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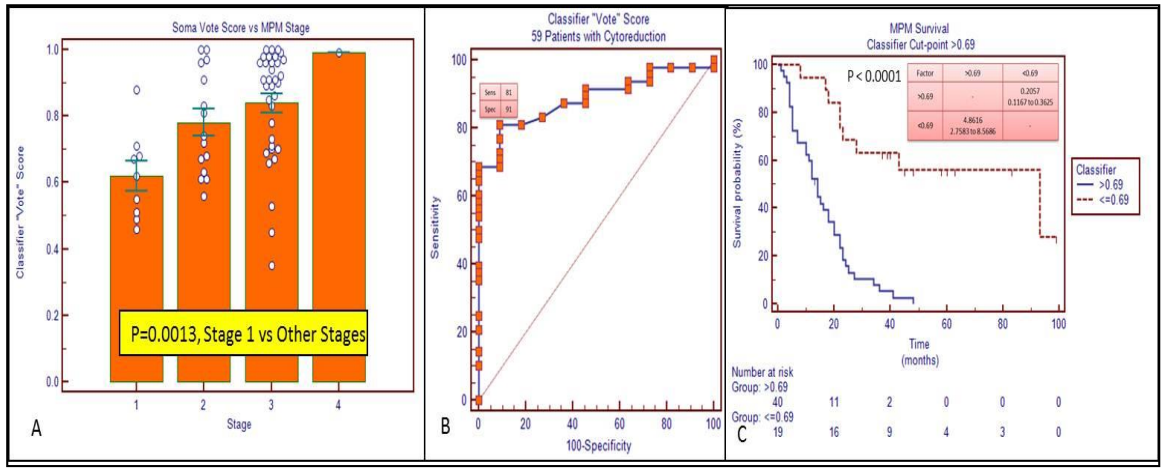
Gene Name	Gene ID	Protein Target	SwissProt ID	Function	MM vs Asbestos*	KS test p-value	t test p-value
APOA1	335	Apo A-I	P02647	Lipid transport	Down	2.99E-08	6.32E-11
C9	735	C9	P02748	Adaptive immune response	Up	6.47E-07	1.14E-07
CCL23	6368	Ck-b-8-1	P55773	Cellular ion homeostasis, inflammatory response	Up	2.81E-06	4.00E-08
CDK5/CDK5R1	1020/8851	CDK5/p35	Q00535/Q15078	Cell morphogenesis	Up	1.22E-06	8.64E-09
CXCL13	10563	BLC	O43927	Immune system development	Up	1.67E-09	6.31E-08
F9	2158	Coagulation Factor IX	P00740	Coagulation cascade	Up	2.46E-07	9.61E-09
FCN2	2220	FCN2	Q15485	Immune effector	Up	3.38E-09	6.09E-11
FN1	2335	Fibronectin	P02751	Cell morphogenesis	Down	9.23E-06	9.41E-06
ICAM2	3384	sICAM-2	P13598	Cell adhesion	Up	2.67E-05	1.75E-06
KIT	3815	SCF sR	P10721	Immune system development, receptor tyrosine kinase	Down	3.83E-06	1.14E-08
MDK	4192	Midkine	P21741	Regulation of cell division	Up	2.99E-08	8.54E-02
SERPINA4	5267	Kallistatin	P29622	Serine protease inhibitor	Down	2.05E-07	4.56E-07
TNFRSF8	943	CD30	P28908	Regulation of cytokines & cell proliferation	Up	8.02E-08	3.94E-06

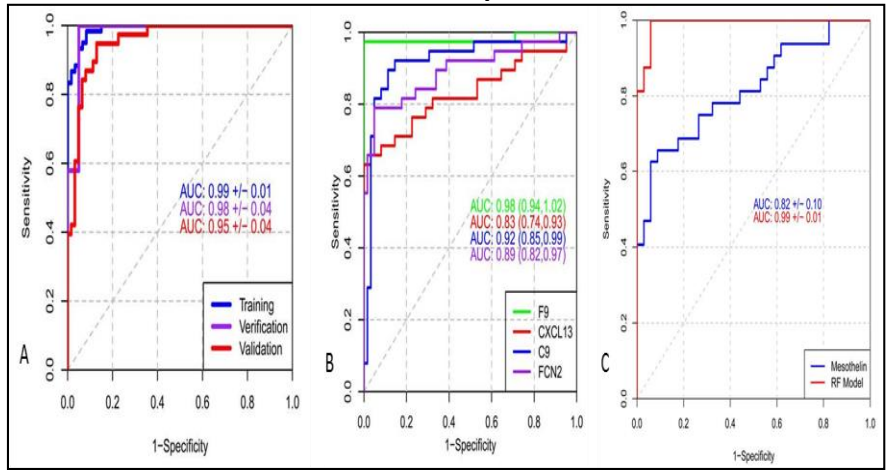
*Up or down regulation in MM cases relative to controls.

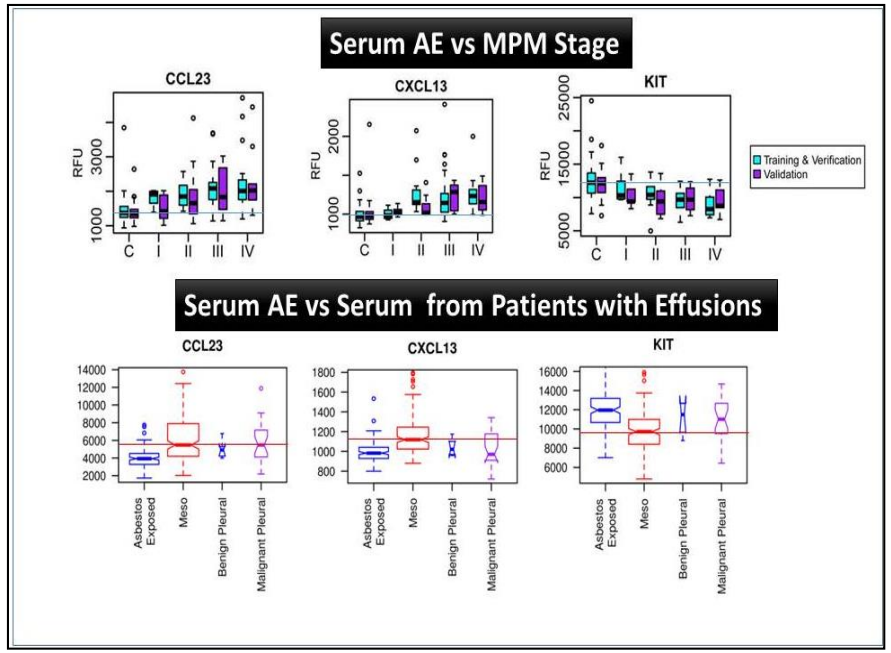
Proteins detected by SOMAscan to separate AE from MPM serum. Yellowed serum markers were also the most significant in separating individuals with MPM effusions from those with non-MPM effusions.



Prognosis of MPM with SOMAmer technology. A)Classifier vote increases with Stage of MPM, B) ROC curve separates living vs dead from the time of serum harvest. C) Dichotomous separation of survival by classifier cut-point. Kolmogorov–Smirnov test

SomaMPM 13 is Superior to SMRP

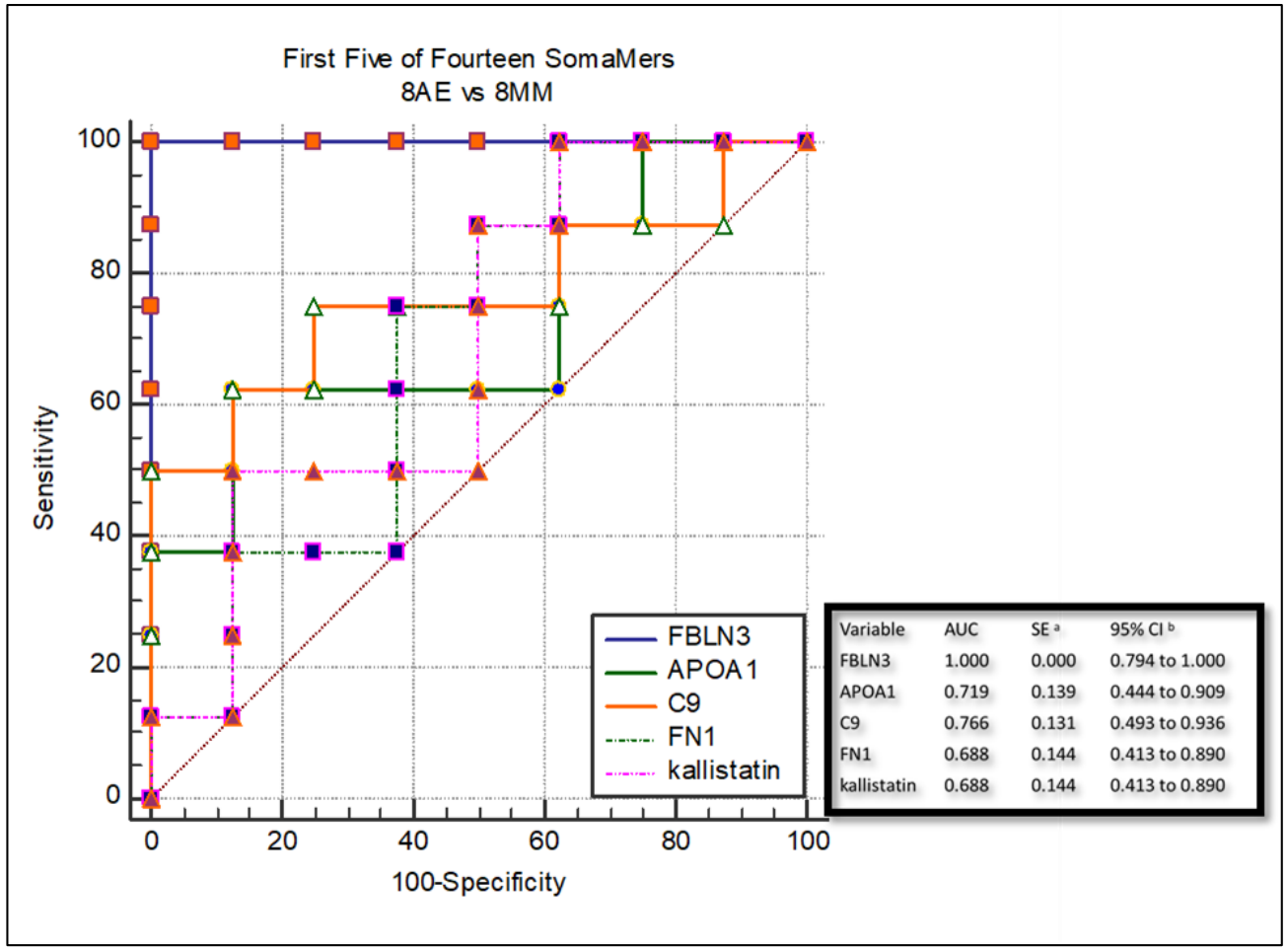




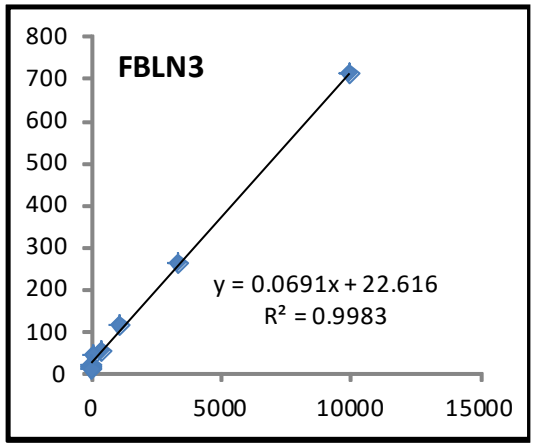
SOMAmer diagnosis of MPM vs AE. A)ROC curves for discovery and validation, B) ELISA validation of selected SOMAmer data, C) Head to head comparison of SMRP and SOMA 13 panel shows better characteristics for the latter. LOWER PANEL. Serum levels of patients with MPM effusions compared to those with non-MPM effusions suggests that 3 markers may have specificity capabilities.

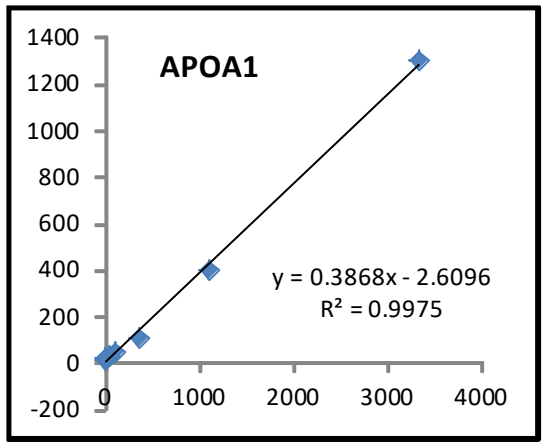
PLoS One. 2012;7(10):e46091.

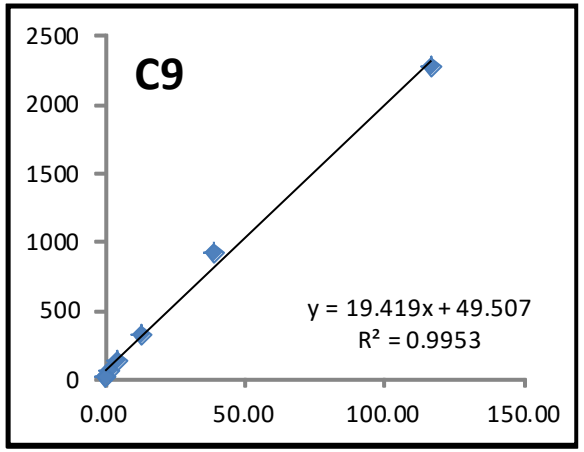
The Other SomaMers

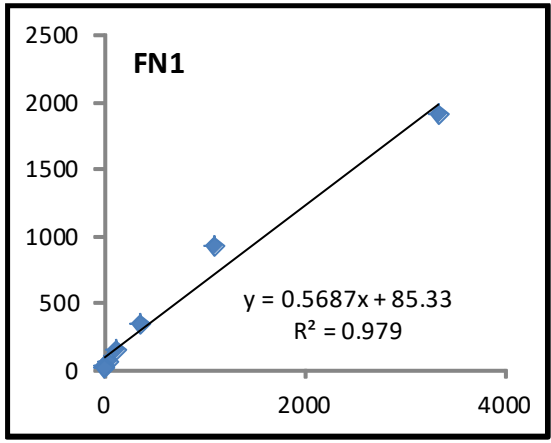


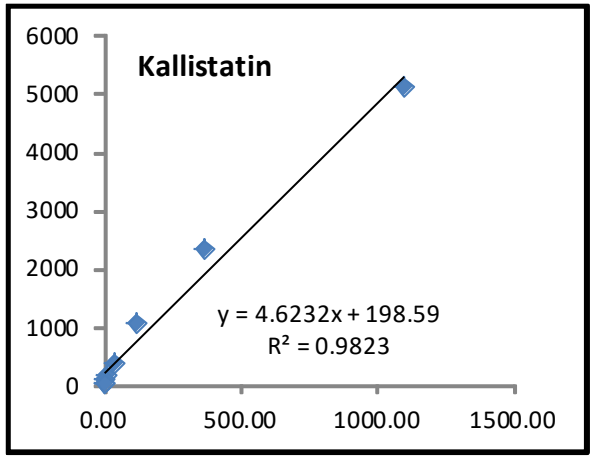
Variable	AUC	SE [a]	95% CI [b]
FBLN3	1.000	0.000	0.794 to 1.000
APOA1	0.719	0.139	0.444 to 0.909
C9	0.766	0.131	0.493 to 0.936
FN1	0.688	0.144	0.413 to 0.890
kallistatin	0.688	0.144	0.413 to 0.890











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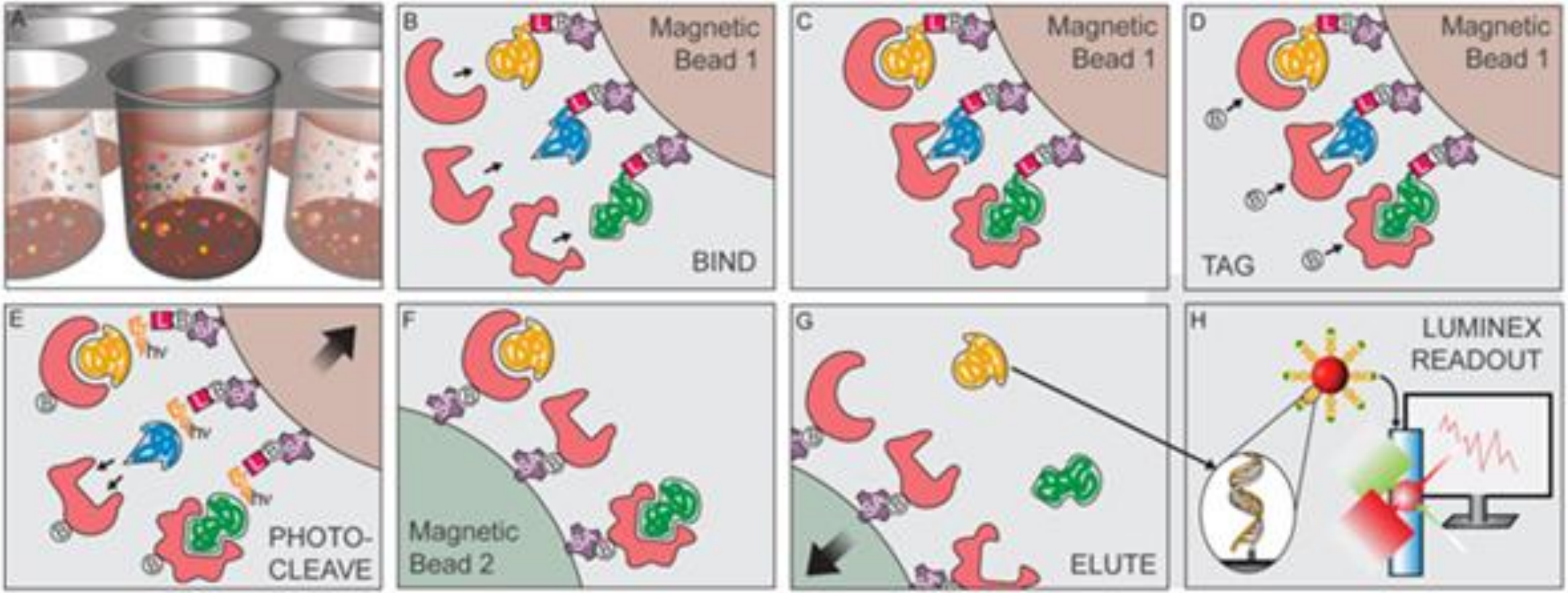
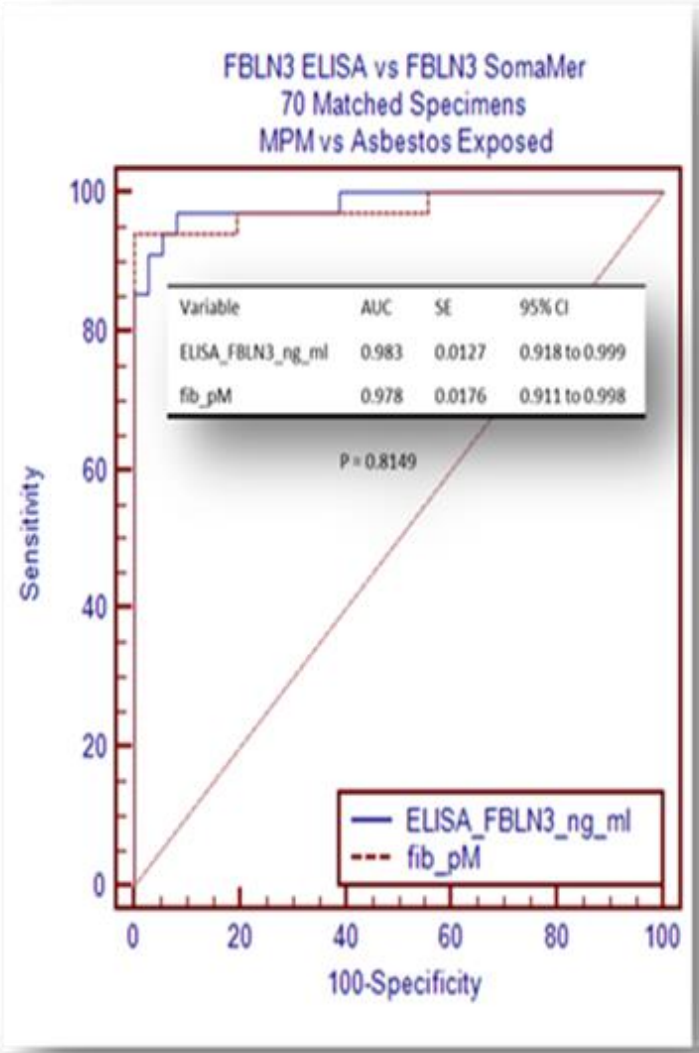
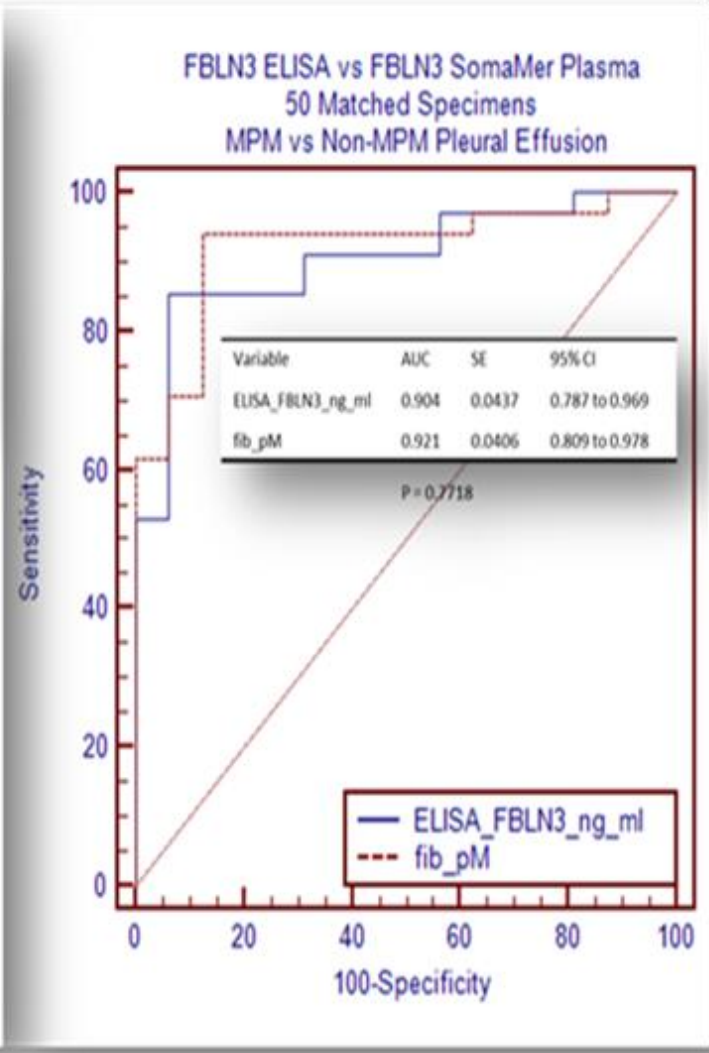
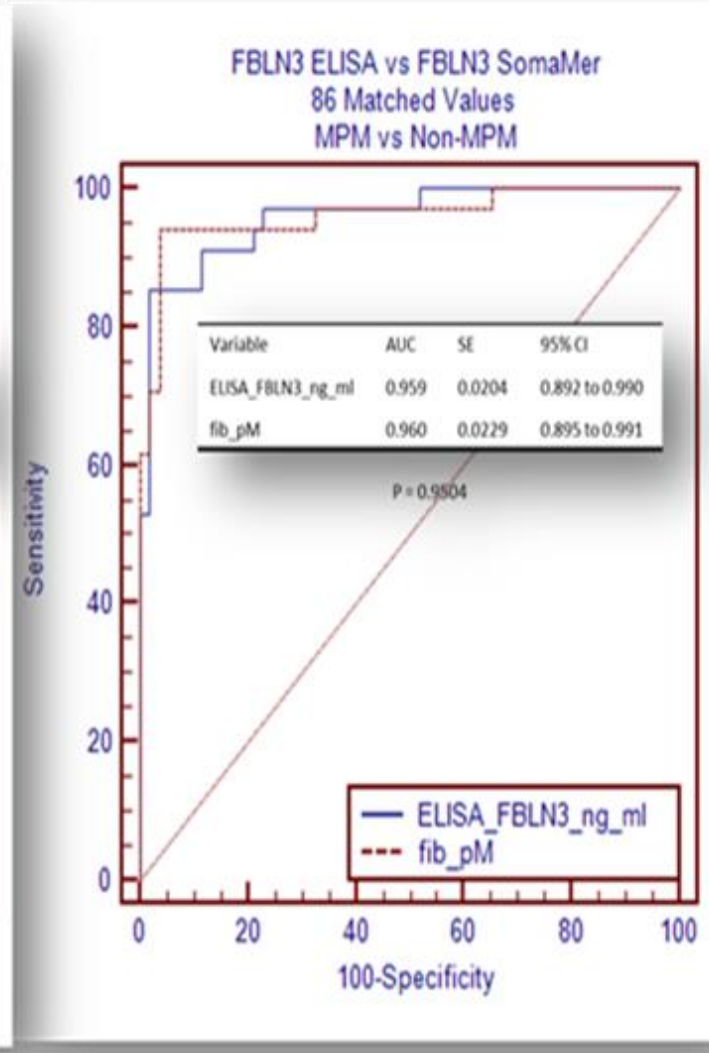
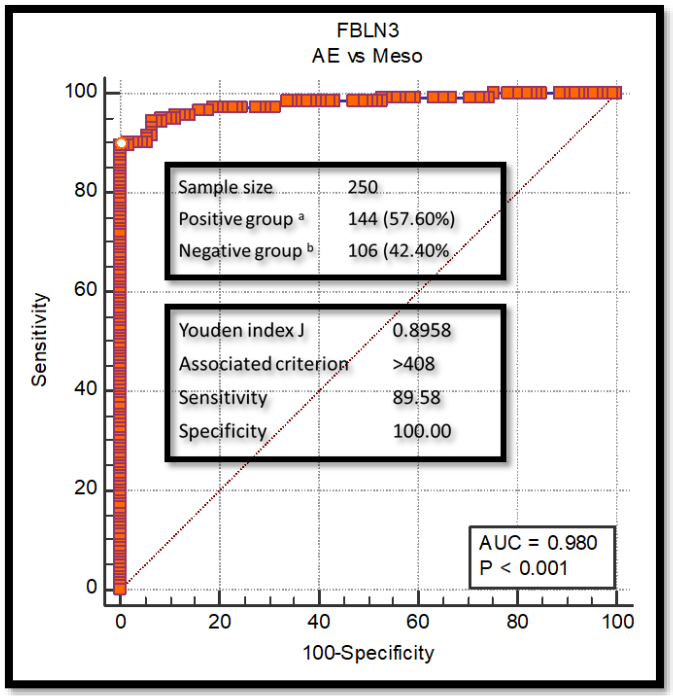


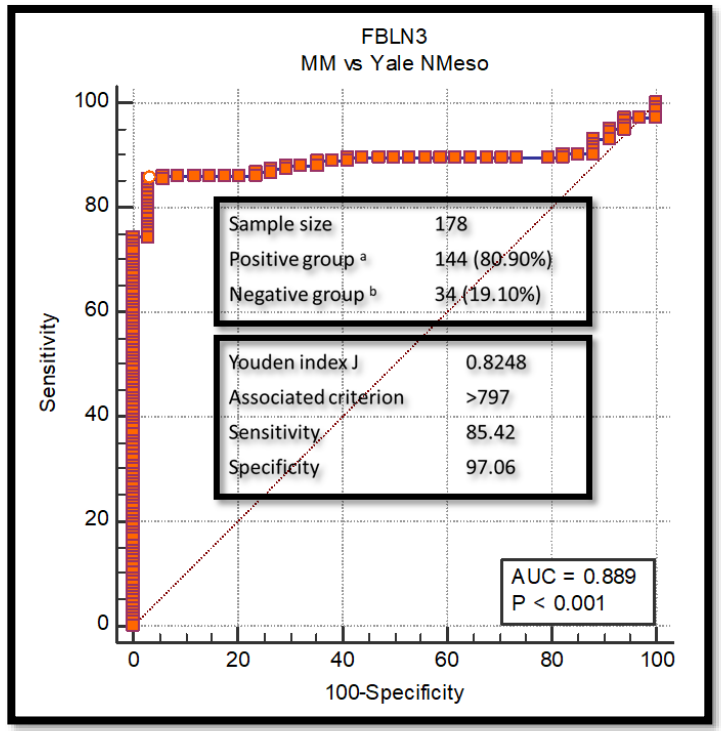
(A) SOMAmer with 5' biotin and a photo-cleavable linker between the SOMAmer and the 5' biotin are pre-bound to streptavidin coated beads (either magnetic or agarose beads can be used) and beads are added to samples in microwells (B-H) Schematic sequence of assay steps leading to quantitative readout of target proteins. (B) Proteins, shown as different shapes, and beads with SOMAmers are mixed in solution (C) SOMAmers attached to magnetic beads bind to proteins specifically (gold and green) and some non-specifically (blue). Unbound proteins are washed away (*Catch 1*) (D) *Tagging*: Proteins bound to SOMAmers are tagged with NHS-biotin. (E) *Photocleavage* and *kinetic challenge*: UV light (hν) cleaves the linker (L) between the SOMAmer and the 5' biotin, releasing SOMAmers into solution. Taking advantage of a SOMAmer's slow-off rate from its target protein, further specificity of a SOMAmer to its protein target is derived from a *kinetic challenge,* by adding excess anionic competitor ("random" SOMAmers) to the SOMAmer-protein complex in solution; cognate complexes (gold and green) dissociate slowly, but non-cognate complexes (blue SOMAmer) dissociate rapidly and competitor prevents re-binding. (F) *Catch 2*: The SOMAmer-protein complexes that remain after the *kinetic challenge* are captured onto new streptavidin (SA) coated magnetic beads by the biotin tag on the protein from the NHS-biotin labeling of the protein (D) and unbound SOMAmers are washed away. (G) *Elution*: SOMAmers are eluted into solution by disrupting complexes (e.g. proteins denatured with sodium perchlorate) (H) *Readout*: Eluted SOMAmers are hybridized to complimentary probe sequences on coded Luminex beads and quantified by flow cytometry on Luminex

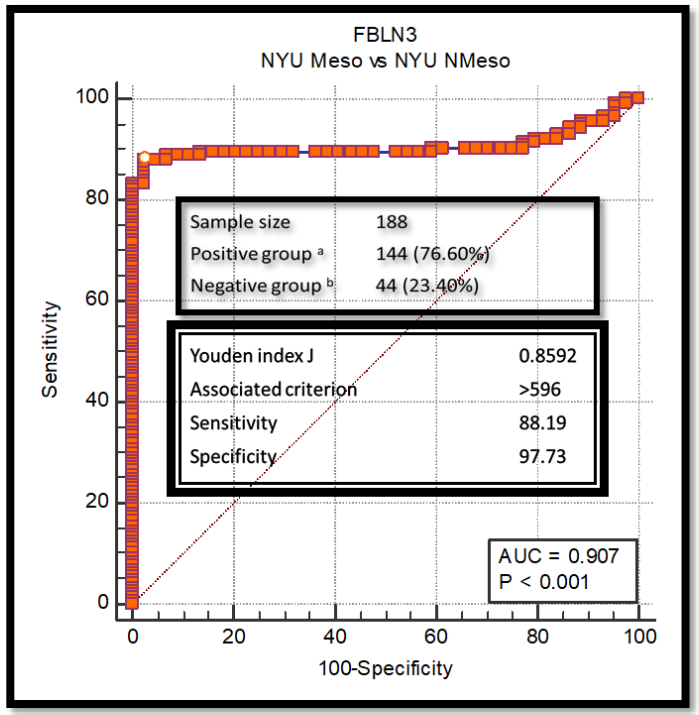

FBLN3 ELISA vs FBLN3 SomaMer
70 Matched Specimens
MPM vs Asbestos Exposed
Variable AUC SE 95% CI
ELISA_FBLN3_ng_ml 0.983 0.0127 0.918 to 0.999
fib_pM 0.978 0.0176 0.911 to 0.998
P = 0.8149
ELISA_FBLN3_ng_ml
fib_pM
Sensitivity
100-Specificity
0
20
40
60
80
100

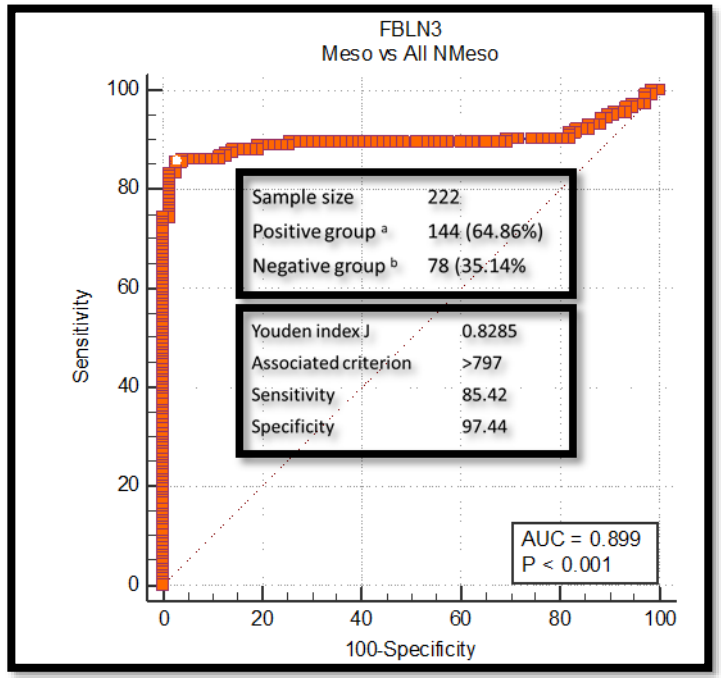

FBLN3 ELISA vs FBLN3 SomaMer Plasma
50 Matched Specimens
MPM vs Non-MPM Pleural Effusion
Variable AUC SE 95% CI
ELISA_FBLN3_ng_ml 0.904 0.0437 0.787 to 0.969
fib_pM 0.921 0.0406 0.809 to 0.978
P = 0.7718
ELISA_FBLN3_ng_ml
fib_pM
Sensitivity
100-Specificity
0
20
40
60
80
100


FBLN3 ELISA vs FBLN3 SomaMer
86 Matched Values
MPM vs Non-MPM
Variable AUC SE 95% CI
ELISA_FBLN3_ng_ml 0.959 0.0204 0.892 to 0.990
fib_pM 0.960 0.0229 0.895 to 0.991
P = 0.9504
ELISA_FBLN3_ng_ml
fib_pM
Sensitivity
100-Specificity
0
20
40
60
80
100


FBLN3
AE vs Meso
Sample size 250
Positive group a 144 (57.60%)
Negative group b 106 (42.40%
Youden index J 0.8958
Associated criterion >408
Sensitivity 89.58
Specificity 100.00
AUC = 0.980
P < 0.001
Sensitivity
100-Specificity


FBLN3
MM vs Yale NMeso
Sample size 178
Positive group a 144 (80.90%)
Negative group b 34 (19.10%)
Youden index J 0.8248
Associated criterion >797
Sensitivity 85.42
Specificity 97.06
AUC = 0.889
P < 0.001
Sensitivity
100-Specificity


FBLN3
NYU Meso vs NYU NMeso
Sample size 188
Positive group a 144 (76.60%)
Negative group b 44 (23.40%)
Youden index J 0.8592
Associated criterion >596
Sensitivity 88.19
Specificity 97.73
AUC = 0.907
P < 0.001
Sensitivity
100-Specificity


FBLN3
Meso vs All NMeso
Sample size 222
Positive group a 144 (64.86%)
Negative group b 78 (35.14%
Youden index J 0.8285
Associated criterion >797
Sensitivity 85.42
Specificity 97.44
AUC = 0.899
P < 0.001
Sensitivity
100-Specificity

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- Subaim 1c: Validate the plasma prognostic accuracy of the Soma 14 NYU MPM assay
  - ***Nope, we developed a new Fibulin 3 ELISA***

New Antibodies

Published OnlineFirst November 16, 2017; DOI: 10.1158/1078-0432.CCR-17-1628

Cancer Therapy: Preclinical

Clinical Cancer Research

Development of a Function-Blocking Antibody Against Fibulin-3 as a Targeted Reagent for Glioblastoma

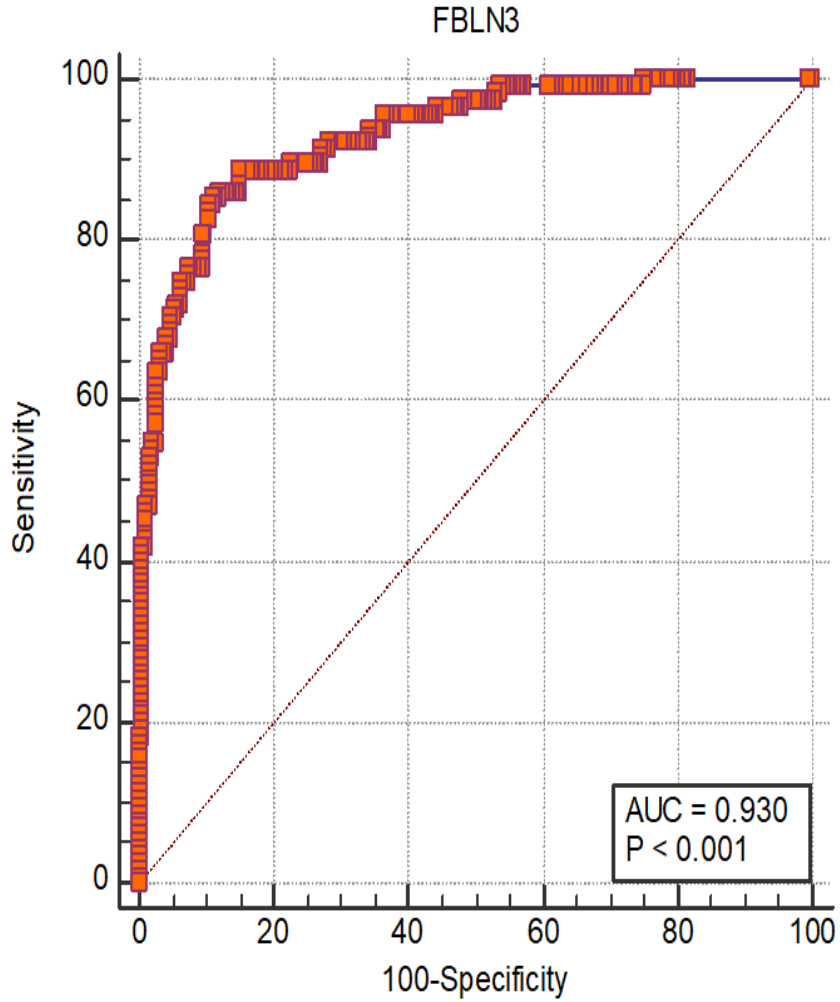
Mohan S. Nandhu[1,2], Prajna Behera[1,2], Vivek Bhaskaran[1], Sharon L. Longo[3], Lina M. Barrera-Arenas[2], Sadhak Sengupta[4], Diego J. Rodriguez-Gil[5], E. Antonio Chiocca[1], and Mariano S. Viapiano[1,2,3]

A Theranostic Antibody-Cytokine Reagent for Diagnosis and Multipronged Therapy of Malignant Mesothelioma	VIAPIANO, MARIANO S	CA170319	W81XWH-18-1-0183	Institution: NEW YORK, STATE UNIVERSITY OF, UPSTATE MEDICAL UNIVERSITY
Engineering T Cells Against the Tumor Extracellular Matrix for Enhanced Immunotherapy of Mesothelioma	VIAPIANO, MARIANO S	CA160356	W81XWH-17-1-0444	Institution: NEW YORK, STATE UNIVERSITY OF, UPSTATE MEDICAL UNIVERSITY

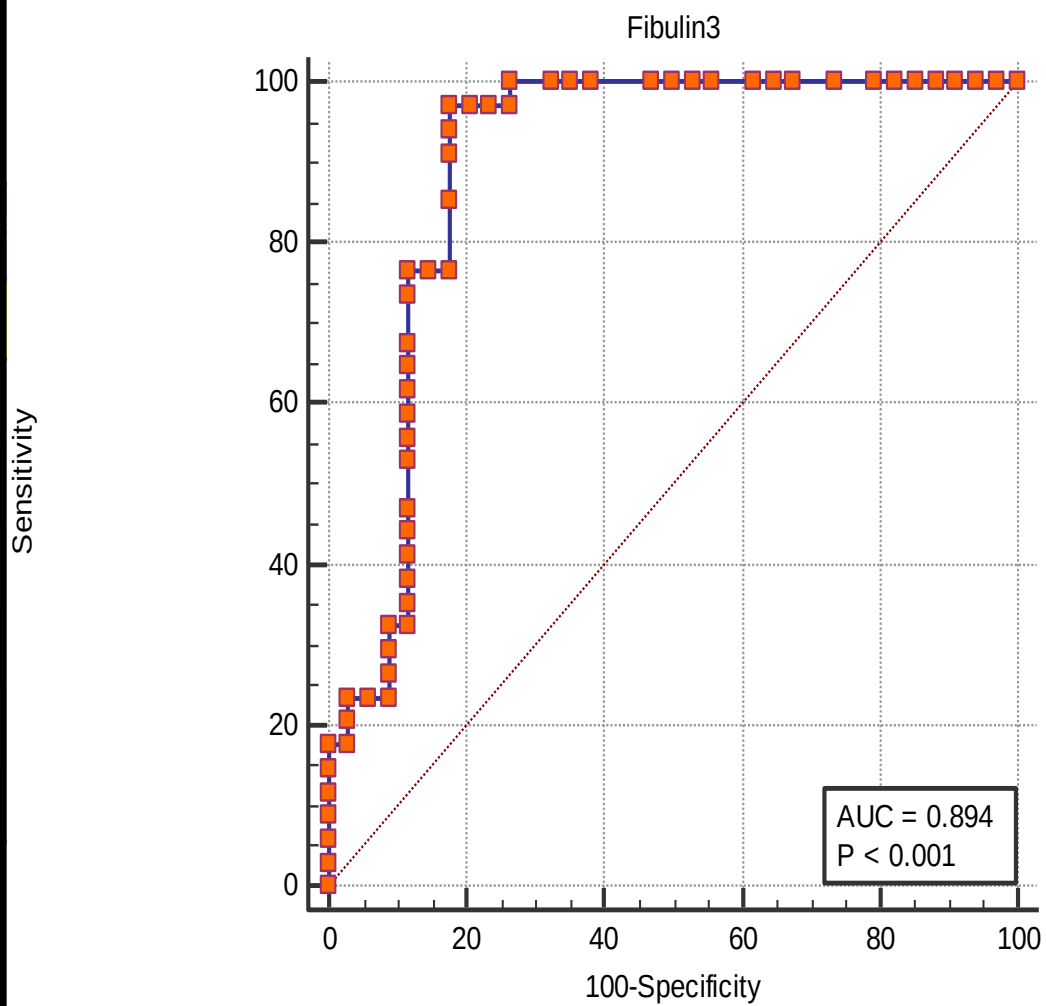
So what happened to the Biomarker??

- Our lab made a new ELISA using the Viapiano antibody mAB428.2
- ***But we had to answer basic questions***
  - Any difference between serum and plasma?
  - Any difference between arterial (OR Blood) and venous (Clinic Blood)
  - Any difference between blood plasma FBLN3 levels between
    - Asbestos exposed vs MM
    - Patients with non MM effusions and Patients with MM

All NYU Meso Plasma (115) Vs All Non Meso Plasma (192)



Blinded Validation University Pennsylvania MM (61) vs Non Meso High Risk (34)



Plans for Fibulin 3, Aim 1

- Blinded mutual validation of Fibulin3 by Institute for Prevention and Occupational Medicine of the German Social Accident Insurance and Calretinin by the NYU Mesothelioma Biomarker Discovery Lab

MATERIAL TRANSFER AND COLLABORATION AGREEMENT

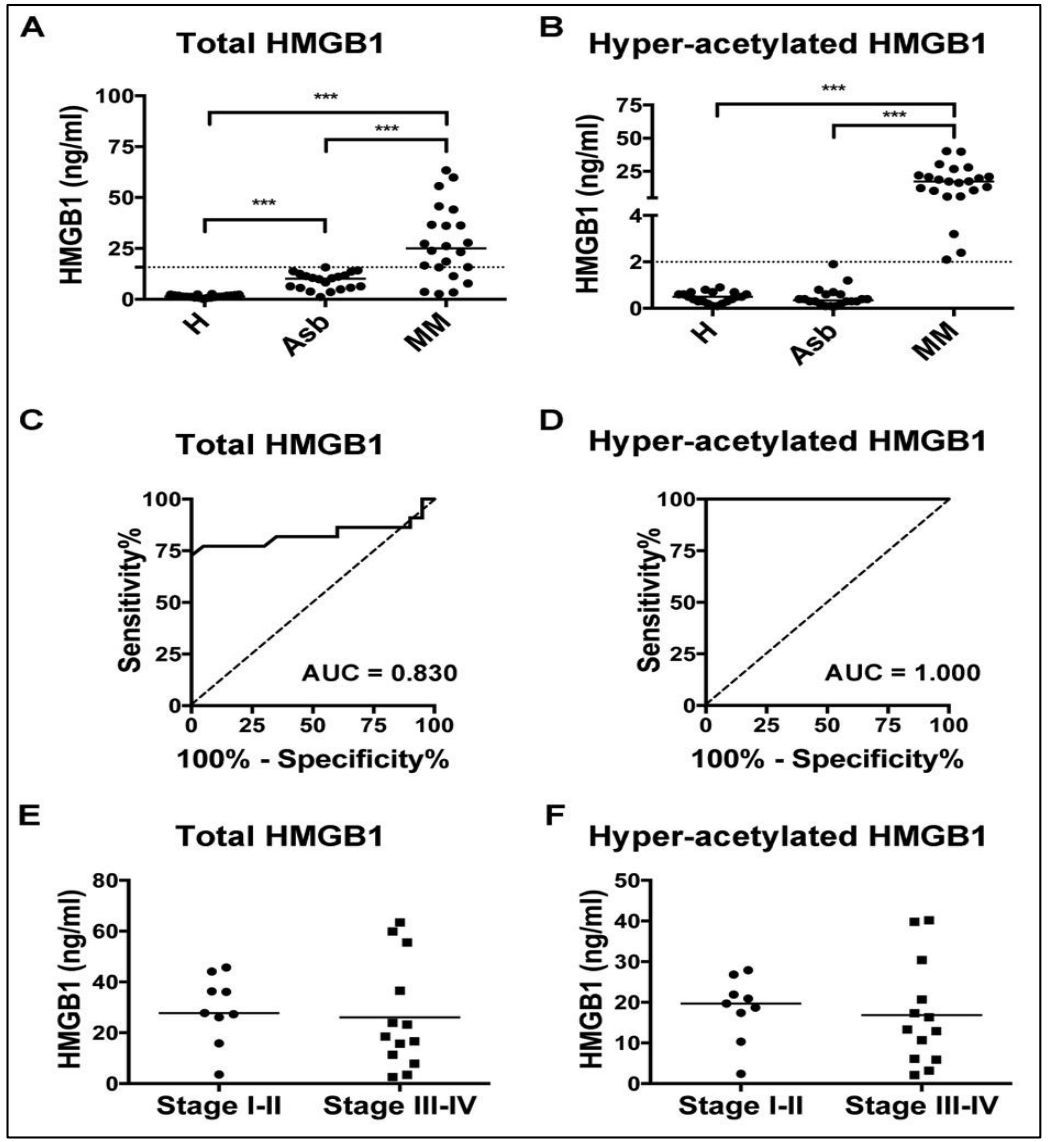
This Material Transfer and Collaboration Agreement (the "Agreement") between **NYU Grossman School of Medicine**, an administrative unit of New York University, an education corporation organized and existing under the laws of the State of New York and having a place of business at 70 Washington Square South, New York, New York 10012 (hereinafter "NYU"), and **Berufsgenossenschaft Rohstoffe und chemische Industrie (BG RCI)** located at Kurfuersten-Anlage 62, 69115 Heidelberg, Germany, acting for the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany (hereinafter "Collaborator"). NYU and Collaborator may hereinafter be referred to individually as a "Party", and/or collectively as the "Parties". The effective date of this Agreement shall be the date of execution (the "Effective Date").

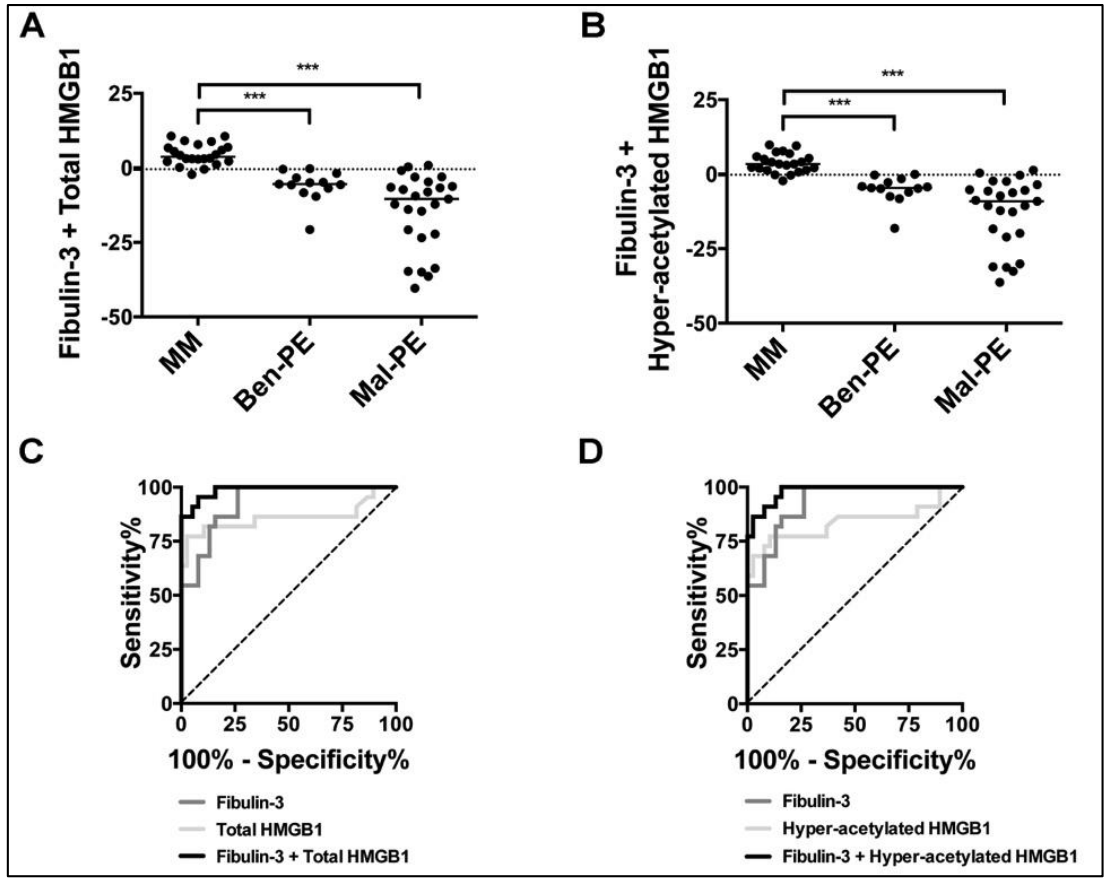
Provider	Background Materials
NYU	Plasma from: • 120 mesotheliomas, • 50 asbestos-exposed individuals, and • 30 individuals with pleural effusions not mesothelioma.
COLLABORATOR	Plasma from: • 80 patients with mesothelioma (including 16 duplicate samples with 5-10 freeze/thaw cycles), and • 75 asbestos-exposed patients

- CORE funds for Specificity of Fibulin 3 in Patients with Pleural Effusions
  - Thoracic Surgery Oncology Group: American Association for Thoracic Surgery
    - 23 member institutions
      - MPM Centers: Baylor, Duke, MDA, Pittsburgh, Toronto, MSKCC
      - Prospective collection of blood and pleural effusion for patients presenting with pleural effusion
      - Hopefully conducted through DMCC
- Humanized Fibulin 3 antibody
  - Three lots of antibodies being tested for dilutions and sensitivity/specificity

Aim 2: Investigate HMGB1 and its Isoforms in the Diagnosis of the MPM Pleural Effusion

Total and hyper-acetylated HMGB1 are biomarkers for asbestos exposure and MM





Harvey I. Pass (PI)
Haining Yang (co-PI)

- The major goal of this project is to evaluate whether by measuring total HMGB1 and its isoforms, we can accurately differentiate pleural effusions that are MPM from non-MPM effusions.

- Develop clinically applicable MS based quantitative assay for:
  - Total HMGB1
  - Acetylated HMGB1
  - Redox HMGB1
- *In collaboration with Dr. Justyna Fert-Bober, Weston Spivia and Dr. Jennifer Van Eyk at Cedars-Sinai Medical Center.

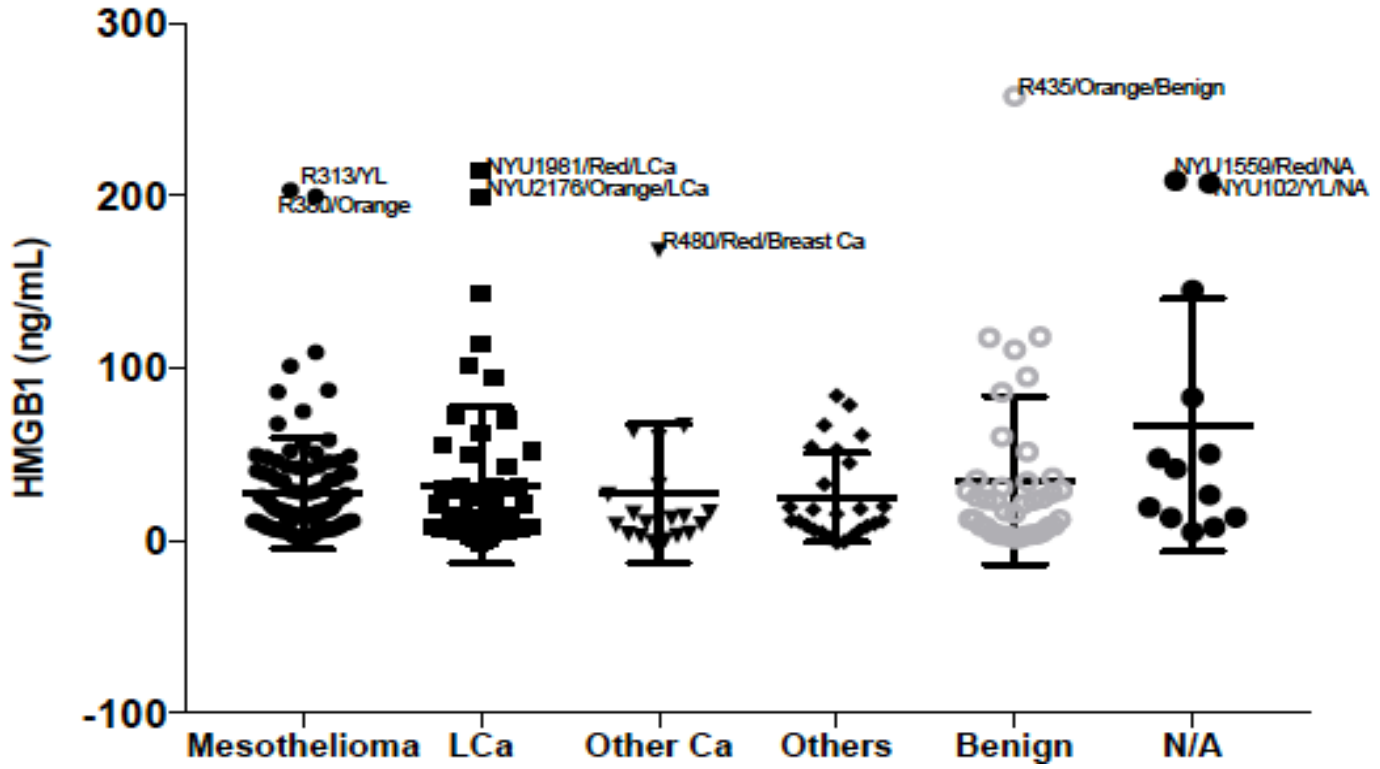
Harvey I. Pass (PI)
Haining Yang (co-PI)

HMGB1 Mass Spec measurement in pleural effusion and serum samples

Total HMGB1 measured by the mass spec assay for the NYU pleural effusion and serum samples gives the overall concentration of HMGB1 with these samples. The amount of fully acetylated, as well as unacetylated, HMGB1 relative to standard gives the proportion of post-translationally modified HMGB1 in serum.

Study ID	ELISA HMGB1 (ng/mL)	PE MS results of total HMGB1	Serum (ng/ml) MS results	Total HMGB1 Relative Quant by GluC - DMA	Unacetyl HMGB1 Relative Quant (Serum)	Acetylated HMGB1 Relative Quant (Serum)
NYU1	118.36	16.62	689.38	1.1916	64.8084	Below LOD
NYU1295	49.69	15.55	56.95	0.12885	0.1554	Below LOD
NYU1306	51.68	17.65	29.18	0.0651	0.08535	Below LOD
NYU1318	1.86	-2.85	64.7	0.1735	0.21945	Below LOD
NYU1336	4.73	-1.66	31.99	0.0729	0.0992	Below LOD
NYU1338	52.48	10.52	36.06	0.1318	0.2094	Below LOD
NYU1353	22.88	1.01	95.23	0.06585	0.1061	Below LOD
NYU1373	5.44	-1.8	58.22	0.11955	0.15015	Below LOD
NYU1621	5.13	-0.39	132.63	0.432	0.38535	Below LOD
NYU1660	117.96	3.5	44.6	0.0967	0.08965	Below LOD
NYU1661	15.71	5.7	53.15	0.1132	0.1562	Below LOD
NYU181	18.52	13.66	145.35	0.2772	0.30785	Below LOD
NYU1937	26.89	12.21	17.29	0.0118	0.02415	Below LOD
NYU207	86.11	24.11	48.66	0.1275	0.194	Below LOD
NYU2190		-2.25	25.6	0.0789	0.0952	Below LOD
NYU250	8.78	23.82	111.82	0.18655	0.2493	Below LOD
NYU540	16.5	-0.87	70.05			Below LOD
NYU754 A	203.3	75.26	139.05	0.2525	0.3103	Below LOD
NYU754 B	60.1	21.73	35.51	0.0818	0.1214	Below LOD
NYU826	38.87	20.65	138.2	0.2599	0.3296	Below LOD
NYU851	4.66	-2.63	53.41	0.1338	0.19775	Below LOD
NYU872	6.89	3.29	330.66	0.5827	0.59475	Below LOD
NYU93	52.11	24.81	108.12	0.23295	0.4012	Below LOD
NYU937	6.15	0.58	62.22	0.1478	0.19035	Below LOD
R489	17.41	6.54	69.1	0.1853	0.22295	

HMGB1 ELISA assays on 263 pleural effusion samples

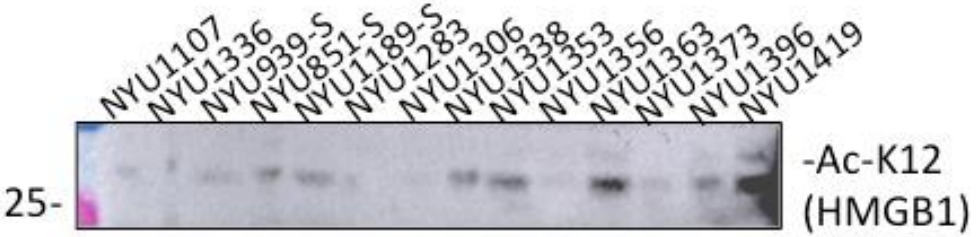


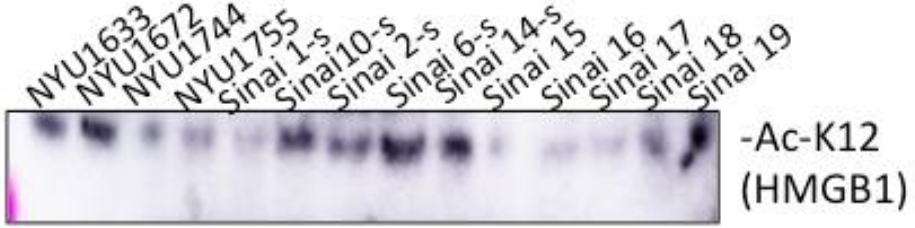
Total HMGB1 levels measured by ELISA assay using patients' pleural effusions samples obtained from patients with different disease status.

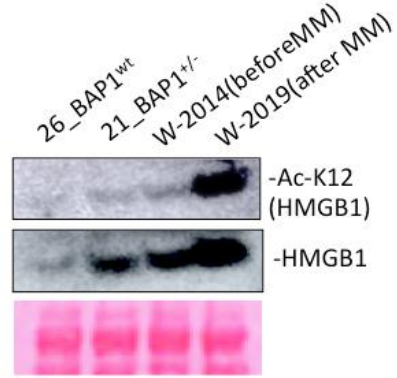
(Note: We labeled the color of the samples with relatively high HMGB1 levels, as it has been reported that hemolyzed red blood cells could release HMGB1 into the fluid, which might contribute to the relatively high levels of HMGB1 measured in those samples.

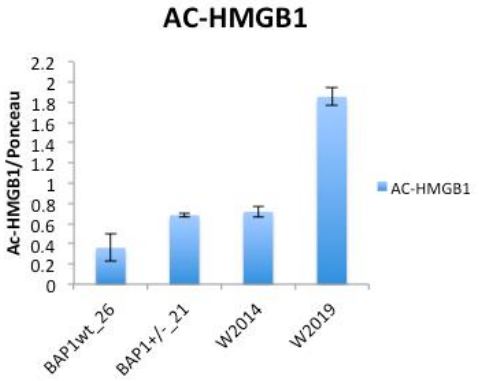
New data developed recently

1. We are able to detect acetylated HMGB1 by Western blot, and we are setting up the ELISA assay

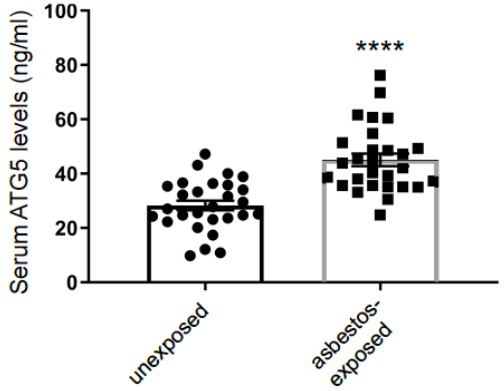


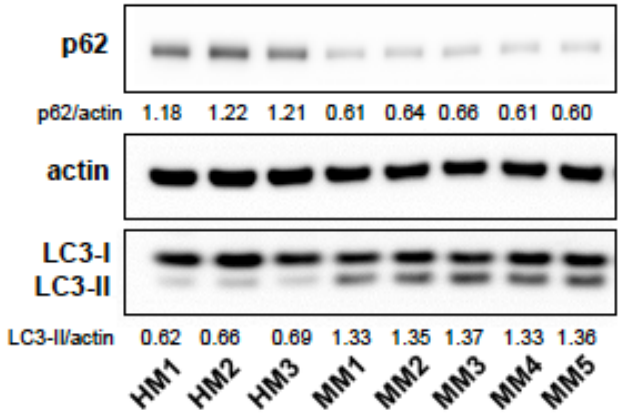


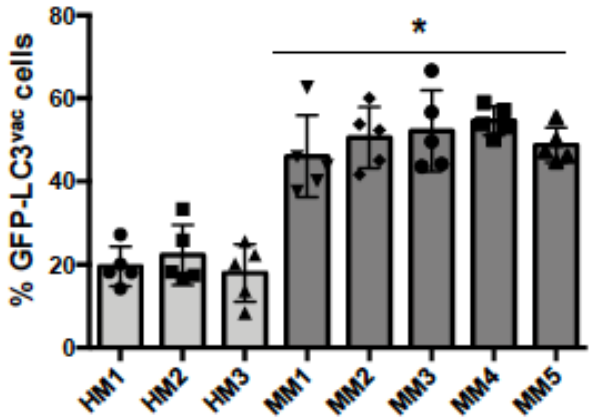




2. We found that autophagy levels are increased in asbestos exposed individuals and MPM patients, which can be the new marker.







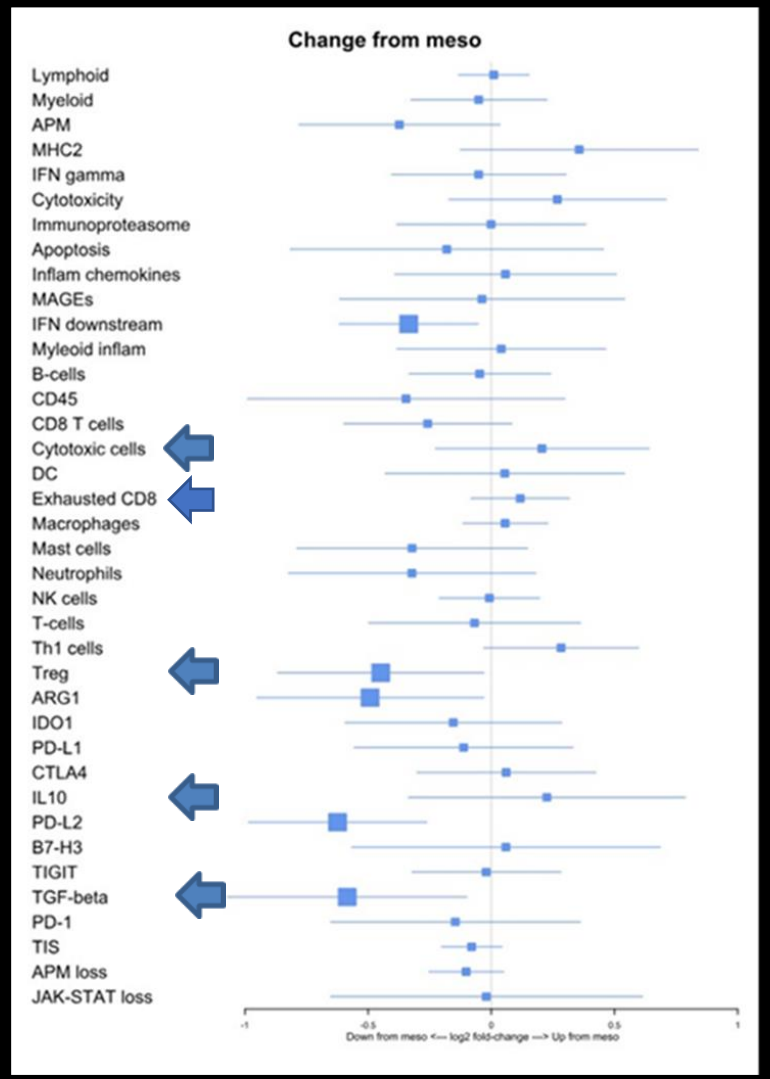
Aim 3: To determine whether buffy coat immuno-oncologic RNA expression can define asbestos exposure and diagnose MPM

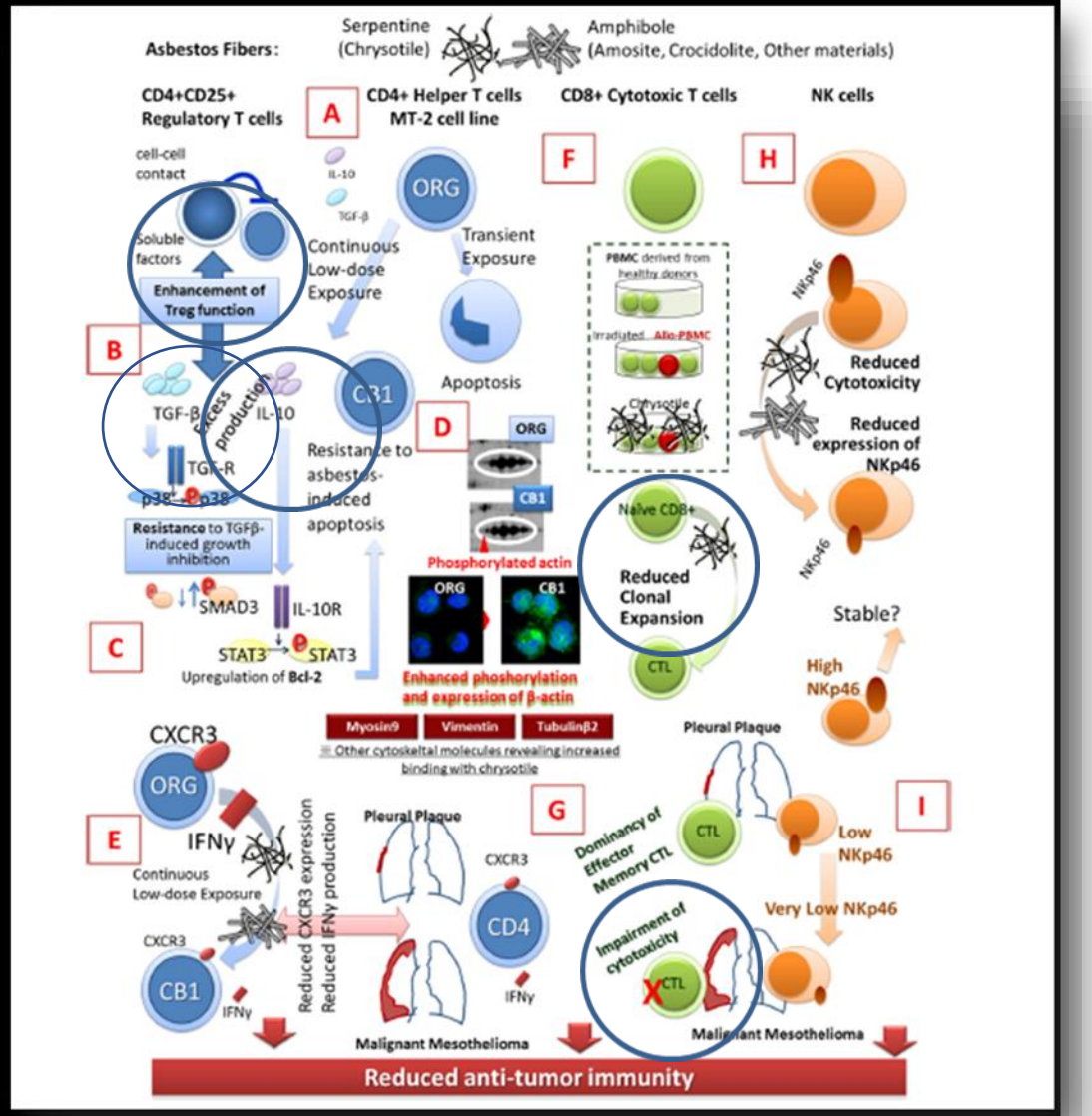
- **Subaim 3a:** Further refine and validate Nanostring Immuno-oncology profiles in the diagnosis of asbestos exposure and MPM
- **Subaim 3b:** Blindly validate locked in Nanostring Immuno-oncology profiles for healthy, non-AE vs AE, AE vs MPM, and MPM vs non-MPM using buffy coat from the Princess Margaret Cancer Center

Buffy Coat Immunotranscriptomics: Mesothelioma

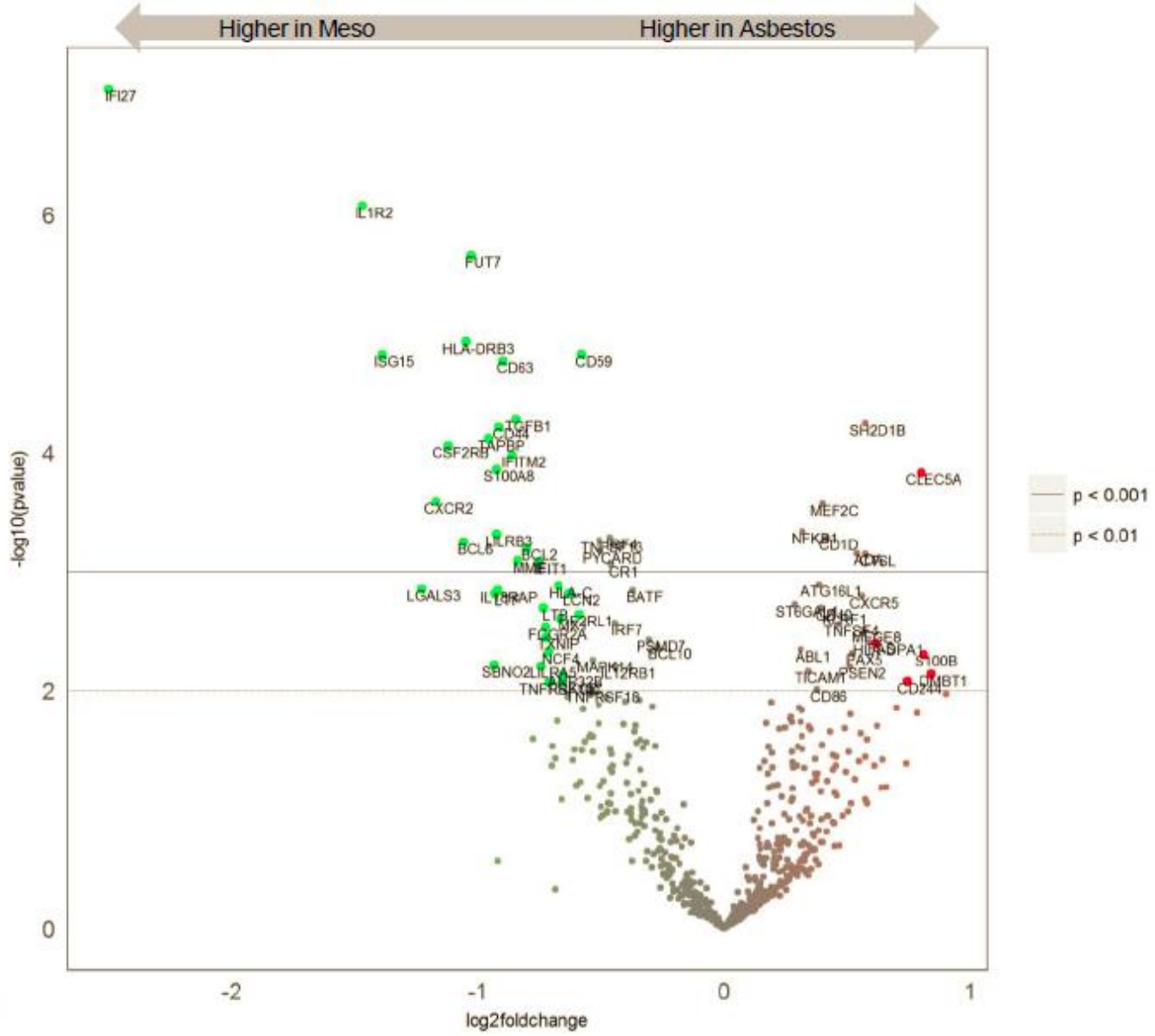
- Patient samples
  - 40 mesothelioma patients (NYU#)
  - 44 asbestos exposure patients (SINAI#)
- Gene expression panel
  - NanoString PanCancer Immune Profiling panel V1.1 (730 IO targets + 40 HK references)
- Analysis objectives
  - Perform data QC and normalization
  - Perform differential expression (DE) analysis
  - Perform gene set analysis (GSA)
  - Perform immune cell type profiling
  - Identify a gene expression signature relating to diagnosis

Circulating microenvironment: MPM vs Asbestos Exp



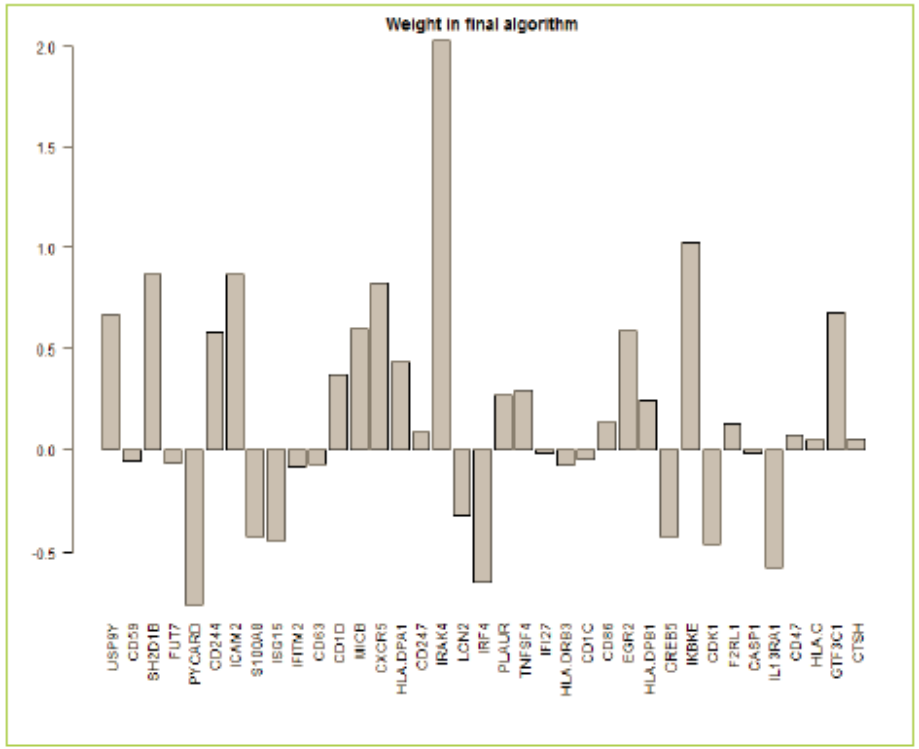


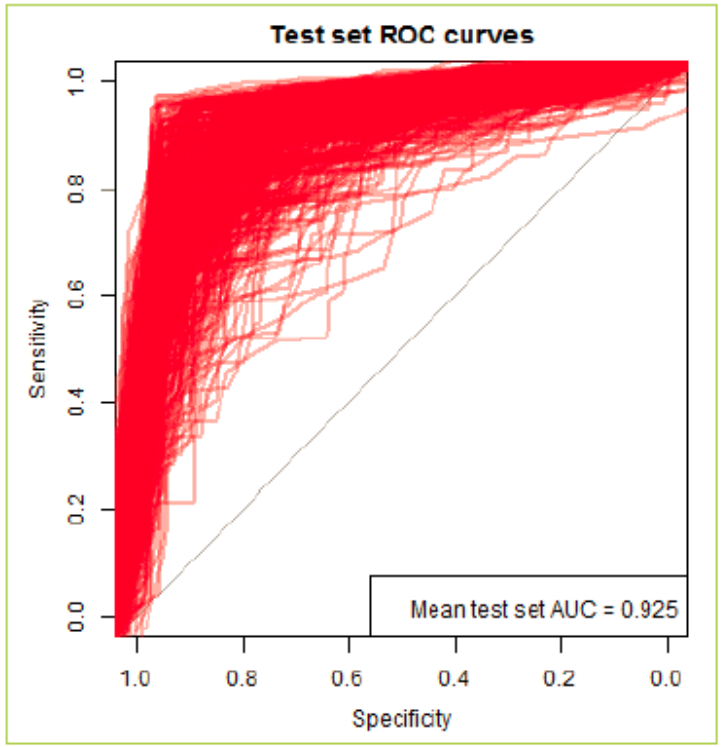
Circulating microenvironment: MPM vs Asbestos Exposed



	Log2 fold change	P-value	Gene sets
IFI27-mRNA	-2.5	4.86E-07	Chemokines
MEF2C-mRNA	0.486	8.64E-07	
IL1R2-mRNA	-1.45	3.70E-06	Cytokines
FUT7-mRNA	-1.1	4.52E-06	Leukocyte Functions
CD59-mRNA	-0.616	2.12E-05	
CD1D-mRNA	0.443	2.37E-05	B-Cell Functions, Cell Functions, T-Cell Functions
SH2D1B-mRNA	0.604	2.75E-05	Leukocyte Functions
ISG15-mRNA	-1.32	3.98E-05	
CD63-mRNA	-0.846	5.39E-05	
CLEC5A-mRNA	0.779	6.33E-05	
HLA-DRB3-mRNA	-0.98	7.11E-05	Antigen Processing
CD44-mRNA	-0.872	0.00014	Senescence, Transporter Functions
TAPBP-mRNA	-0.929	0.000144	Antigen Processing
TGFB1-mRNA	-0.775	0.000159	Interleukins, Regulation
PIK3CG-mRNA	0.236	0.000182	
NFKB1-mRNA	0.309	0.000231	
IFITM2-mRNA	-0.855	0.000247	
KLRF1-mRNA	0.531	0.000251	Cell Functions, NK Cell Functions
CSF2RB-mRNA	-1.07	0.000303	Chemokines
HLA-DPA1-mRNA	0.733	0.000355	Antigen Processing

Modeling Differences between MPM and AE BC Immunogenes

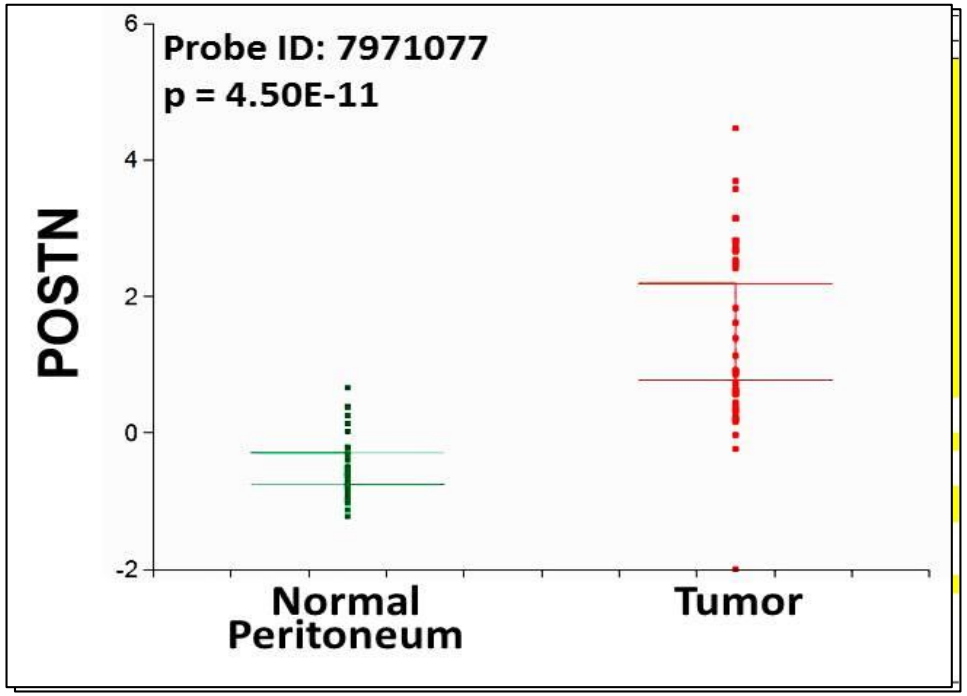


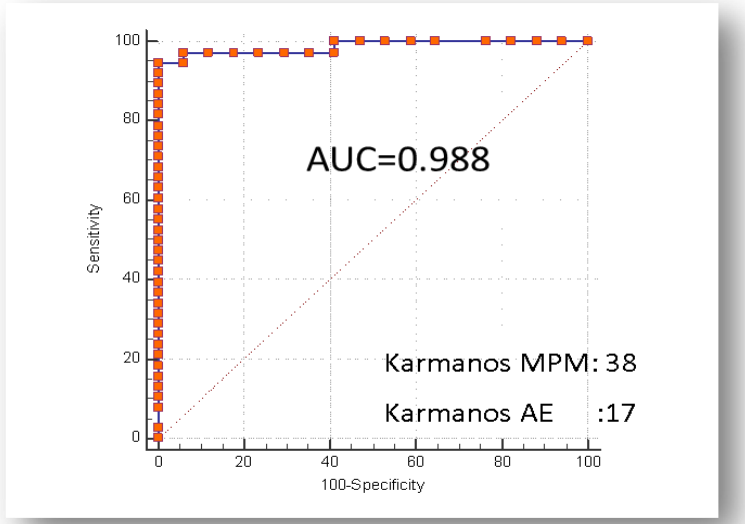


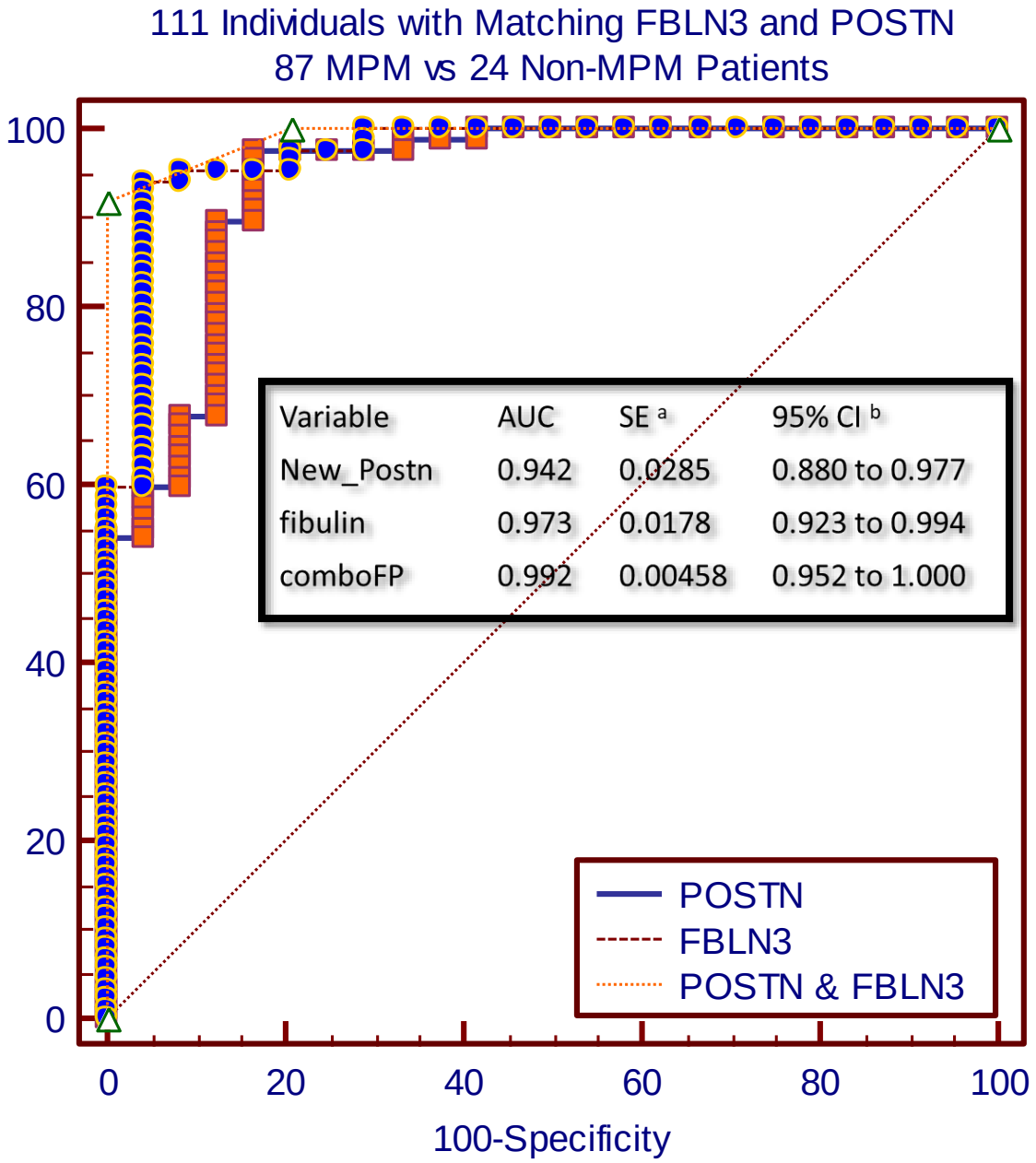
Set-Asides

- Year 1: Wasted on the proposed LPT3 Prognostic Project
- Year 2: Periostin
- Year 3: BC and Lung Cancer

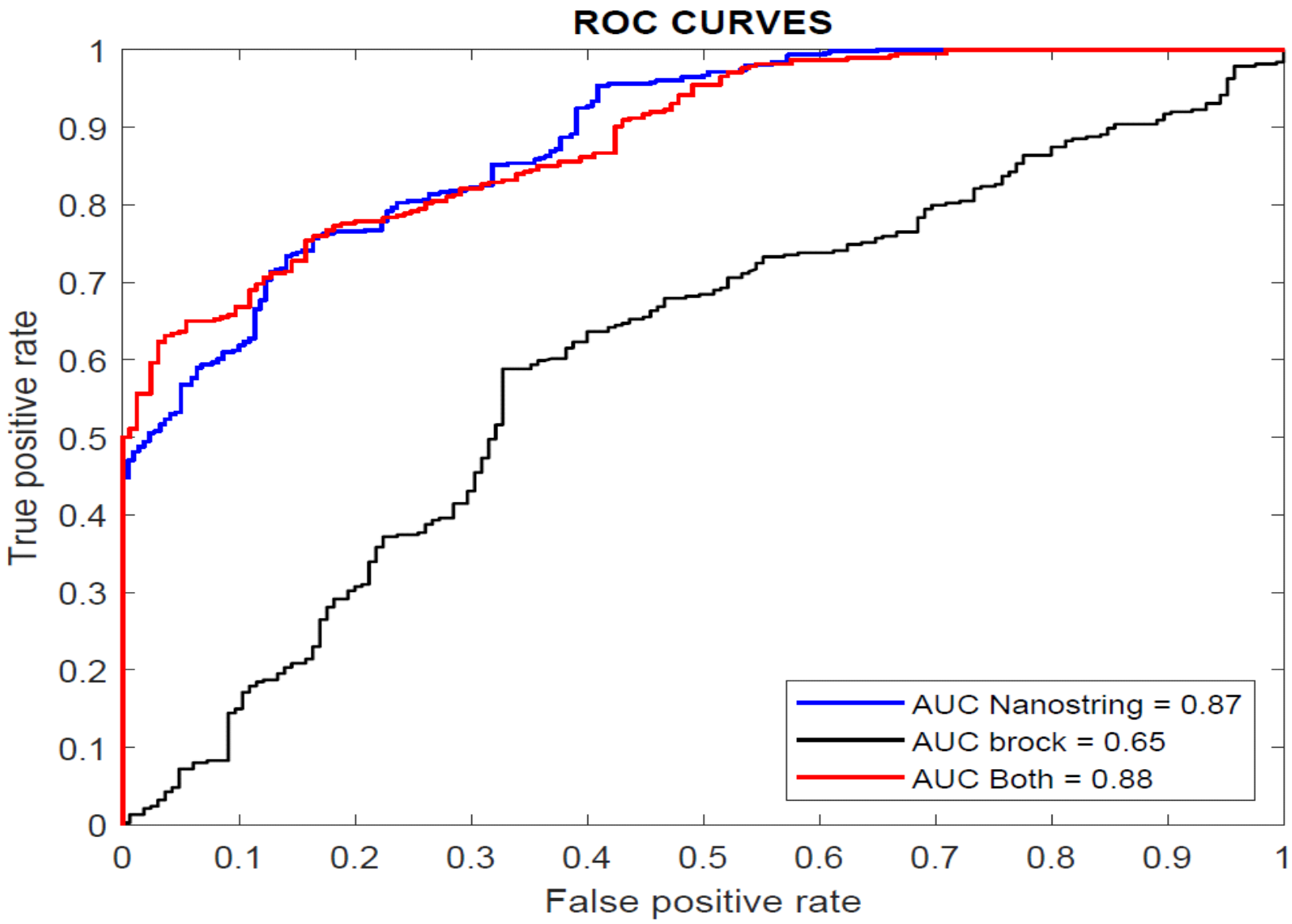
Periostin, son of Fibulin





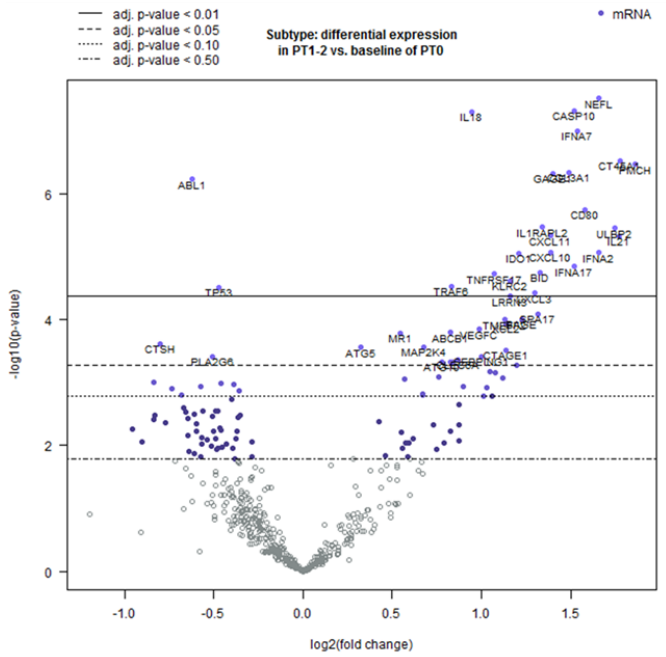


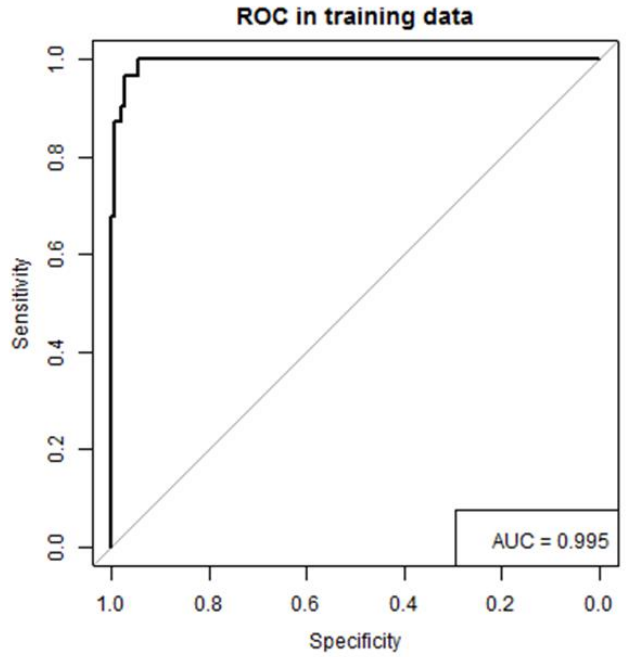
Set Asides: Buffy Coat Immunotranscriptomics for Diagnosis Early Stage Adenocarcinoma: 207 Stage I Adenocarcinomas vs 100 Benign Nodules

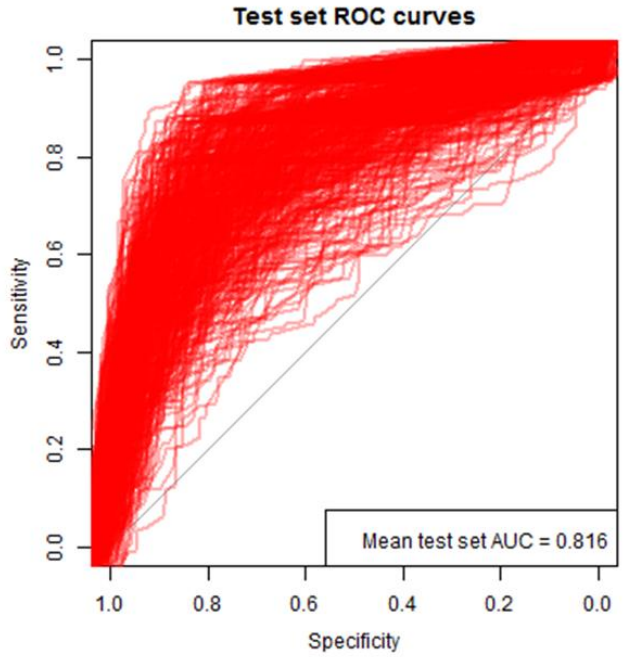


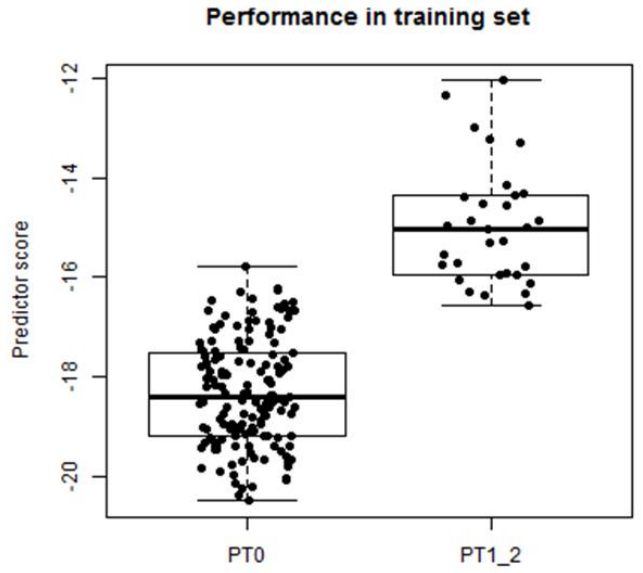
	No Progression n=148		Progression n=31			
	Mean	SD	Mean	SD	95% CI	P [a]
Age	68.5068	9.5707	71.9032	8.0844	-0.2425 to 7.0354	0.0672
Gender	109F/39M		17F/14M			
Pack_per_year	26.2588	30.9382	35.4355	29.3345	-2.7794 to 21.1328	0.1316
Predominant	MP/Solid 25		MP/Solid 12		0.1342 to 0.6823	0.0037
Size_cm	1.7568	0.7593	2.1452	0.9081	0.08184 to 0.6950	0.0133
LVI	12		13		0.2120 to 0.4646	<0.0001
Pleural_invasion	15		8		0.02761 to 0.2858	0.0176

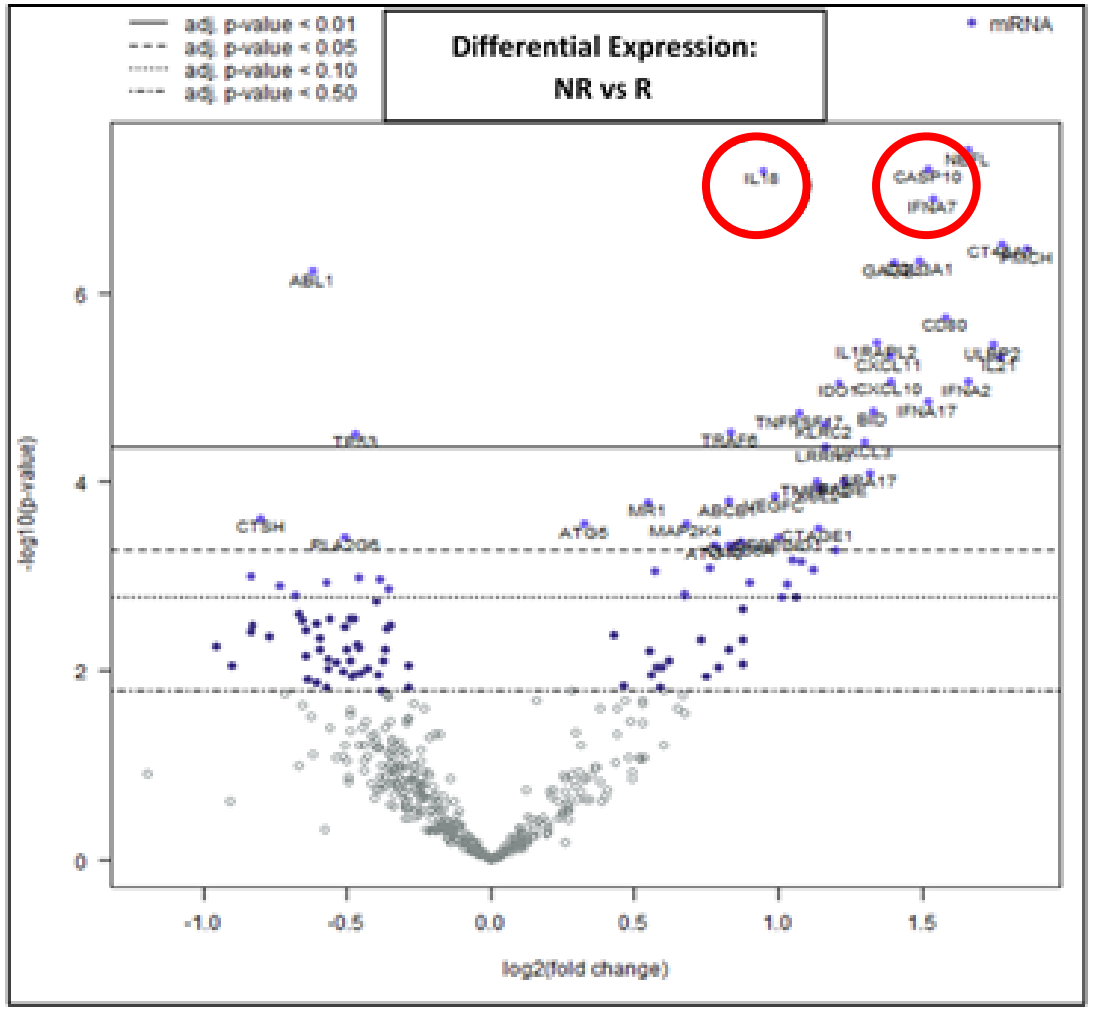
148 PT(0) vs. 31 PT(1-2)





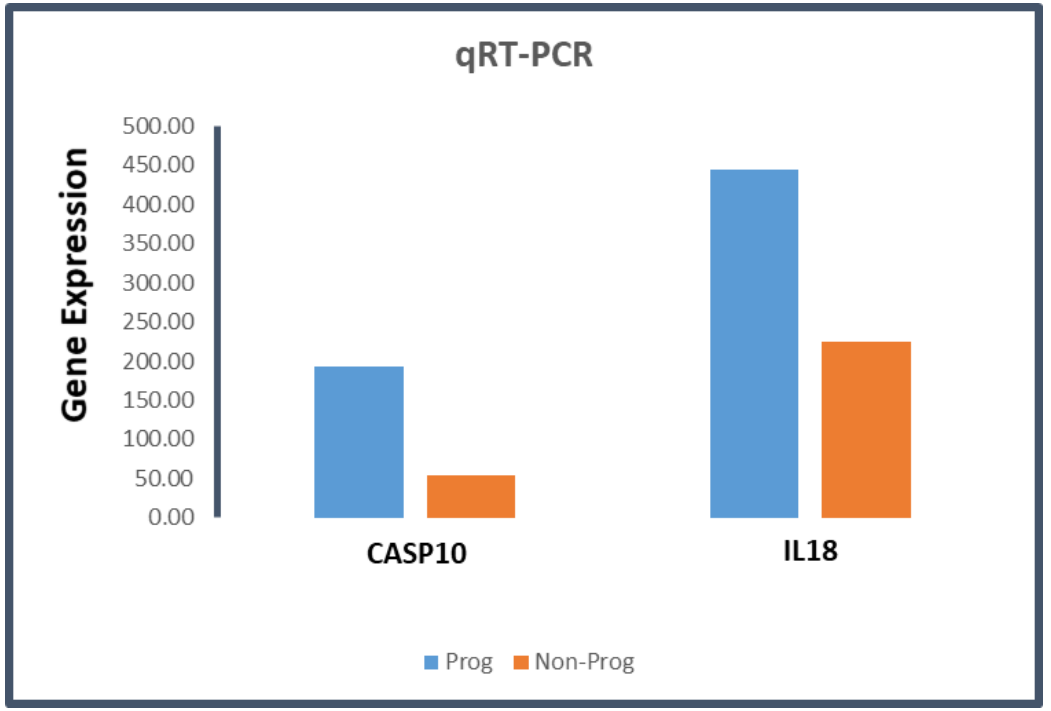


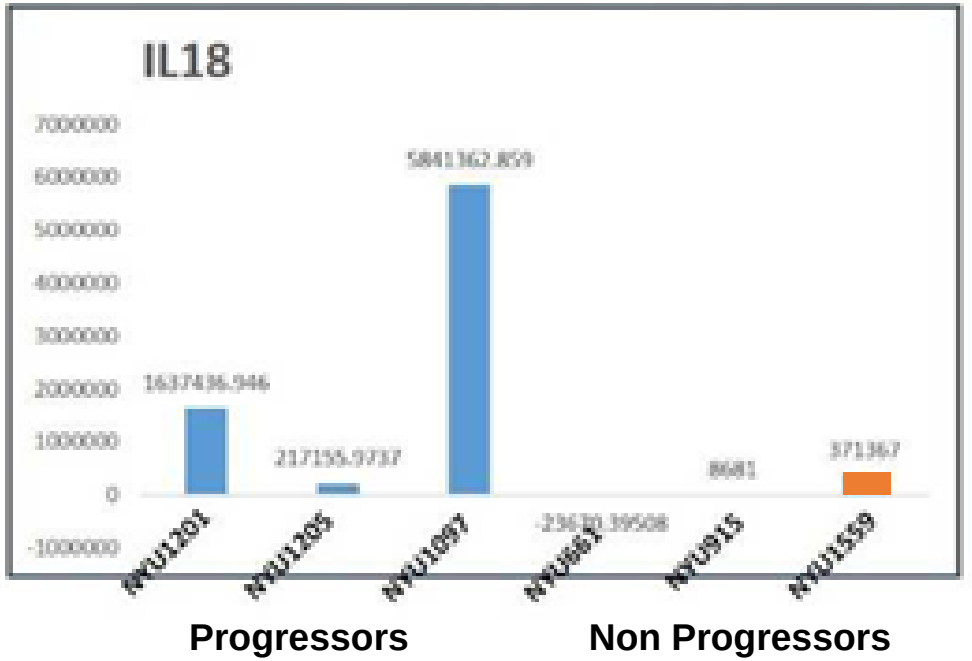


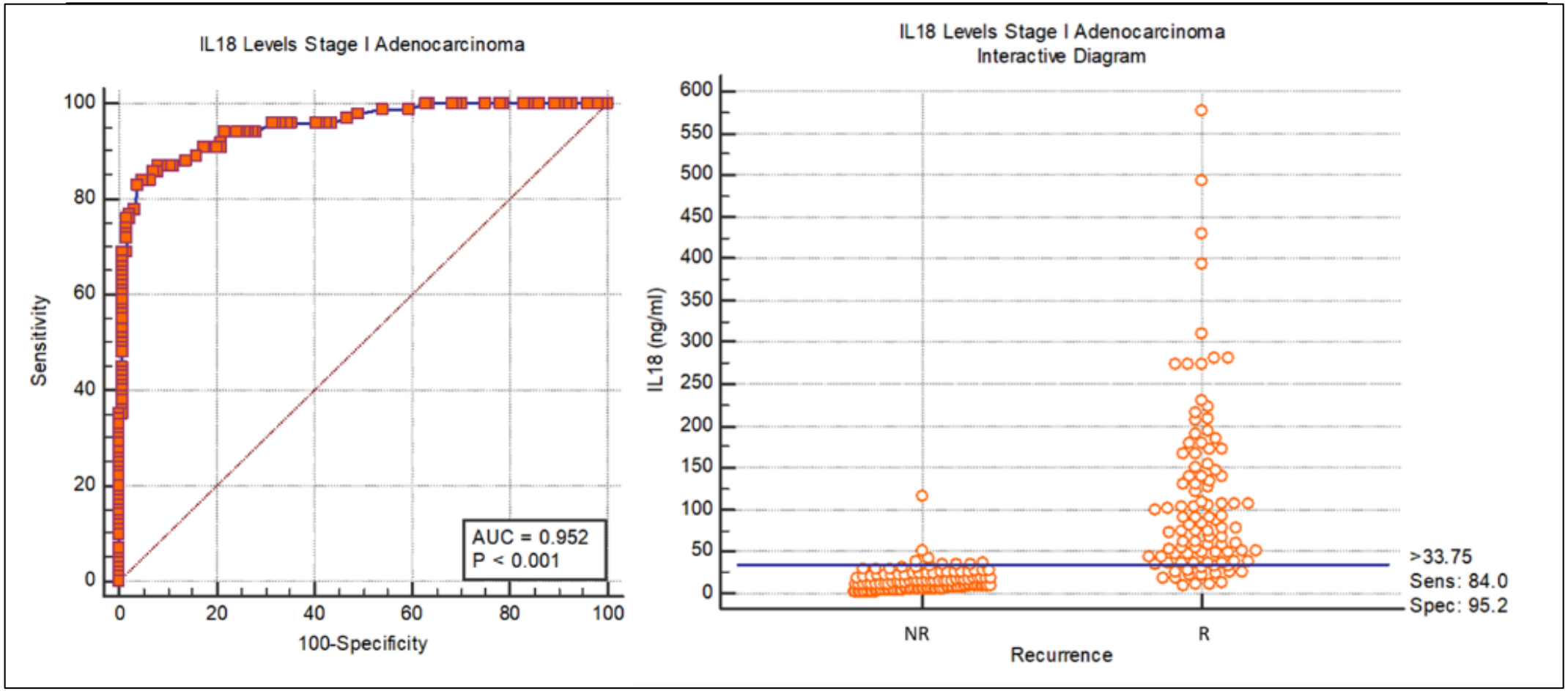


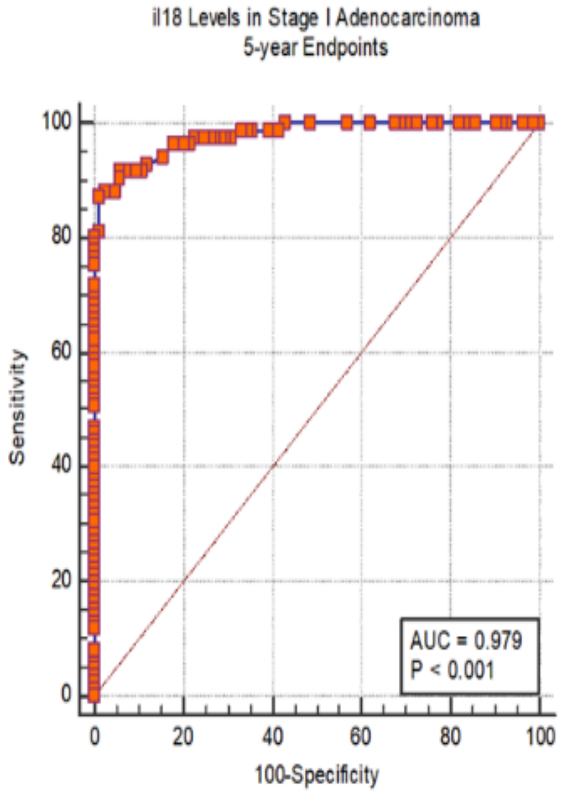
	Log2 FC	SE (log2)	Lower confidence limit (log2)	Upper confidence limit (log2)	Linear FC	Lower confidence limit (linear)	Upper confidence limit (linear)	p
NEFL-mRNA	1.67	0.292	1.1	2.25	3.19	2.14	4.74	7.60E-05
IL18-mRNA	0.948	0.168	0.619	1.28	1.93	1.54	2.42	7.60E-05
CASP10-mRNA	1.53	0.271	0.999	2.06	2.89	2	4.17	7.60E-05
IFNA7-mRNA	1.54	0.276	0.998	2.08	2.9	2	4.22	7.94E-05
GAGE1-mRNA	1.41	0.261	0.894	1.92	2.65	1.86	3.78	0.000135
CT45A1-mRNA	1.78	0.333	1.13	2.43	3.44	2.18	5.4	0.000135
PMCH-mRNA	1.87	0.35	1.18	2.55	3.65	2.27	5.87	0.000135
COL3A1-mRNA	1.5	0.281	0.945	2.05	2.82	1.93	4.13	0.000135
ABL1-mRNA	-0.677	0.137	-0.947	-0.408	0.625	0.519	0.754	0.000754

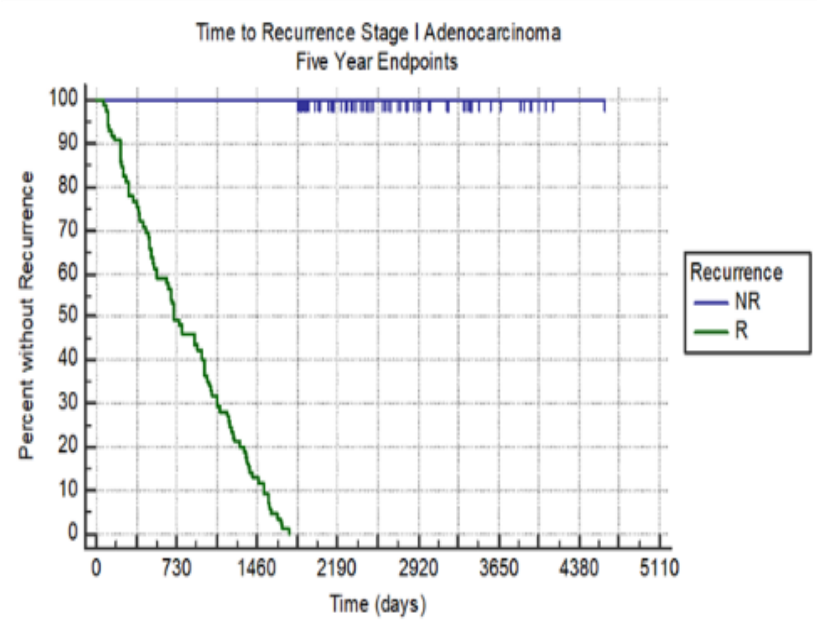
FC, fold change



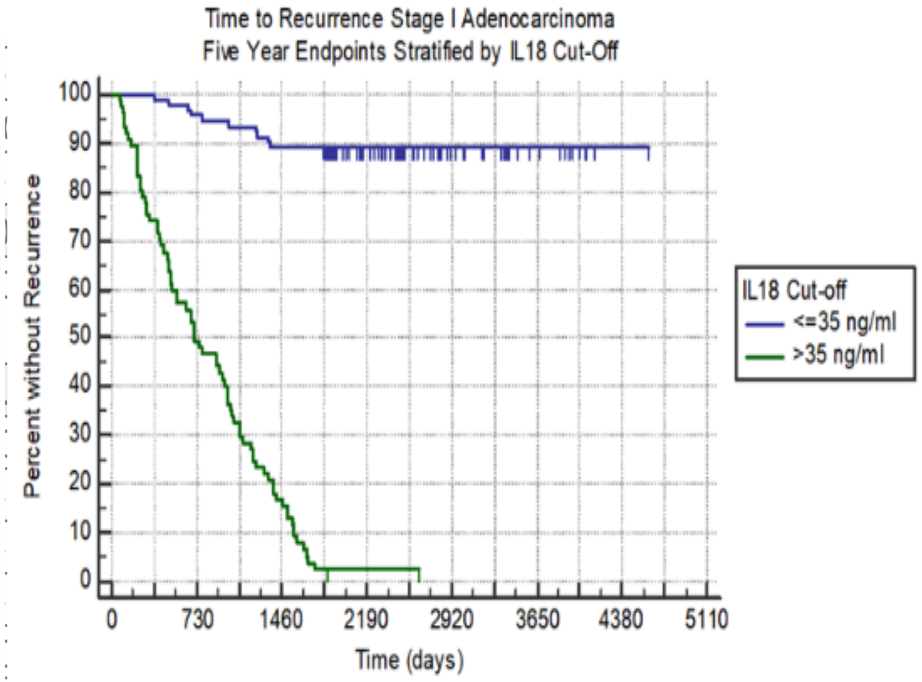



IL18 Levels Stage I Adenocarcinoma
Sensitivity
100-Specificity
AUC = 0.952
P < 0.001
IL18 Levels Stage I Adenocarcinoma
Interactive Diagram
IL18 (ng/ml)
Recurrence
NR
R
>33.75
Sens: 84.0
Spec: 95.2

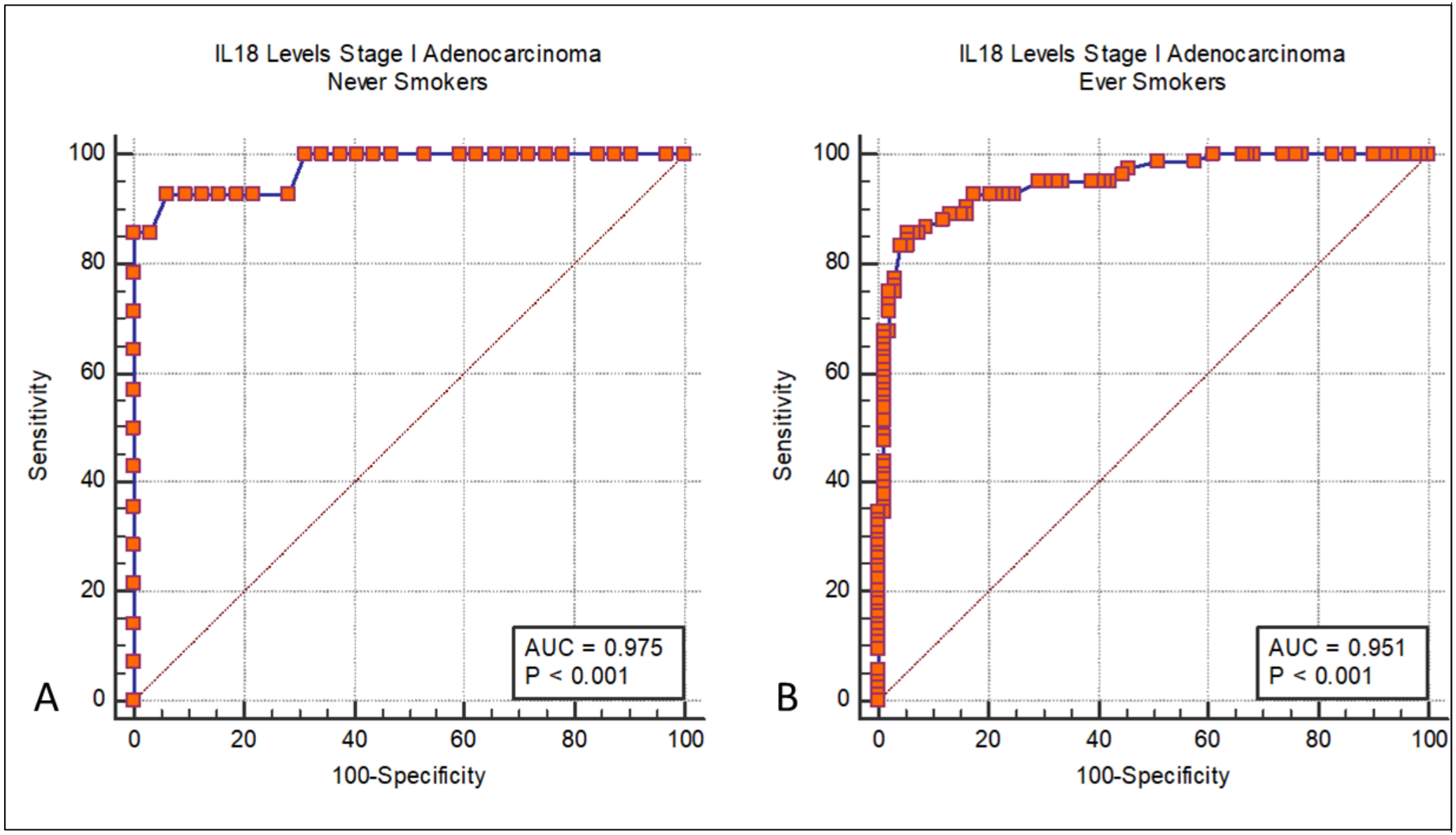


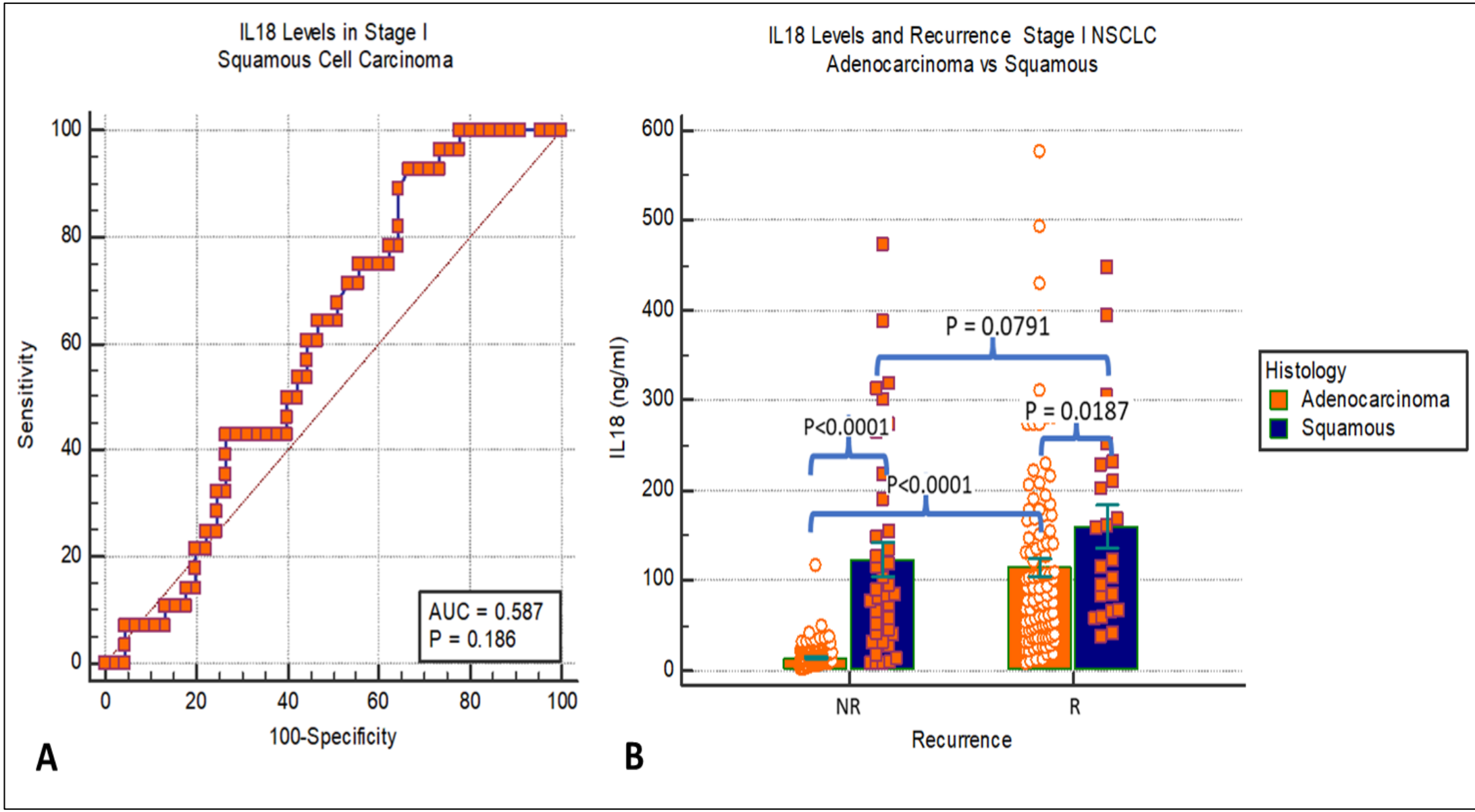


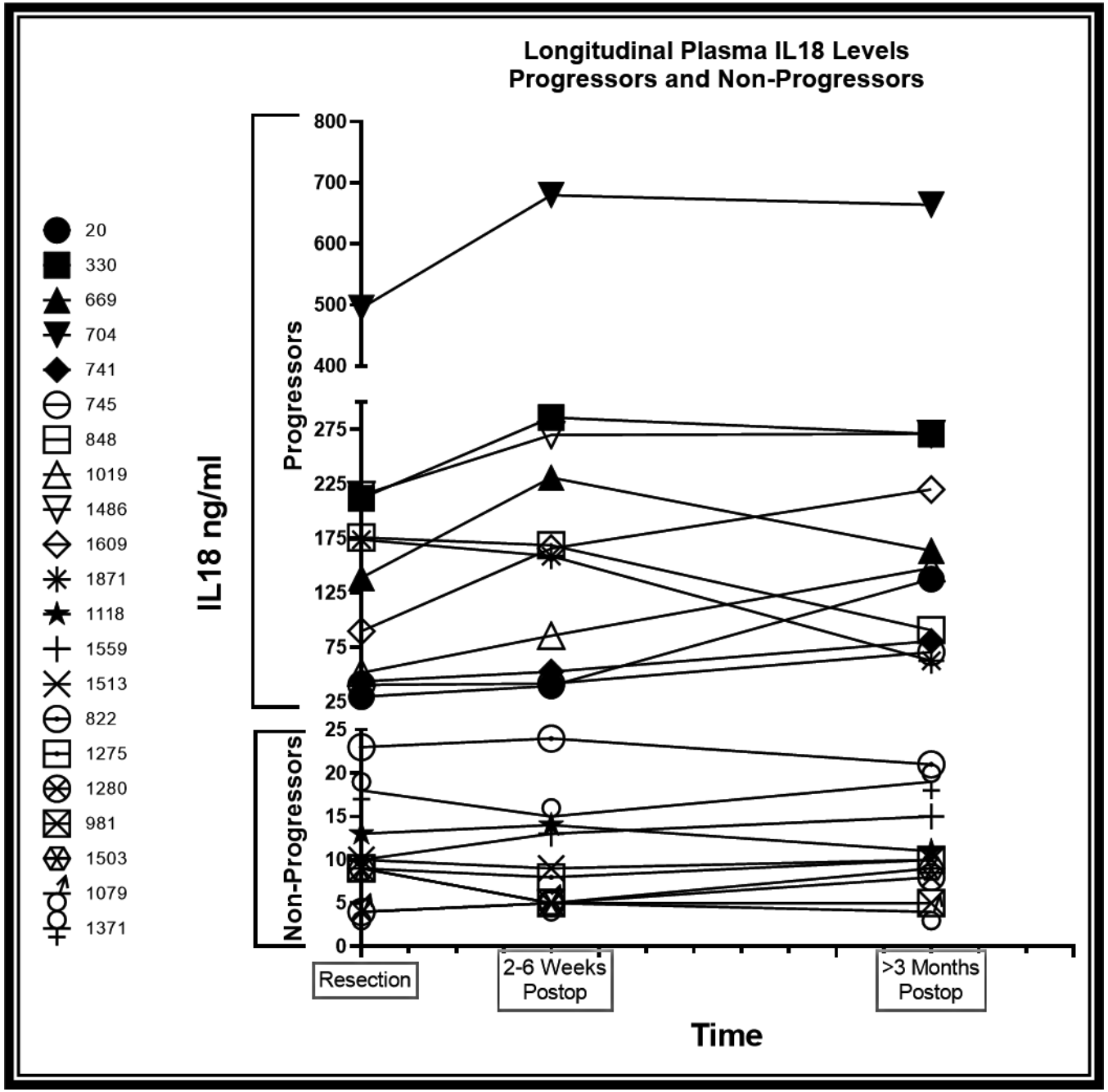
Number at risk
Group: NR
84 84 84 84 84 84 57 40 24 18 10 4 1 0
Group: R
85 65 42 27 11 0 0 0 0 0 0 0 0 0



Number at risk
Group: <=35 ng/ml
92 92 88 86 82 82 56 39 24 18 10 4 1 0
Group: >35 ng/ml
77 57 38 25 13 2 1 1 0 0 0 0 0 0


IL18 Levels Stage I Adenocarcinoma
Never Smokers
Sensitivity
100-Specificity
0
20
40
60
80
100
AUC = 0.975
P < 0.001
A
IL18 Levels Stage I Adenocarcinoma
Ever Smokers
Sensitivity
100-Specificity
AUC = 0.951
P < 0.001
B


IL18 Levels in Stage I
Squamous Cell Carcinoma
Sensitivity
100-Specificity
AUC = 0.587
P = 0.186
A
IL18 Levels and Recurrence Stage I NSCLC
Adenocarcinoma vs Squamous
IL18 (ng/ml)
P = 0.0791
P = 0.0187
P<0.0001
P<0.0001
NR
R
Recurrence
Histology
Adenocarcinoma
Squamous
B


Longitudinal Plasma IL18 Levels
Progressors and Non-Progressors
IL18 ng/ml
Progressors
Non-Progressors
800
700
600
500
400
275
225
175
125
75
25
25
20
15
10
5
0
20
330
669
704
741
745
848
1019
1486
1609
1871
1118
1559
1513
822
1275
1280
981
1503
1079
1371
Resection
2-6 Weeks Postop
>3 Months Postop
Time