgkin lymphoma 11,200 (4%)
Kidney 19,500 (3%)	Melanoma of the skin 24,300 (3%)	Esophagus 9,900 (4%)	Leukemia 9,800 (4%)
Oral cavity 18,200 (3%)	Thyroid 16,300 (3%)	Liver 9,200 (3%)	Uterine corpus 6,800 (3%)
Leukemia 17,900 (3%)	Pancreas 15,800 (2%)	Urinary bladder 8,600 (3%)	Brain 5,800 (2%)
Pancreas 14,900 (2%)	Urinary bladder 15,200 (2%)	Kidney 7,400 (3%)	Multiple myeloma 5,500 (2%)
All sites 675,300 (100%)	All sites 658,800 (100%)	All sites 285,900 (100%)	All sites 270,600 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.
Percentages may not total 100% due to rounding.

©2003, American Cancer Society, Inc., Surveillance Research

PROPERTIES OF PROSTATE CANCER

- Most common cancer in men. More than 200,000 cases and 40,000 deaths per year.
- Slow growing tumors. Less than 15% progress to metastasis. Metastatic tumors have poor prognosis.
- PSA test has greatly improved prostate cancer diagnosis but cannot distinguish localized from metastatic cancer.
- Current treatments are not generally effective in men with metastatic prostate cancer.

CANCER MARKERS

DIAGNOSTIC

PREDICTIVE

PSA Specificity in CaP Diagnosis

False-Positive Results:

- BPH (PSA elevated in up to 80% of patients)
- Prostatitis (acute/chronic)
- Urinary Retention

False-Negative Results:

- Up to 25% of CaP patients have normal PSA levels

Marker Discovery

Sources	Methods
• Tissue	
	Genomics
• Serum	
	Proteomics
• Urine	

Proteomics

- Advantages:
  - Does not require cell capture
  - Can detect proteins in circulating fluids
  - Can detect protein modifications

- Disadvantages:
  - Lower sensitivity
  - Technology rapidly developing

Urinary Proteomics

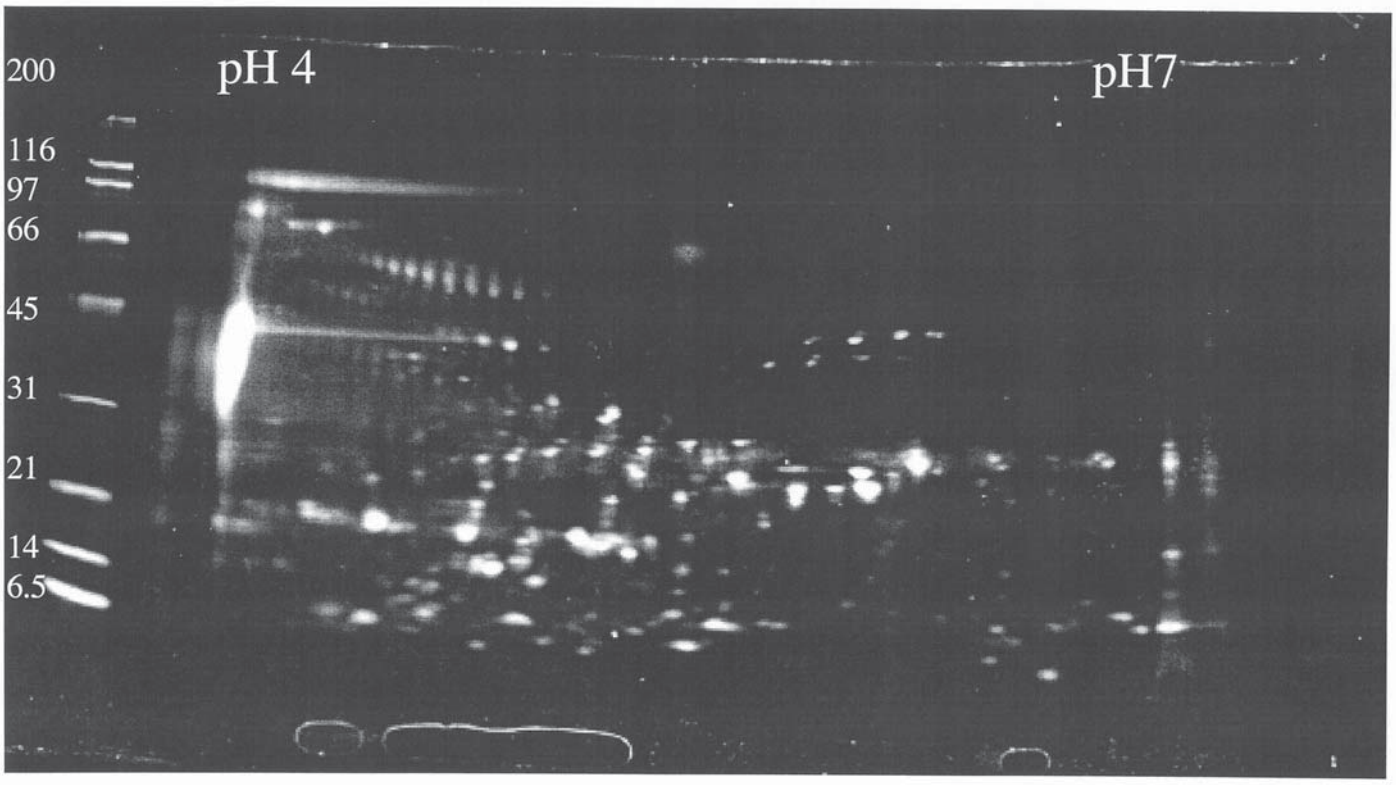
Advantages:

- Non-invasive sample collection
- Smaller number of proteins
- Lower dynamic range

Challenges:

- Sample preparation (Protein loss, Salt concentration)
- Smaller number of proteins
- Low protein concentration (10-15 μg/ml)

2-D Gel Urinary Profile



Analysis Groups

Controls | **Prostate Cancer**

Age-matched | Pre-treatment | Post-treatment | Post-treatment PSA failure

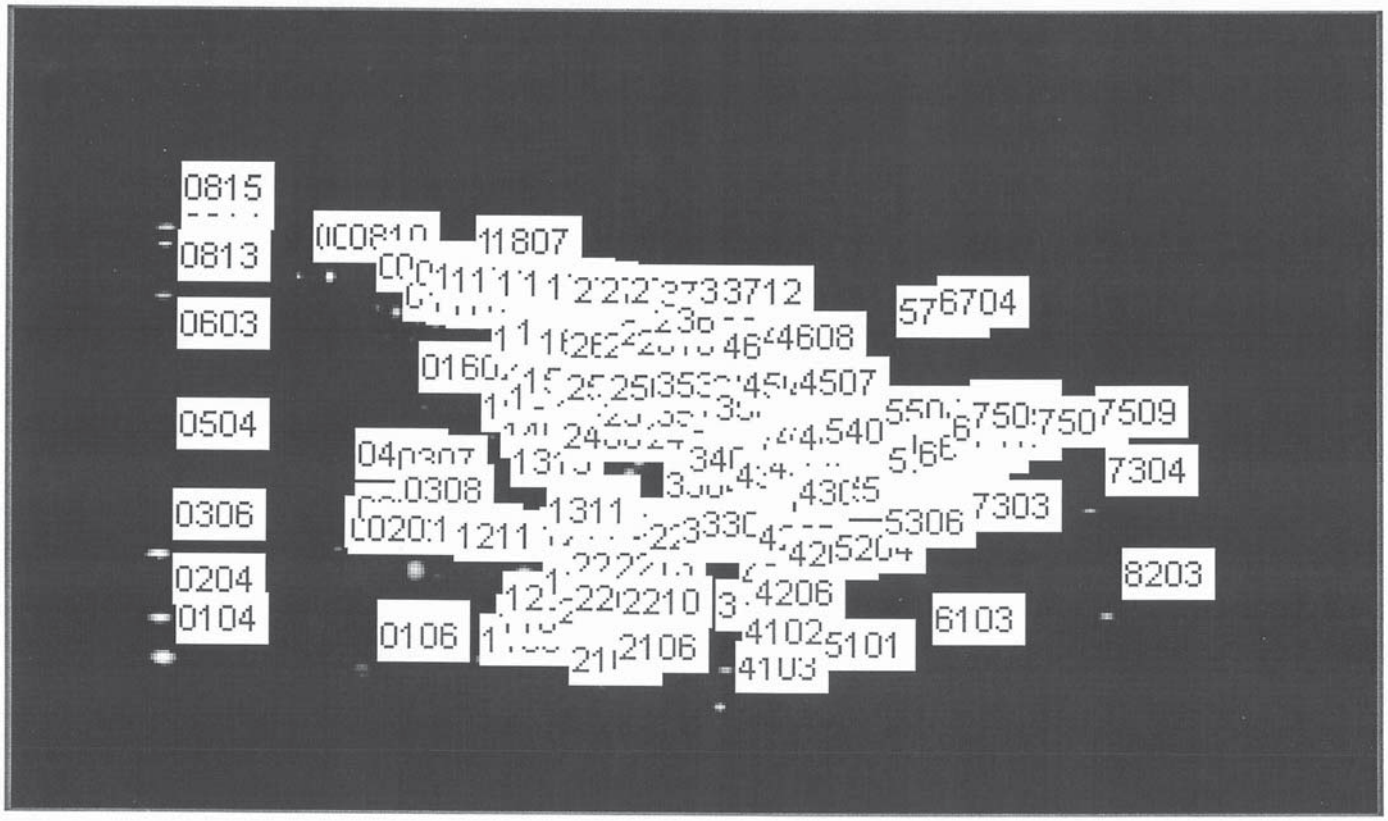
{Combined Matchset}

Matchset Properties

- 100 2D Gels
- 300 Unique Spots
- MW Range: 4 - 100 kD
- pH Range: 4 - 7
- Detection limit ~ 2ng

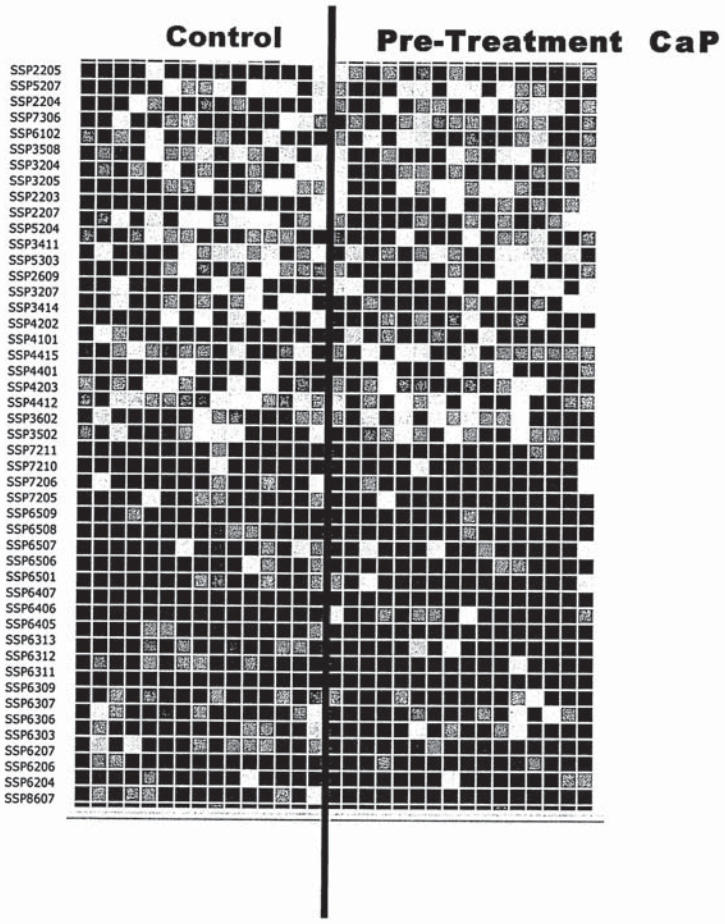
Combined Matchset

Unique Spot Identifiers

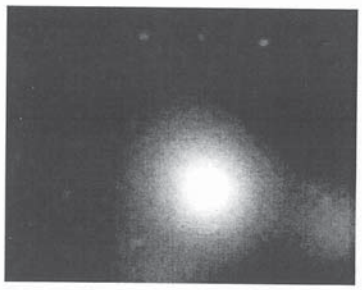


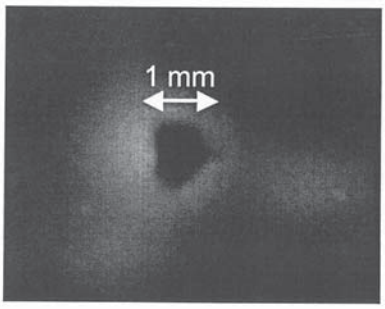
Comparative Spot Analysis

Urinary Protein Analysis

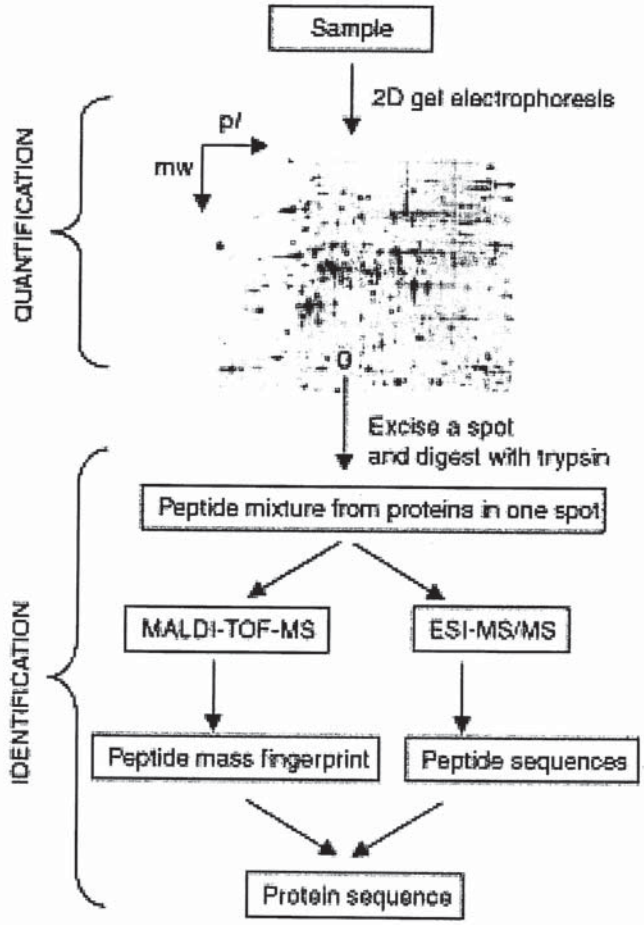


Spot Excision





Mass Spec Analysis



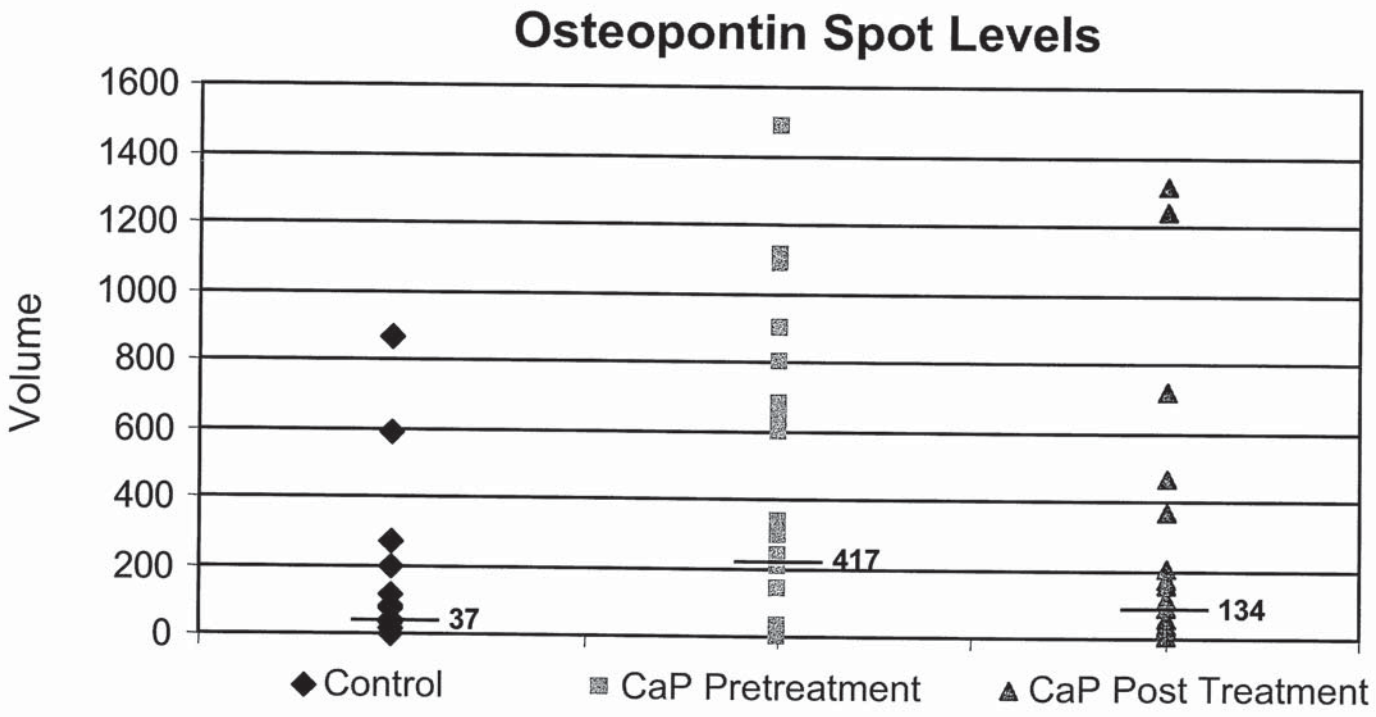
Junmin Peng and Steven P. Gygi
J. Mass Spectrom. 2001; 36: 1083-1091

Tetranectin

- Lectin, 4x 21kD Polypeptide
- Protease activator (plasminogen)
- Tissue remodeling (proteolysis), Osteogenesis
- Expressed in gastric adenocarcinoma, colorectal cancer, metastatic melanoma.
- Prognostic marker in ovarian cancer,breast cancer and colorectal cancer

Osteopontin

- 36 kD Phosphoprotein
- Expressed in colorectal cancer, breast cancer, ovarian cancer, hepatocelluar cancer
- Elevated serum levels in prostate cancer and breast cancer,
- Prognostic marker in ovarian cancer.


Osteopontin Spot Levels
Volume
1600
1400
1200
1000
800
600
400
200
0
37
417
134
Control
CaP Pretreatment
CaP Post Treatment

Osteopontin Correlates Inversely with Prostate Cancer Survival

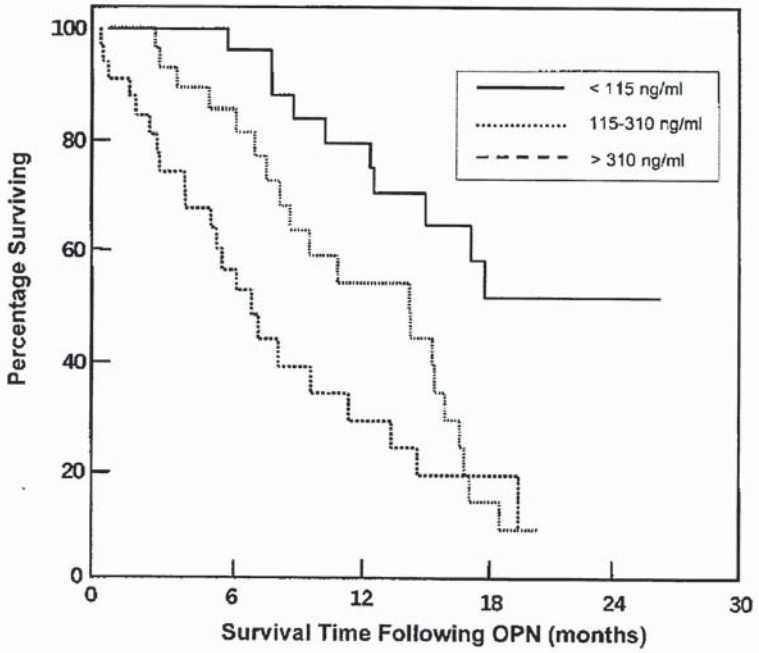


FIGURE 1. Overall survival of men with hormone-refractory prostate carcinoma by exact terciles of osteopontin (OPN) levels (log-rank test; $P < 0.001$).

Cancer 2002 Aug 1;95(3):506-12