Mesothelioma - Multidisciplinary Treatment Update

Speaker:

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Mesothelioma, Causes and Prevention

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Disclosures

- FUNDING:
  - University of Hawai‘i Cancer Center
  - P30 CA071789 to MC
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- PATENTS:
  - Awarded and/or pending patent applications on HMGB1 and BAP1.
- CONSULTING:
  - Provides expertise and diagnosis at no cost to patients and colleagues and for a fee to lawyers.

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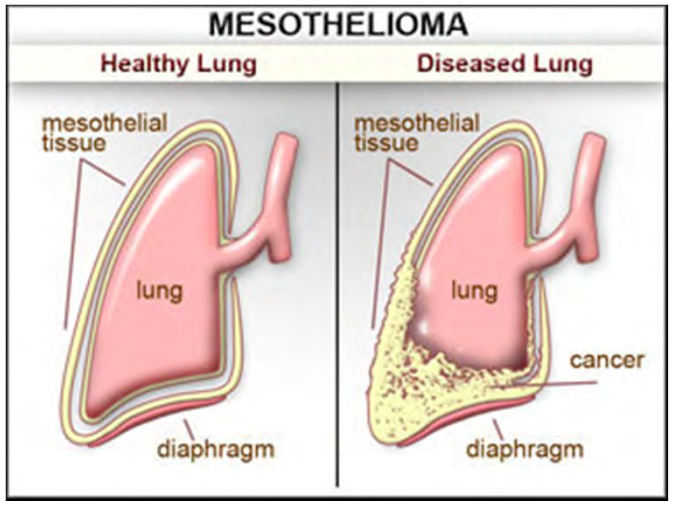
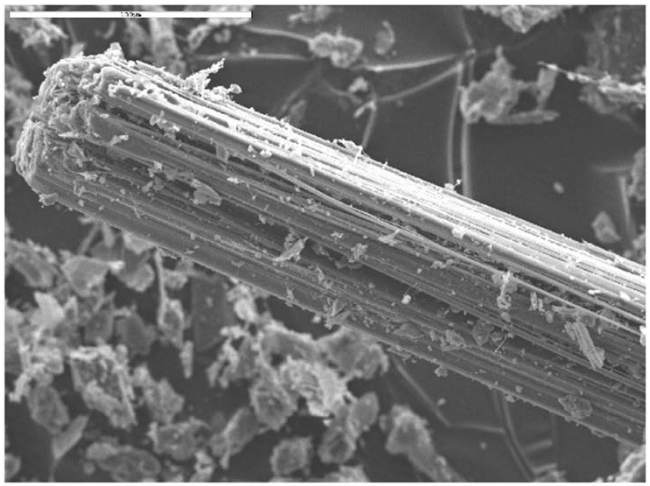
Malignant Mesothelioma (MM)

- MM causes ~3,200 deaths per year in the US, and > 100,00 deaths/year worldwide.
- In the US incidence stable since 2004, in the rest of the world is increasing
- Median survival is ~12 months.
- About 5% diagnosed in Stage I.
- Asbestos and erionite exposure cause most cases of MM.
- >20M people exposed to asbestos in the US





- The latency between initial asbestos exposure and the development of MM is ~30-60 years.
- *About 4.6% of miners who worked in crocidolite asbestos mines for 10+ years developed MM*.
- NGS 2-51 mutations/MM; average 23 (Guo et al., Cancer Res 2015)

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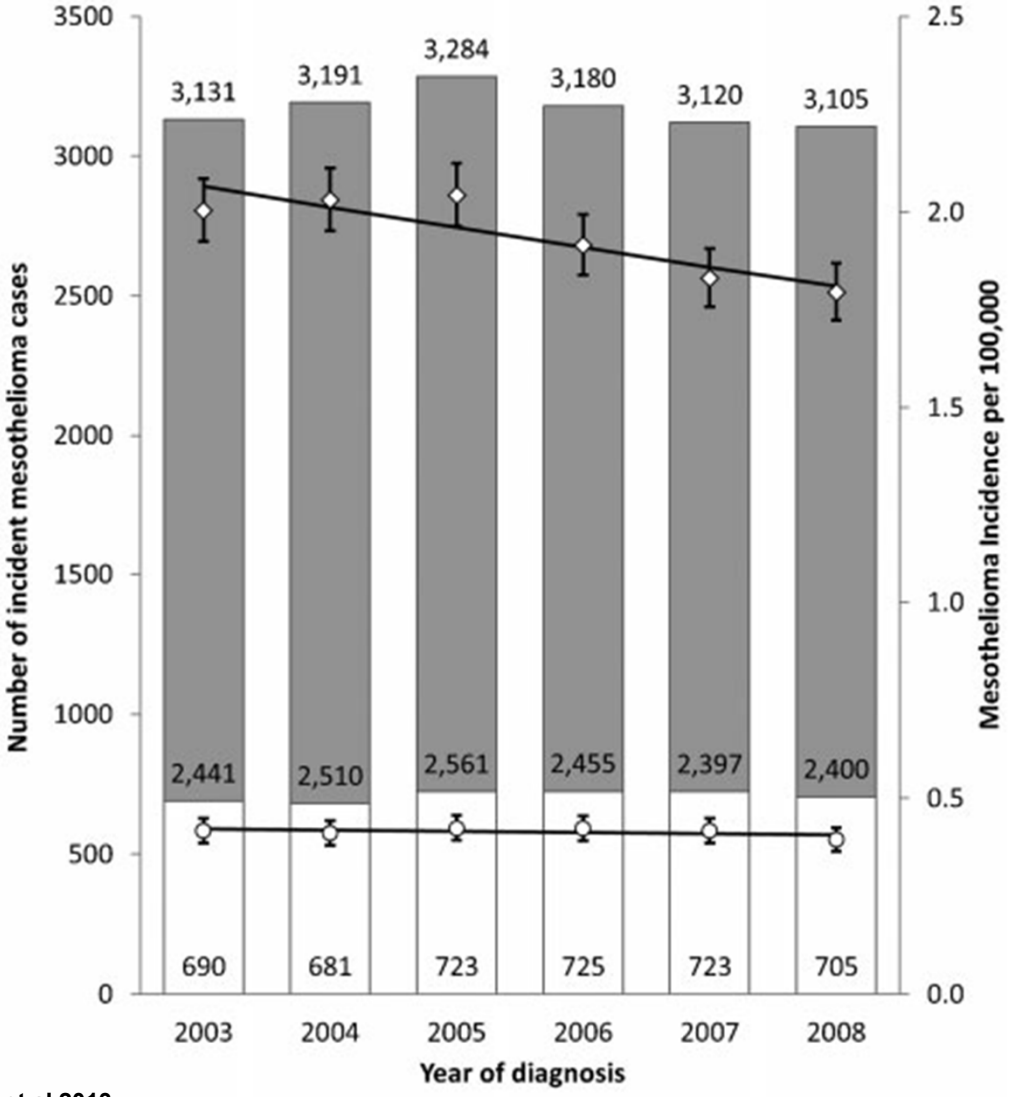
MM cases diagnosed in the US by sex and year, 2003–2008



MM Incidence >75
1999: 42%
2010: 52%

Henley SJ et al 2013

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What is Asbestos?

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The Lancet Oncology, Volume 14, Issue 7, Pages 576 - 578, June 2013
doi:10.1016/S1470-2045(13)70257-2 Cite or Link Using DOI

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Other Articles of Interest

Asbestos is not just asbestos: an unrecognised health hazard

Francine Baumann [a], Jean-Paul Ambrosi [b], Michele Carbone [a]

About 107 000 people die every year from mesothelioma and other asbestos-related diseases. [1] Although all asbestos fibres have been declared carcinogenic, ambiguity exists regarding the definition of asbestos and about which fibres should be regulated. [2] Roughly 400 minerals arise naturally in a fibrous form (table). [3] Of these, only six (actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite) are regulated because, at the time when regulations were introduced, these were the only ...

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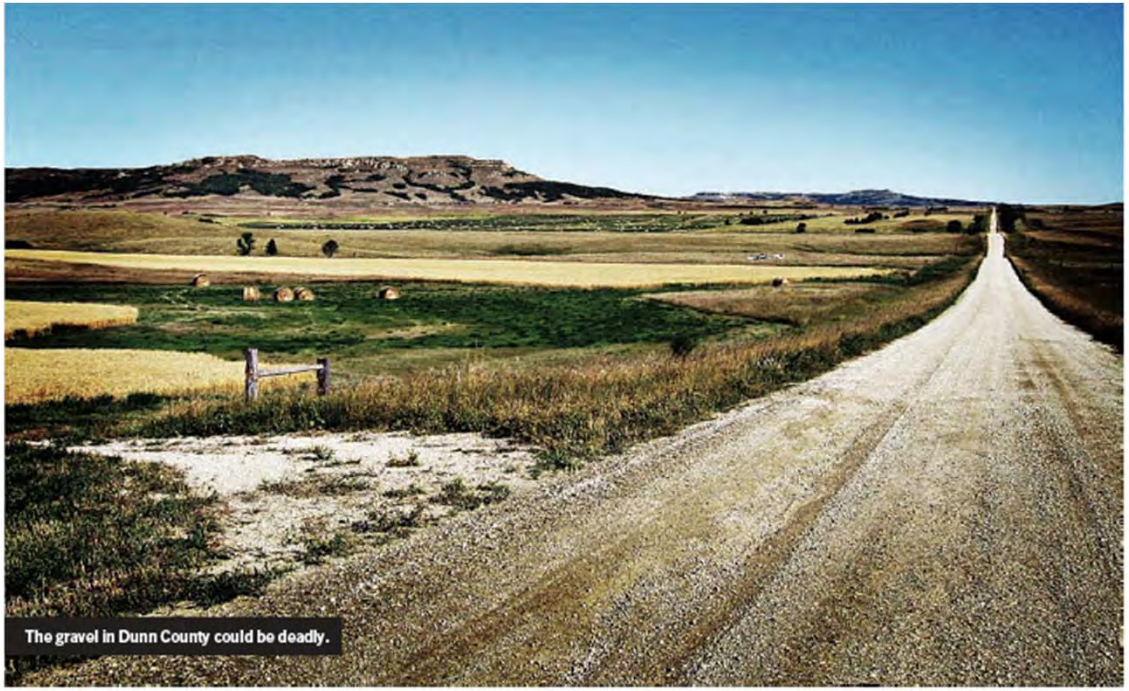
Carbone M et al. Erionite exposure in North Dakota and Turkish villages with mesothelioma. *Proc Natl Acad Sci USA*, 108:13618-23, 2011.


The gravel in Dunn County could be deadly.

Fear in the dust

By Brendan Maher

Cancer epidemics in Turkey could hold the secret to staving off a public health disaster in North Dakota.

University of Hawaii in Honolulu who has worked in both North Dakota and the Turkish villages. "The reason that I find it exciting is that here we have a chance to do something," he says.

Carbone has been visiting Cappadocia since 1996, when he was invited by İzzettin Bariş, a physician who at the time specialized in studying and

M. CARBONE

ORIGINAL ARTICLE

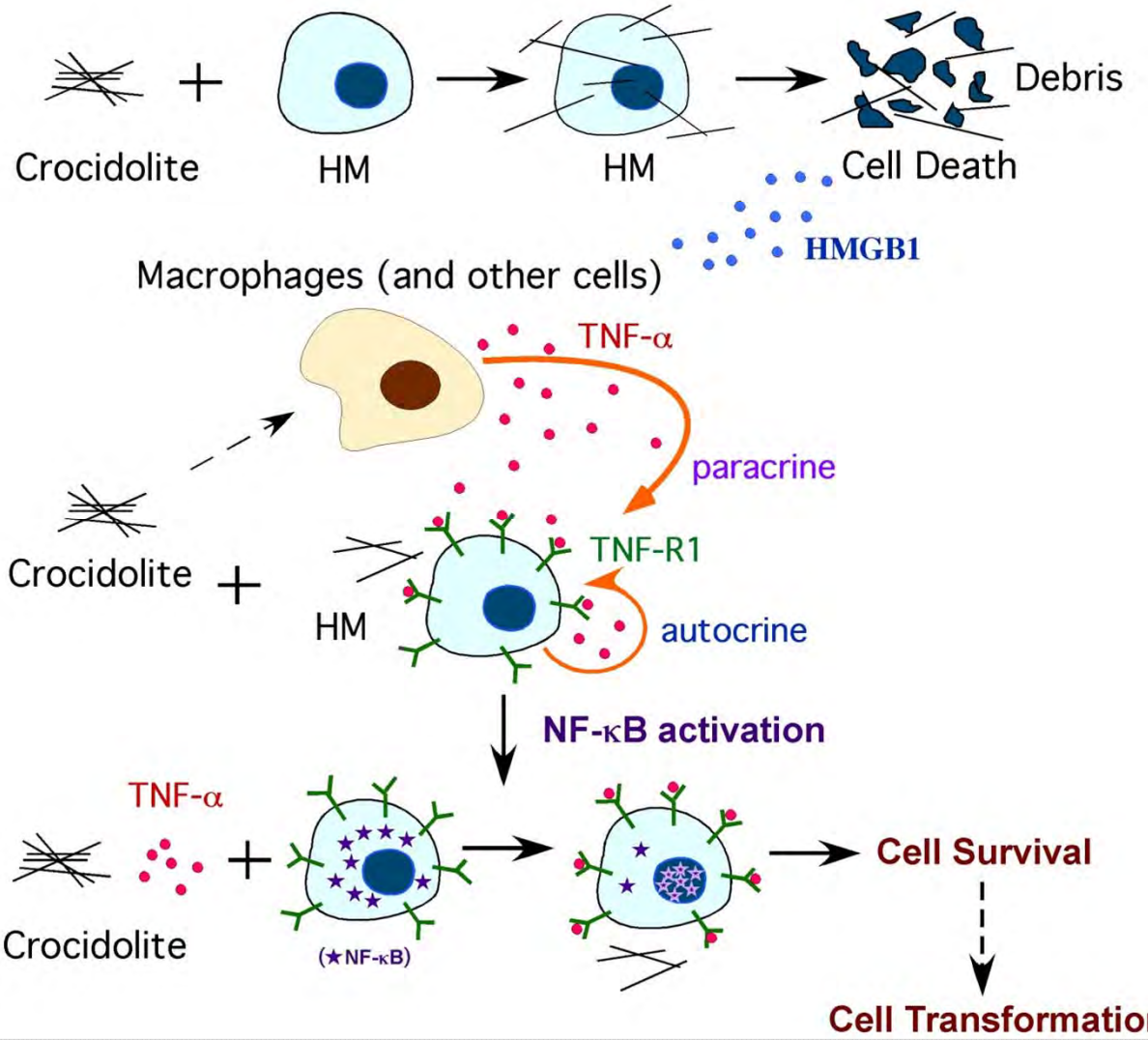
FAST TRACK

The Presence of Asbestos in the Natural Environment is Likely Related to Mesothelioma in Young Individuals and Women from Southern Nevada

Francine Baumann, PhD, Brenda J. Buck, PhD,† Rodney V. Metcalf, PhD,† Brett T. McLaurin, PhD, ‡ Douglas J. Merkler, MSc,§ and Michele Carbone, MD, PhD**

J Thorac Oncol, 10:731-7, **2015**.

Mechanisms of Asbestos Carcinogenesis



Yang H et al PNAS 2006, PNAS 2010, Cancer res 2012, CDD 2015

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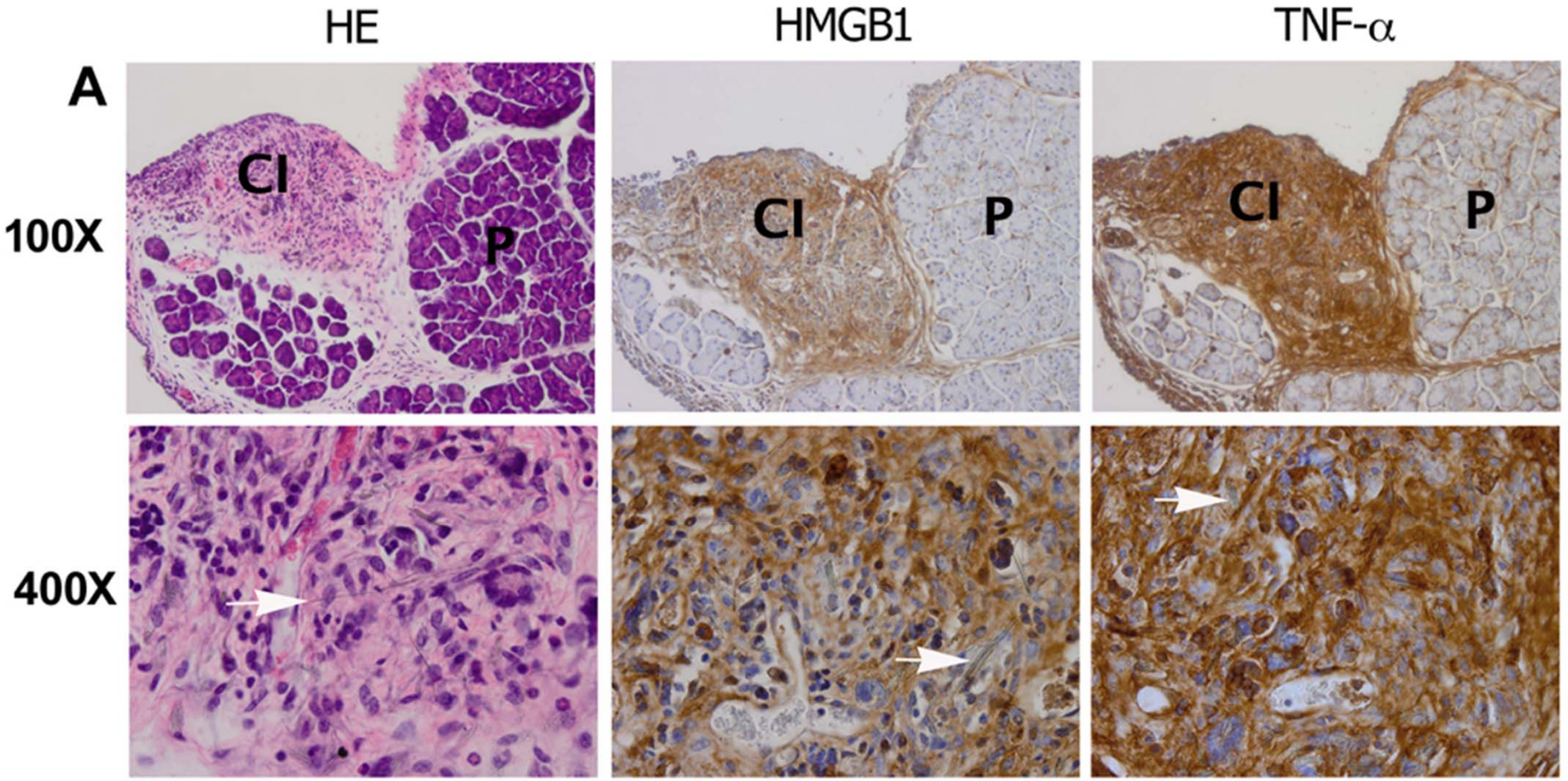
Animal model- mouse injected with asbestos

Strong HMGB1 and TNF-α staining around areas of asbestos deposits



Yang H et al, PNAS 2010

The American Journal of Pathology, Vol. 183, No. 5, November 2013

ELSEVIER

The American Journal of
PATHOLOGY

ajp.amjpathol.org

See related Commentary on page 1378.

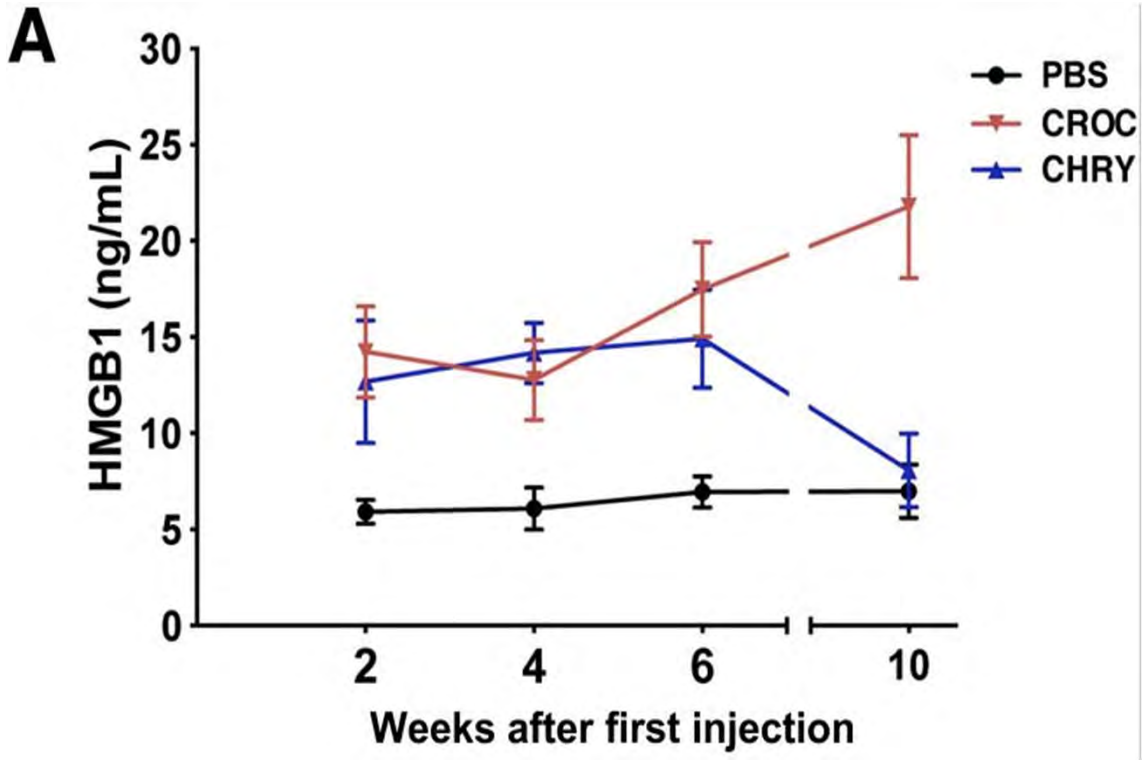
TUMORIGENESIS AND NEOPLASTIC PROGRESSION

Continuous Exposure to Chrysotile Asbestos Can Cause Transformation of Human Mesothelial Cells via HMGB1 and TNF-α Signaling

Fang Qi,[*†] Gordon Okimoto,[*] Sandro Jube,[*] Andrea Napolitano,[*†] Harvey I. Pass,[‡] Rozalia Laczko,[*] Richard M. DeMay,[§] Ghazal Khan,[§] Maarit Tiirikainen,[*] Caterina Rinaudo,[¶] Alessandro Croce,[¶] Haining Yang,[*‖] Giovanni Gaudino,[*] and Michele Carbone[*‖]

Animal model- mouse injected with asbestos

HMGB1 serum levels are long-term persistent after exposure to crocidolite but not to chrysotile



HMGB1 levels in the serum of mice injected with *with a total of 5 mg of crocidolite or chrysotile in a high-dose, short-term protocol with two weekly injections of 2.5 mg each.* ***Qi et al Am j Pathol 2013****.*

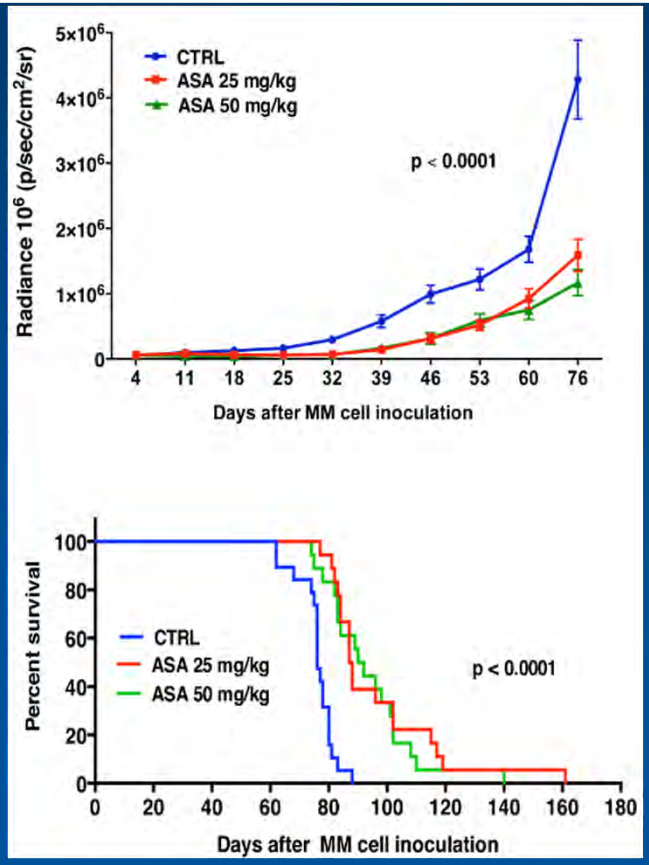
OPEN

Citation: Cell Death and Disease (2015) 6, e1786; doi:10.1038/cddis.2015.153

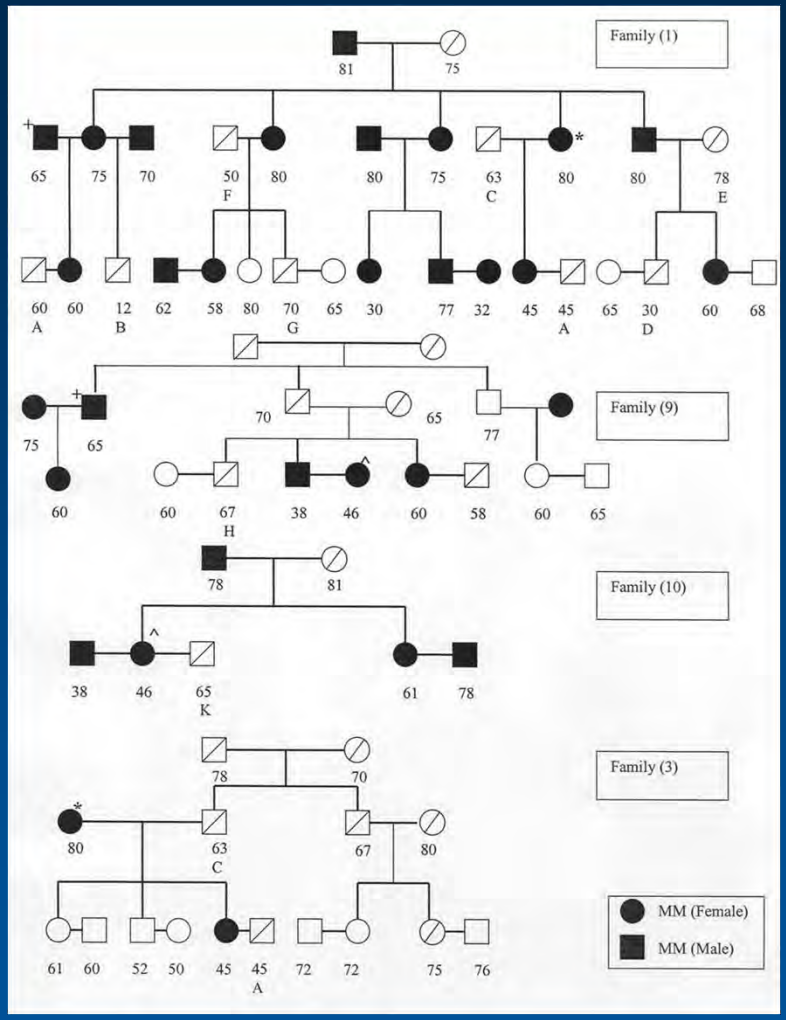
www.nature.com/cddis

Aspirin delays mesothelioma growth by inhibiting HMGB1-mediated tumor progression

H Yang*,[1], L Pellegrini[1], A Napolitano[1,2], C Giorgi[3], S Jube[1], A Preti[4], CJ Jennings[1], F De Marchis[4], EG Flores[1], D Larson[1], I Pagano[1], M Tanji[1], A Powers[1], S Kanodia[5], G Gaudino[1], S Pastorino[1], HI Pass[6], P Pinton[3], ME Bianchi[4] and M Carbone*,[1]



Mesothelioma and Genetics: The hunt for the meso gene



Roushdy-Hammady, ..., & Carbone. Lancet 2001.
Dogan, ..., & Carbone. Cancer Res 2005.
NCI P01 2007-13: M. Carbone PI , Testa, Pass, Cox, co-Pis

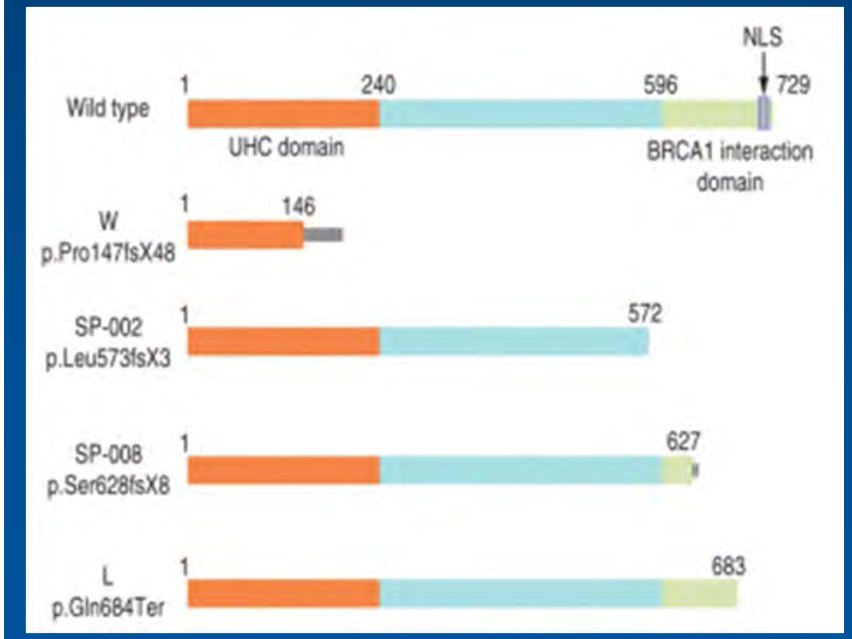
LETTERS

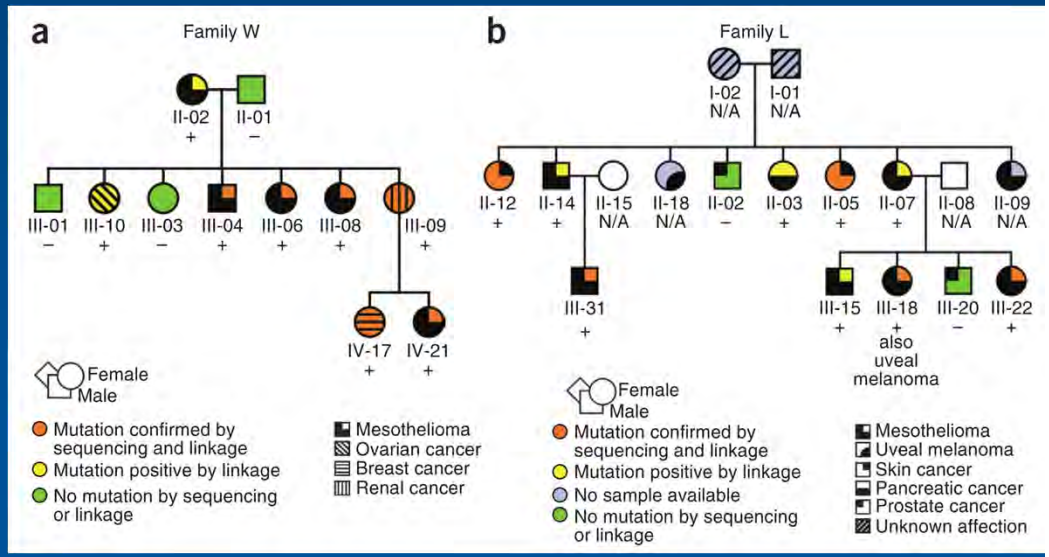
nature genetics

Germline *BAP1* mutations predispose to malignant mesothelioma

Joseph R Testa[1], Mitchell Cheung[1], Jianming Pei[1], Jennifer E Below[2], Yinfei Tan[1], Eleonora Sementino[1], Nancy J Cox[2,3], A Umran Dogan[4,5], Harvey I Pass[6], Sandra Trusa[6], Mary Hesdorffer[7], Masaki Nasu[8,9], Amy Powers[8], Zeyana Rivera[8,9], Sabahattin Comertpay[8,9], Mika Tanji[8,9], Giovanni Gaudino[8], Haining Yang[8,10] & Michele Carbone[8]

VOLUME 43 | NUMBER 10 | OCTOBER 2011 NATURE GENETICS





BAP1 mutations in sporadic mesotheliomas
2/26 carried germline mutations

Sample ID	Age	Gender	MM	MM Histology	Uveal Melanoma	Other Cancers	Germline *BAP1* Mutation
SP-002	55	F	Yes	E	Yes	Leiomyosarcoma	Exon 13 (52,437,444 C del)
SP-008	63	M	Yes	E	Yes	None	Exon 14 (52,437,159-162 TCAC del)
SP-007	55	F	Yes	E	No	Basal cell ca.	None
SP-011	63	M	Yes	B	No	Basal cell ca.	None
SP-015	82	M	Yes	E	No	Basal cell ca.	None
SP-026	66	M	Yes	B	No	Basal cell ca.	None
SP-020	75	M	Yes	E	No	Basal cell ca.; Meningioma	None
SP-025	52	M	Yes	E	No	Basal cell ca.; Squamous cell ca. (skin)	None
SP-005	34	F	Yes	E	No	Breast ca.; Leiomyosarcoma	None
SP-010	69	F	Yes	E	No	Breast ca.; Bronchioalveolar ca.; Pancreatic ca.	None
SP-019	71	M	Yes	B	No	Colon ca.	None
SP-016	74	M	Yes	E	No	Colon ca.; Prostate ca.	None
SP-004	62	F	Yes	B	No	Hairy cell leukemia	None
SP-003	64	M	Yes	E	No	Melanoma (skin)	None
SP-017	74	M	Yes	E	No	Melanoma (skin)	None
SP-018	70	M	Yes	E	No	Prostate ca.	None
SP-013	70	M	Yes	B	No	Prostate ca.	None
SP-021	61	M	Yes	E	No	Prostate ca.	None
SP-012	58	F	Yes	E	No	Squamous cell ca. (skin)	None
SP-001	63	M	Yes	E	No	None	None
SP-006	60	M	Yes	E	No	None	None
SP-009	55	M	Yes	E	No	None	None
SP-014	60	M	Yes	E	No	None	None
SP-022	56	M	Yes	E	No	None	None
SP-023	53	F	Yes	B	No	None	None
SP-024	78	M	Yes	B	No	None	None

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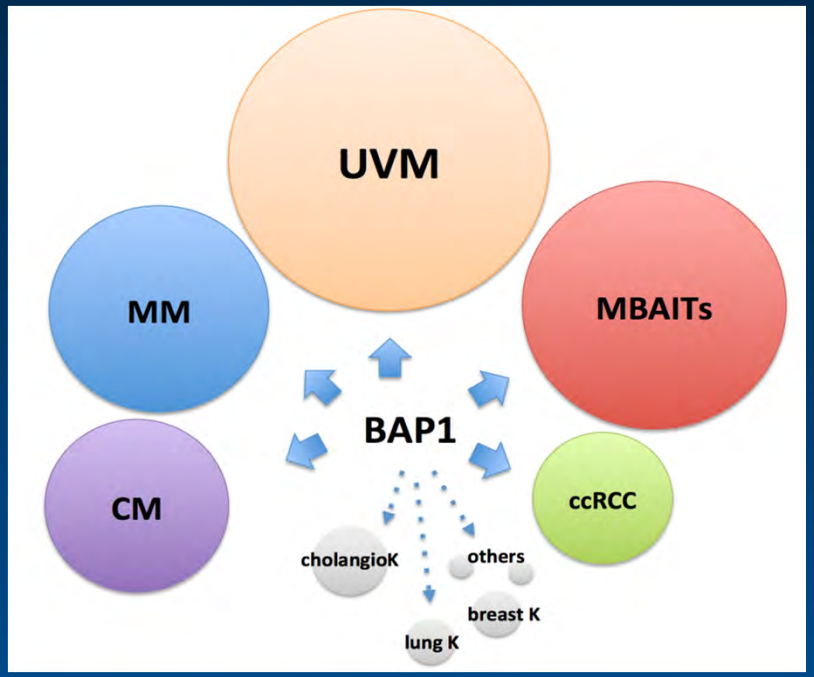
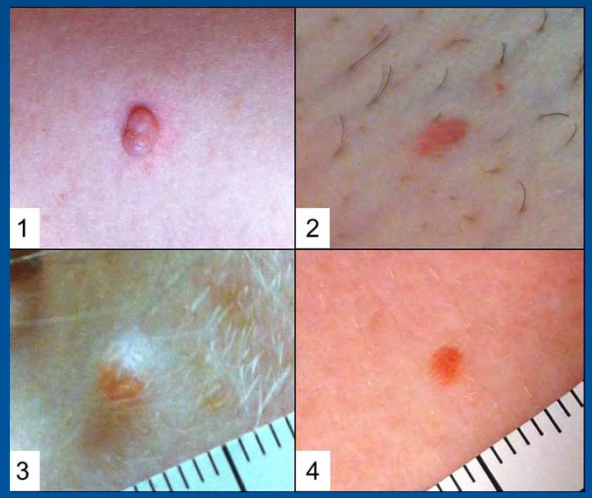
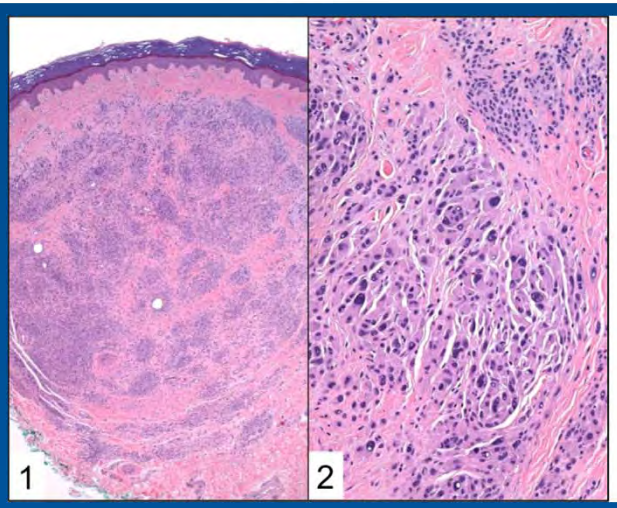
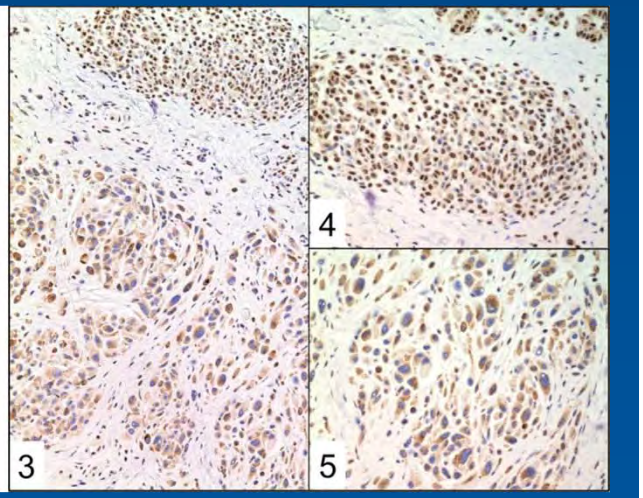
BAP1 cancer syndrome: MM, CM and UVM, MBAITs, Cholangio and Renal Cell Carcinomas, and possibly others. Carbone et al., *Nat. Rev Cancer 2013*.









Oncogene (2015), 1–7

www.nature.com/onc

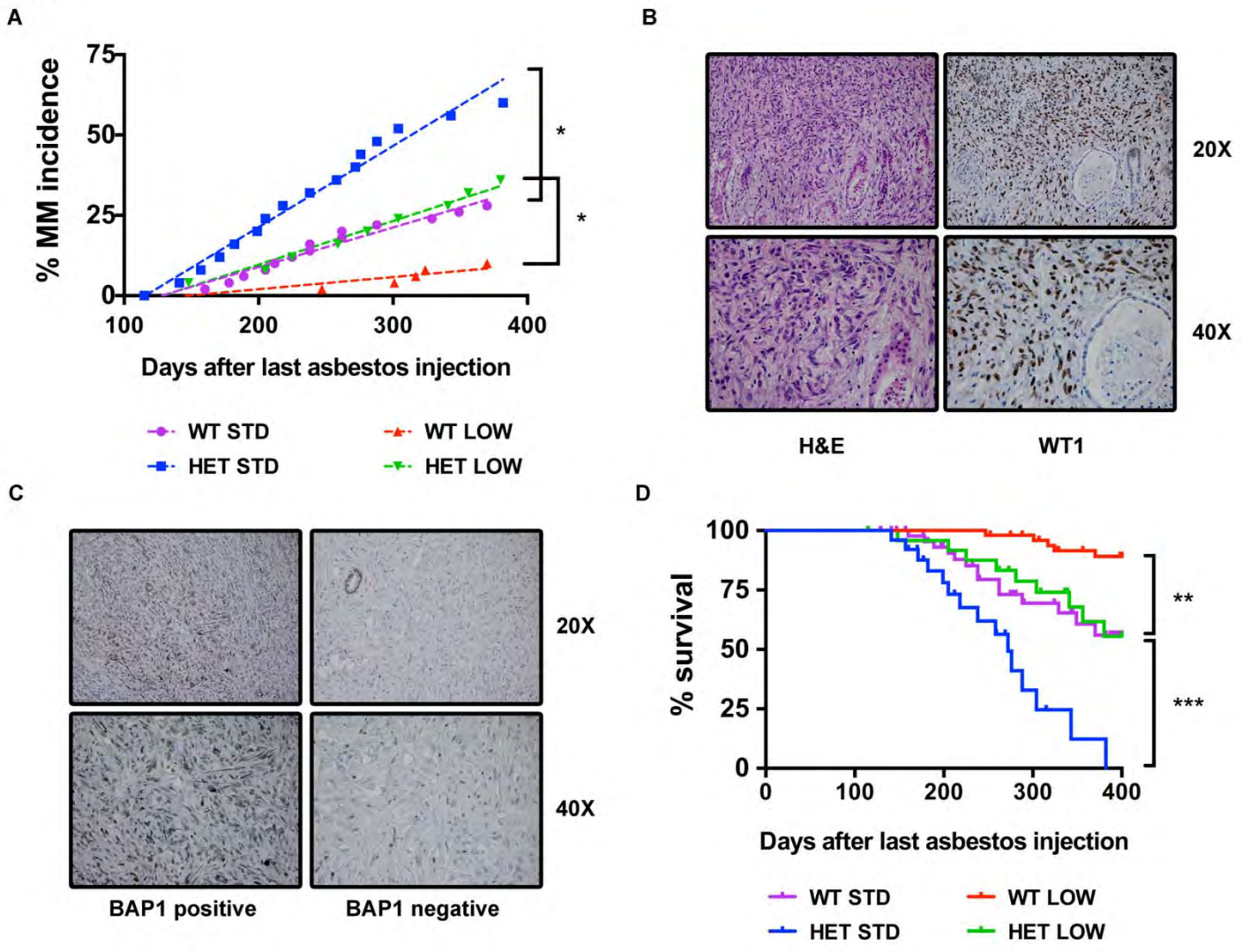
SHORT COMMUNICATION

Minimal asbestos exposure in germline *BAP1* heterozygous mice is associated with deregulated inflammatory response and increased risk of mesothelioma

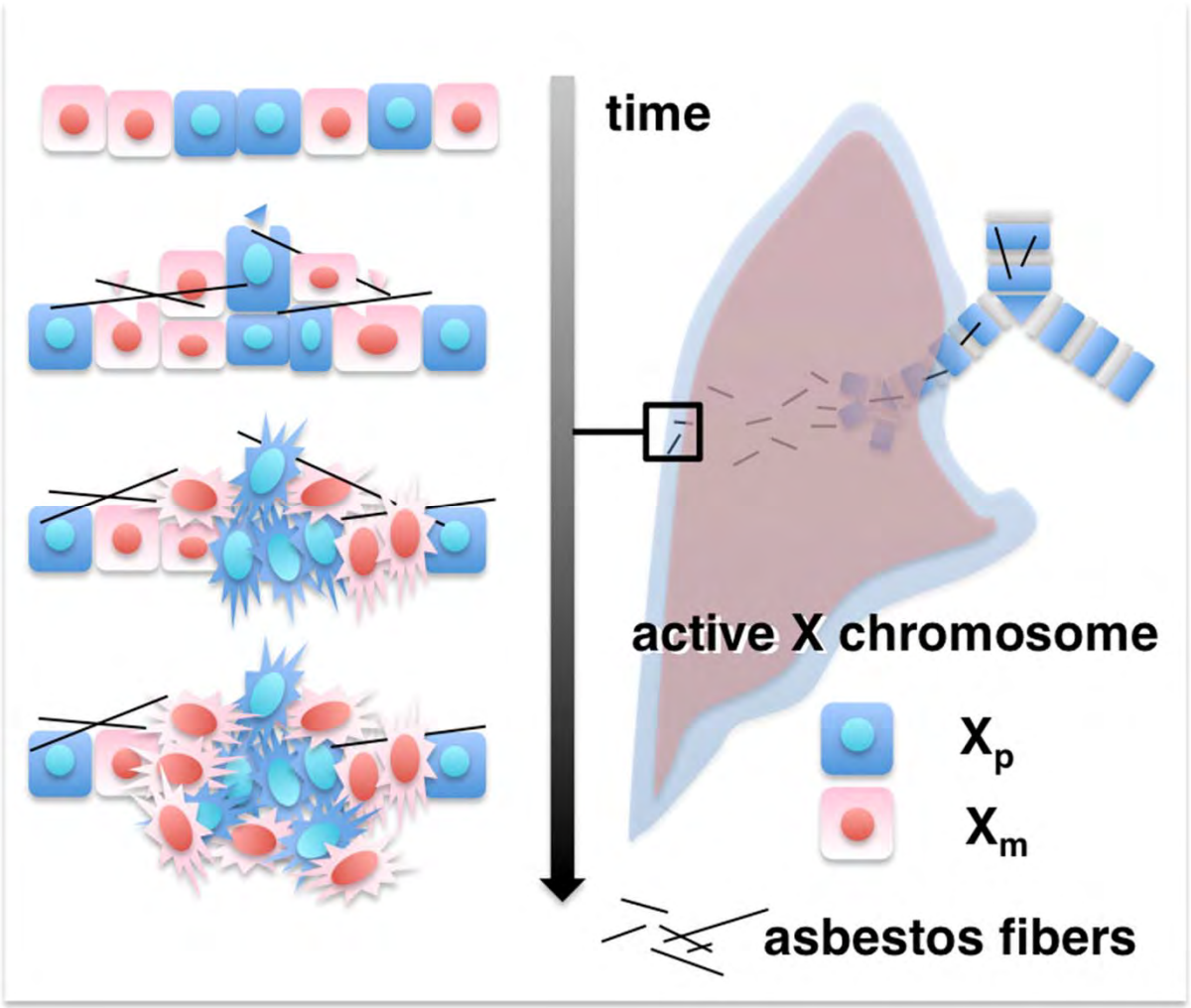
A Napolitano[1,2], L Pellegrini[1], A Dey[3], D Larson[1], M Tanji[1], EG Flores[1], B Kendrick[1], D Lapid[1], A Powers[1], S Kanodia[4], S Pastorino[1], HI Pass[5], V Dixit[3], H Yang[1] and M Carbone[1]

Napolitano, .. Yang & Carbone. Oncogene 7/17/15

Fig. 3



Malignant Mesothelioma are polyclonal tumors. Comertpay, ..Yang & Carbone. JTM 2014



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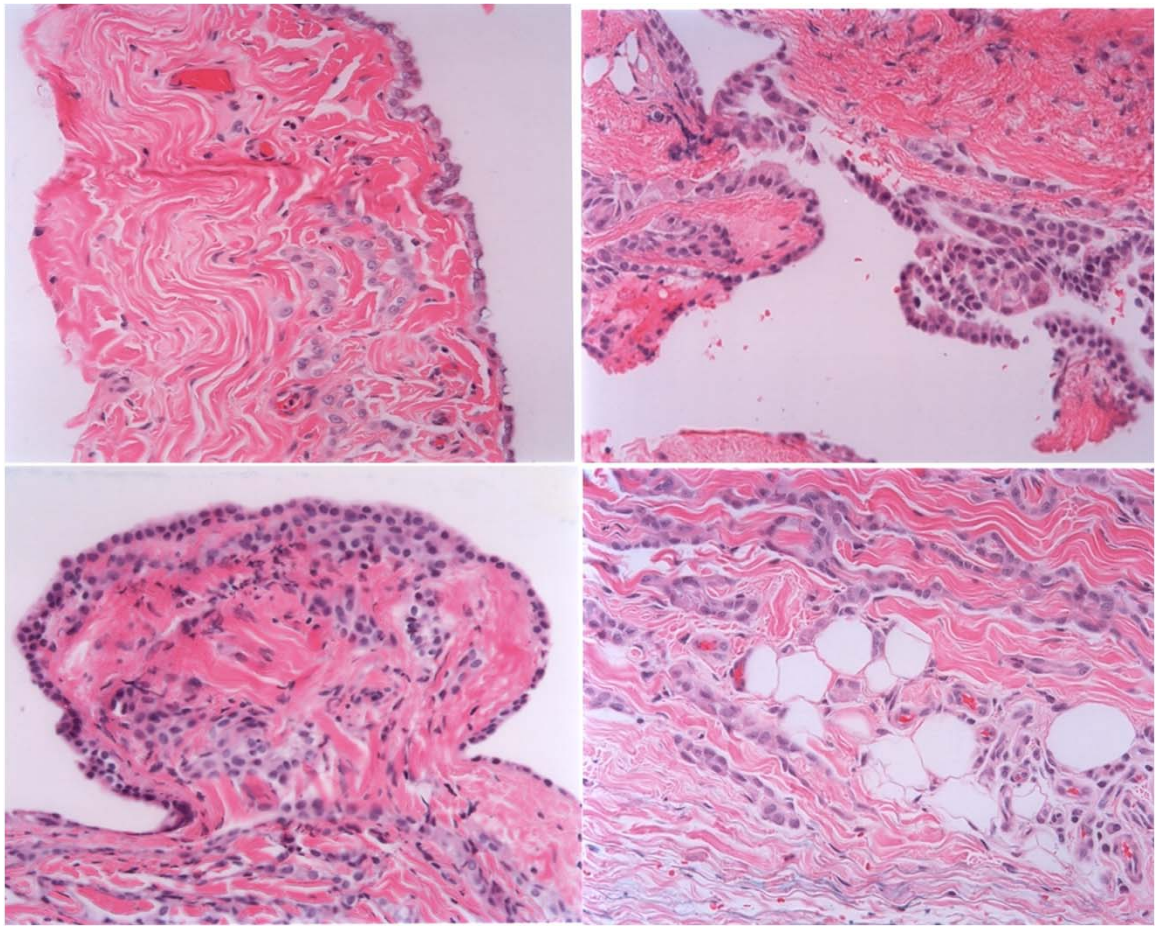
MM in a W-family BAP1+/- carrier



PLOS | GENETICS

RESEARCH ARTICLE

Combined Genetic and Genealogic Studies Uncover a Large BAP1 Cancer Syndrome Kindred Tracing Back Nine Generations to a Common Ancestor from the 1700s

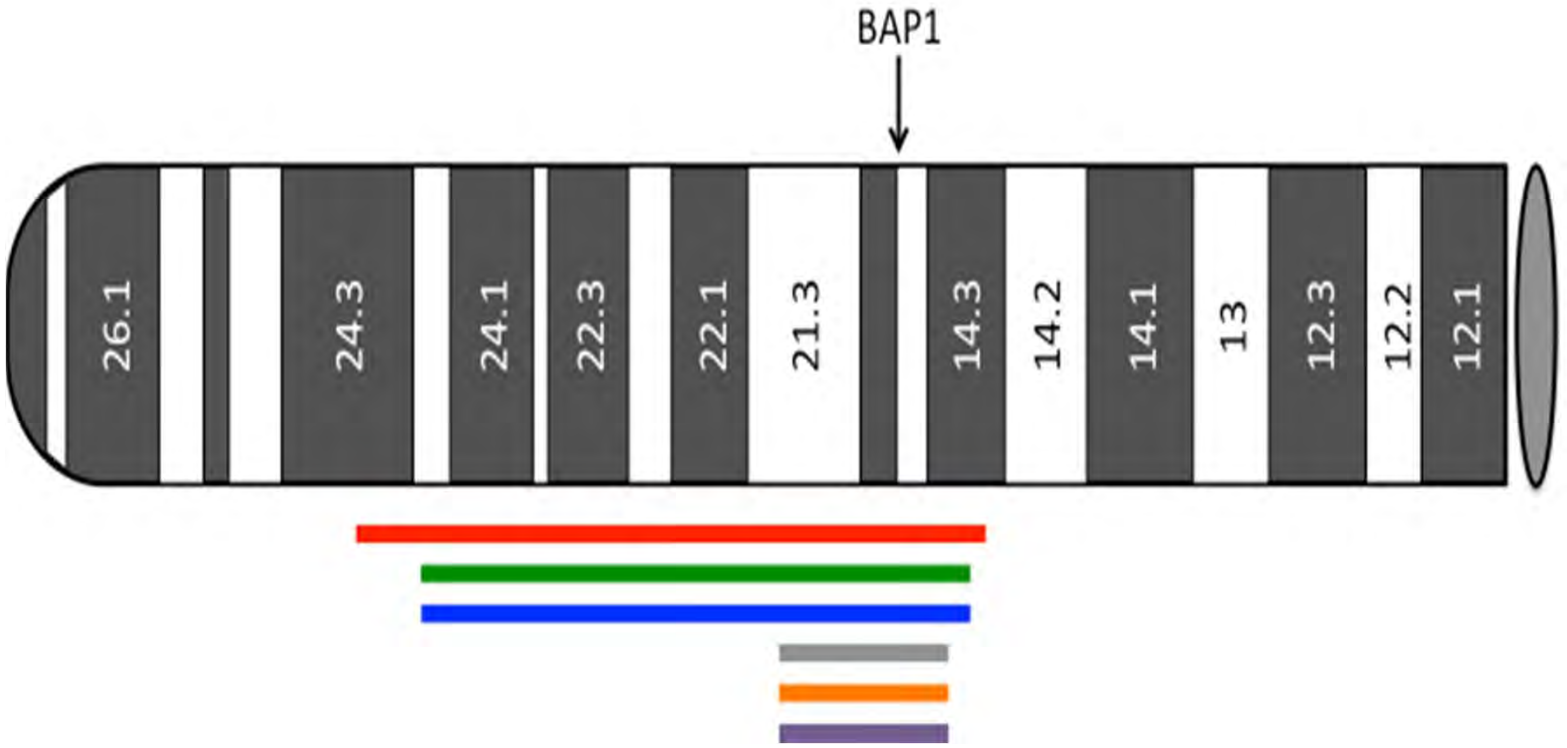
Michele Carbone[1☯*], Erin G. Flores[1☯], Mitsuru Emi[1☯], Todd A. Johnson[2], Tatsuhiko Tsunoda[2], Dusty Behner[1], Harriet Hoffman[3], Mary Hesdorffer[4], Masaki Nasu[1], Andrea Napolitano[1], Amy Powers[1], Michael Minaai[1], Francine Baumann[1], Peter Bryant-Greenwood[1], Olivia Lauk[5], Michaela B. Kirschner[5], Walter Weder[5], Isabelle Opitz[5], Harvey I. Pass[6], Giovanni Gaudino[1], Sandra Pastorino[1], Haining Yang[1]*

4 families identical mutation

Family	ID	Gender	Survival, years after cancer dx*	Cancer (age at dx when known)
MARF2	***IV-2***	***F***	***>18***	***LM (32), UM (48), pMM (55), pIMM (60) GCTB (71)***
MARF2	III-4	M		Prostate, Bone
MARF2	III-5	F		Soft tissue sarcoma
MARF2	III-7	F	3	Brain (57)
MARF2	IV-3	M		Prostate (72)
MARF2	IV-4	F	3	Breast (47)
MARF2	IV-6	M		CM (70)
MARF2	IV-7	F		Breast (67)
MARF2	V-2	M		BCC (29)
MARF2	IV-1	M		UM
MARF11	I-1	M		Cancer
MARF11	II-1	M		Nasal carcinoma (56)
MARF11	II-2	F		Hodgkin's lymphoma
MARF11	II-3	F		pMM
MARF11	***III-1***	***M***	***>4***	***pMM (51)***
MARF11	III-2	M		UM
MARF18	I-3	M		Cancer
MARF18	II-10	M		Cancer
MARF18	II-1	M		Cancer
MARF18	II-5	F		Stomach

Family	ID	Gender	Survival, years after cancer dx*	Cancer (age at dx when known)
MARF18	***III-1***	***F***	***7***	***pIMM/pMM (52)***
MARF18	III-2	F	<1	MM (48)
MARF18	III-3	F	9	pMM (58)
MARF18	II-6	F		Cancer
MARF18	III-4	F		Stomach; Uterus
MARF18	III-5	F		Primary bone cancer
MARF18	III-6	F		Leukemia
MARF18	III-11	F		Pancreatic
MARF18	III-13	F		Brain
MARF40	II-1	F	5	Breast (50), MM (70)
MARF40	II-4	F		pMM
MARF40	II-5	M		SCC
MARF40	II-6	M		Colon
MARF40	III-10	F		Cancer
MARF40	III-11	M		Cancer
MARF40	II-8	F		UM
MARF40	***III-1***	***M***	***4***	***BCC (64, 71), pMM (67), RCC (70), UM (71)***
MARF40	III-3	M		Lung
MARF40	III-4	M		pIMM
MARF40	III-5	F		pIMM (71)

Idiogram showing IBD shared haplotypes of the DNA regions surrounding *BAP1* in the germline of the 4 founder MARF patients studied.



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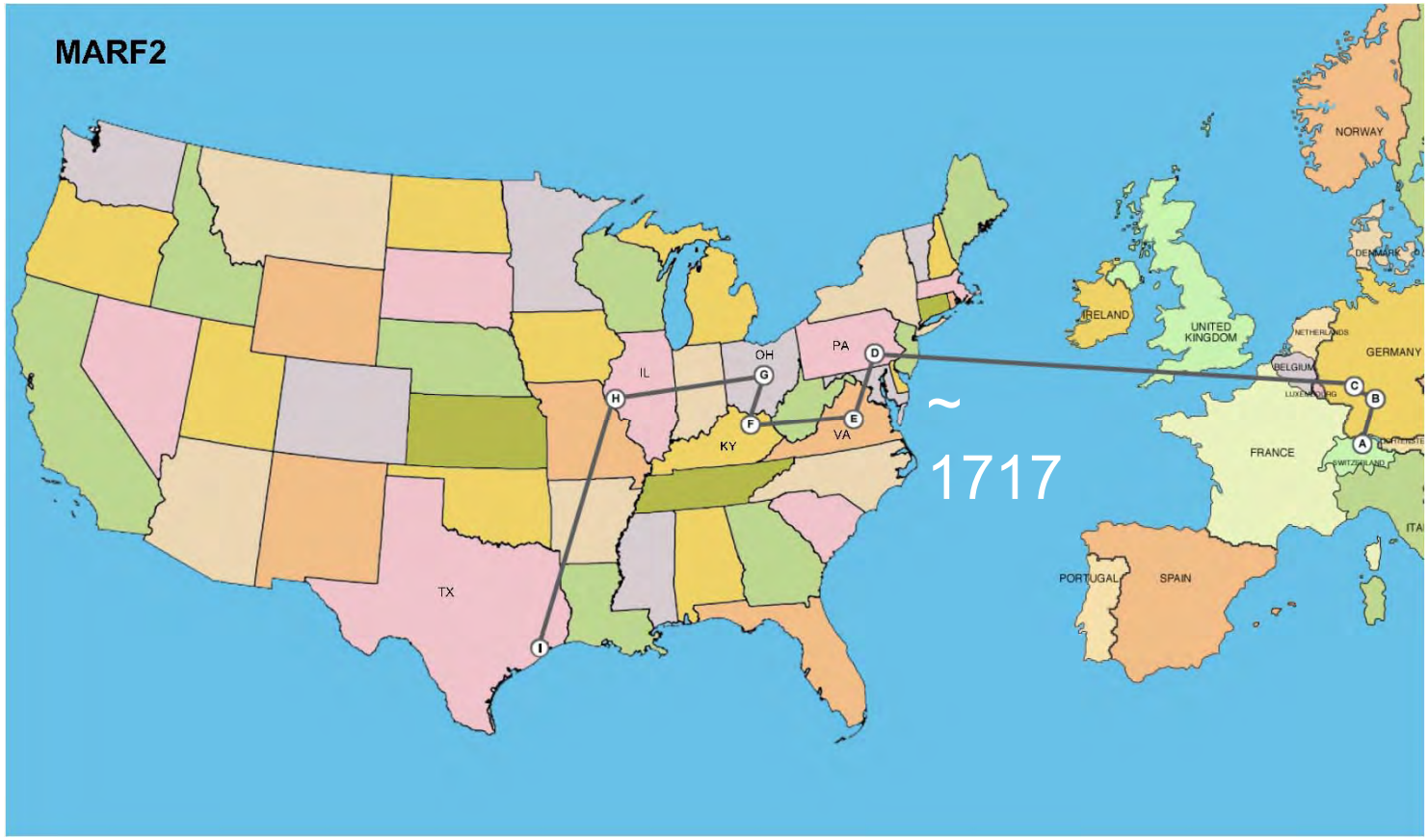
Migration pattern of the K4 kindred from Europe throughout US



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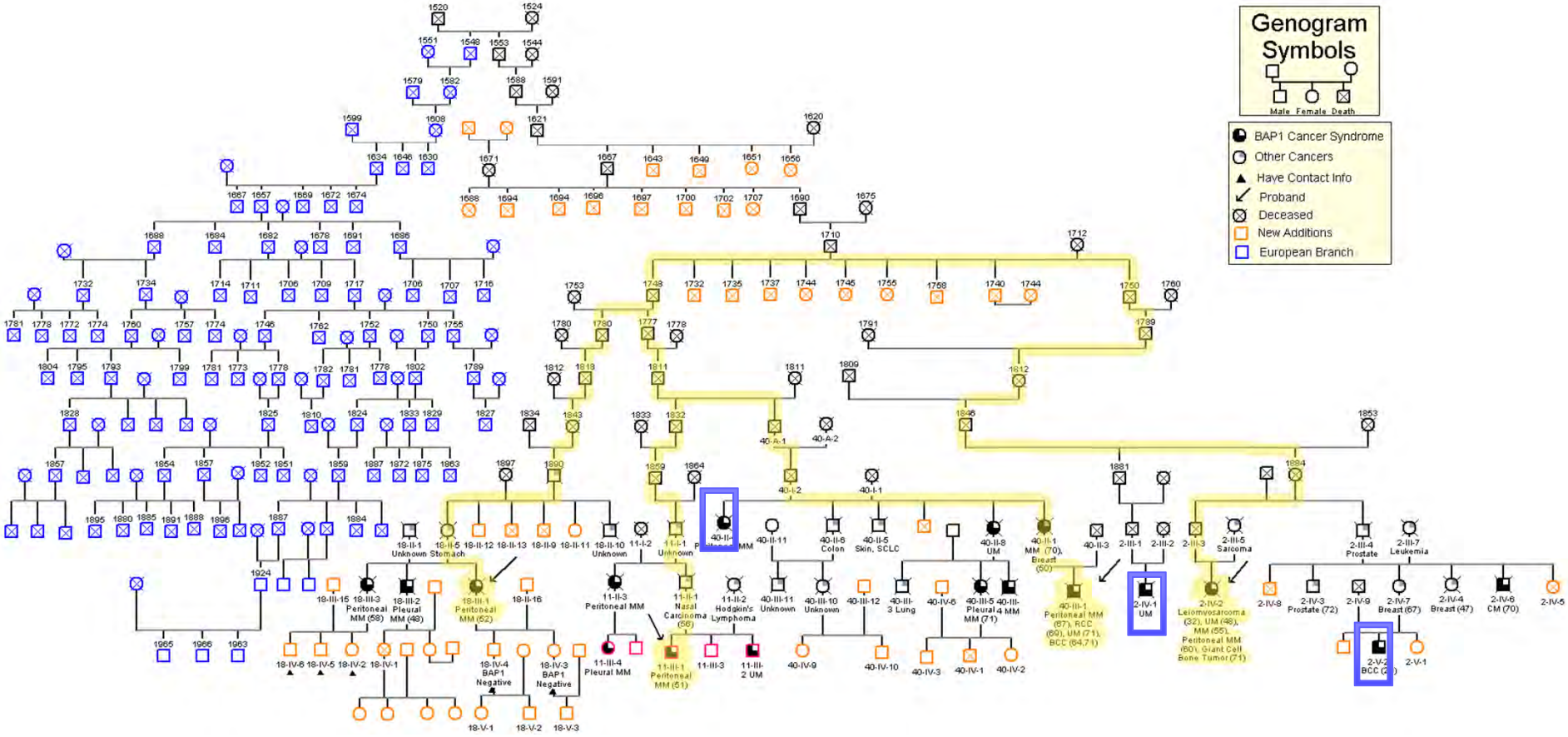
Extended K4 pedigree



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BAP1 mutations in the centuries

PLOS Genetics Dec 8, 2015 Advanced on line publication

- BAP1 mutations are transmitted through multiple generations over the centuries
- These individual are very susceptible to environmental carcinogens, such as UV light and asbestos
- Building large family trees allows to identify additional branches of the family that inherited the mutation and have high incidence of cancers and implement genetic counseling and preventive measures
- The families we study undergo yearly ophtalmological and dermatological examination past age 20 and every 6 months past age 30.
- In addition we are enrolling them in a prospective biomarker clinical trial study for HMGB1 and fibulin.

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Mesothelioma Patients with Germline BAP1 Mutations Have 7-Fold Improved Long-term Survival

Francine Baumann, Erin Flores, Andrea Napolitano, Shreya Kanodia, **Emanuela Taioli**, Harvey Pass, Haining Yang, and Michele Carbone

2015

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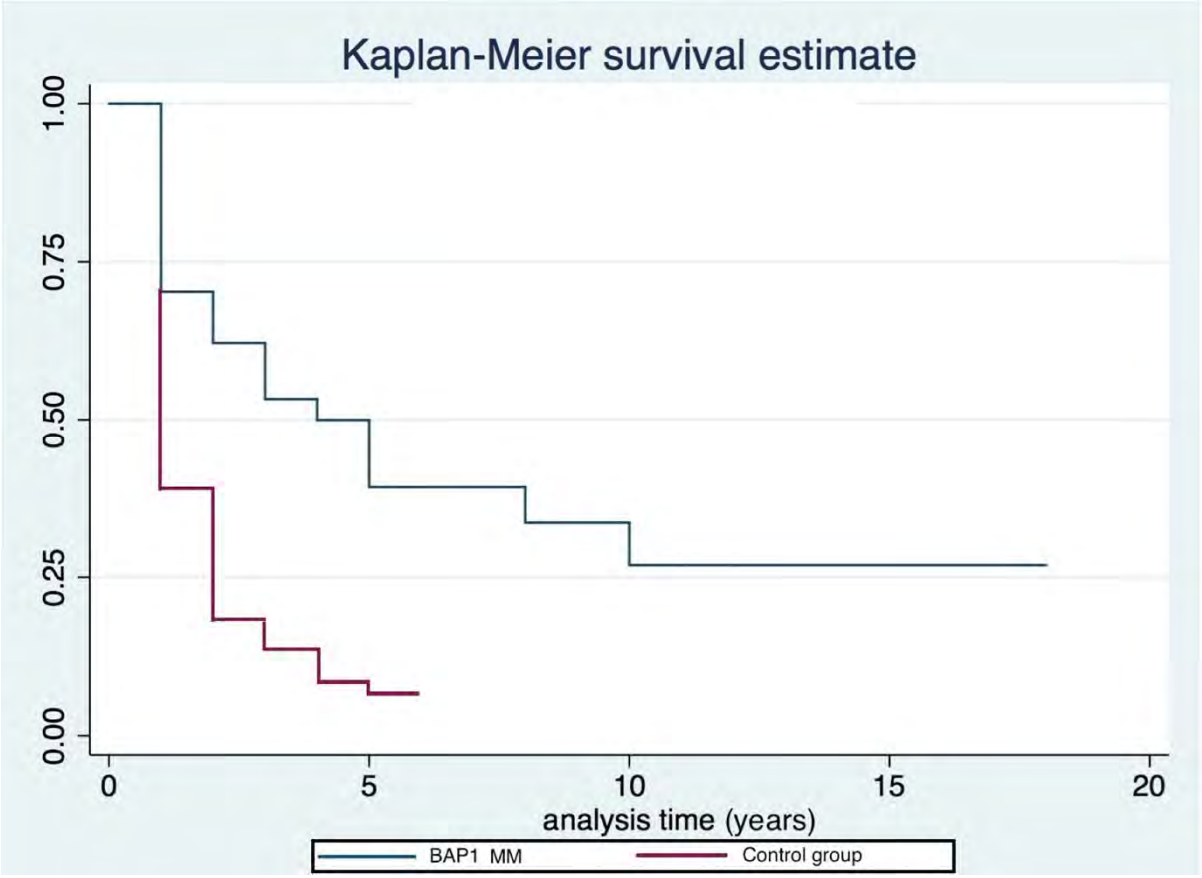
Kaplan-Meier survival curves of the BAP1 MM cohort (N=23) and of the SEER MM cohort (N=10,556)



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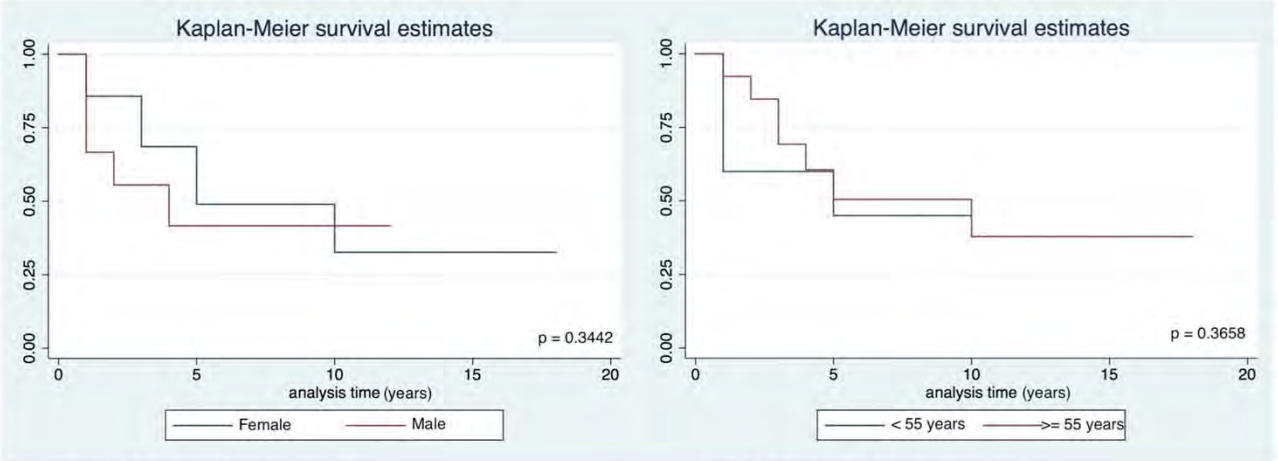
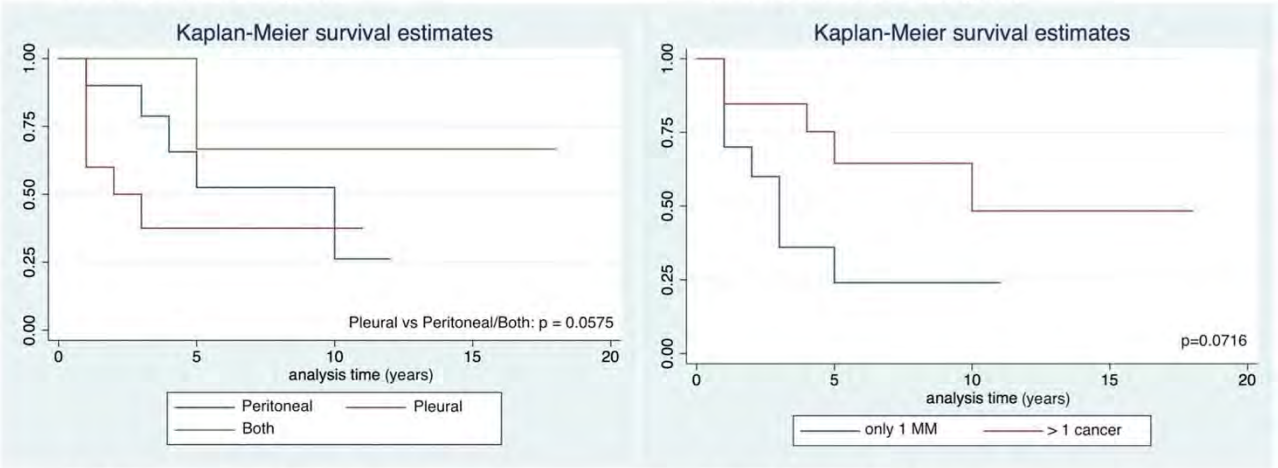
Kaplan-Meier survival curves of the BAP1 MM cohort according to sex, age, MM site, and presence of other cancers



A. MM survival per gender

B. MM survival per age-group



C. MM survival per MM location

D. MM survival per presence of other cancer

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DoD IDEA 2016: New meso-genes. M. Carbone & H. Yang

- **This project will focus on the identification of those genetic predisposing factors that increase susceptibility to asbestos carcinogenicity and contribute to MM pathogenesis.**

No.	Gender	Mutation	Proband Cancer history	Family History of Cancer[p]
1	F	BAP1	LM/UVM/MPerM/MM/Bone	10 immediate relatives with multiple cancers including MM
2	M	BAP1	MPerM/UVM	mother (UVM) and 6 others*
3	M	BAP1	MPerM	aunt & cousin (MPerM) & 3 others*
4	F	BAP1	MPerM/MM	2 sister (MM & MPerM) & 8 others*
5	M	BAP1	MPerM/UM	mother (RCC), maternal line (many other cancers*)
6	M	BAP1	BCC/MM/RCC/UM	mother, aunt & cousin (MM/MPerM) & 6 others*
7	F	BAP1	MM/BCC/Liver	father & 2 sisters (MM/BCC) & 4 others*
8	M	BAP1	RCC/MPerM/MM/MM	mother (MM), Aunt (RCC/skin), cousin (skin)
9	F	XXXX	Breast/MPerM/LM	uncle (pancreatic), uncle (lung), uncle (kidney)
10	F	XXXX	MPerM	3 aunts (breast, uterine, ovarian, lymphoma)
11	F	No[=]	MM	father, sister, brother, brother (MM)
12	F	No[=]	MM	father, sister, brother, brother (MM)
13	F	No[=]	MM	mother, sister, sister, brother (MM)
14	M	No[=]	MM	father, brother, uncle, grand father (MM)
15	M	No[=]	MM	father, uncle, aunt, aunt, sister (MM)
16	F	No[=]	MM	father, uncle, aunt, aunt, brother (MM)
17	M	No[=]	MM	son, grand son, grand son (MM)
18	M	No[=]	MM	brother & 2 nephews (MM)
19	F	No[=]	MM	brother, sister, aunt (MM) & 3 others*
20	M	No[=]	MM	brother (MM) & 4 others*

M: Malignant Mesothelioma, MPerM: Malignant Peritoneal Mesothelioma,
VM: Uveal Melanoma;
CC: Renal Cell Carcinoma; BCC: Basal Cell Carcinoma; SCC: Squamous Cell Carcinoma;
M: Leiomyosarcoma;
Others: other immediate relatives with history of multiple cancers
No mutations were found in BAP1 gene or other know tumor suppressor genes.

Selection criteria: families with 3 or more cases of MM within 2 generations and/or with a strong familial history of cancer including MM.

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ORIGINAL ARTICLE

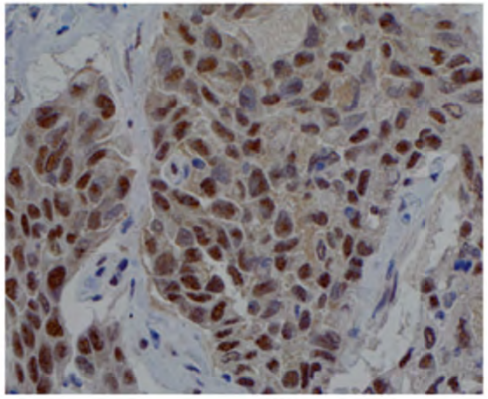
FAST TRACK

High Incidence of Somatic BAP1 Alterations in Sporadic Malignant Mesothelioma

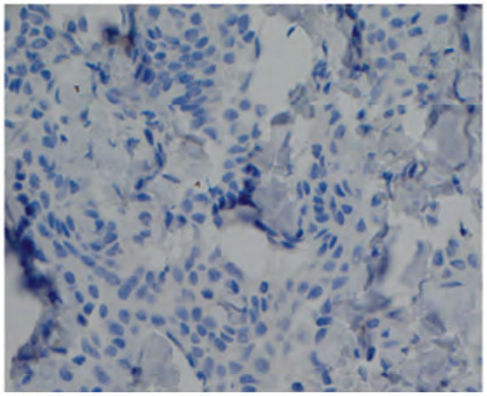
Masaki Nasu, Mitsuru Emi,* Sandra Pastorino,* Mika Tanji,* Amy Powers,* Hugh Luk,* Francine Baumann,* Yu-an Zhang,† Adi Gazdar,† Shreya Kanodia,*‡ Maarit Tiirikainen,* Erin Flores,* Giovanni Gaudino,* Michael J. Becich,§ Harvey I. Pass,‖ Haining Yang,* and Michele Carbone, MD, PhD**

Journal of Thoracic Oncology® • Volume 10, Number 4, April 2015

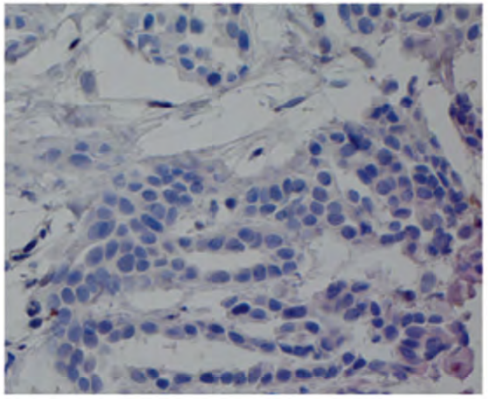
NYU047



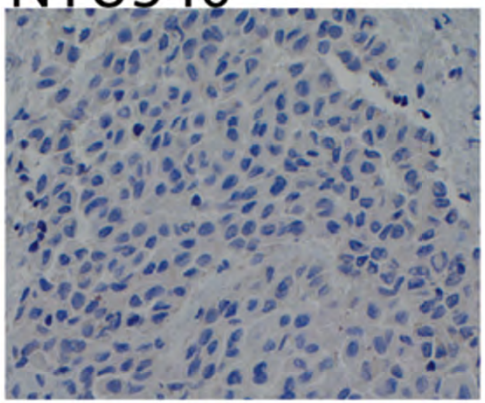
NYU207



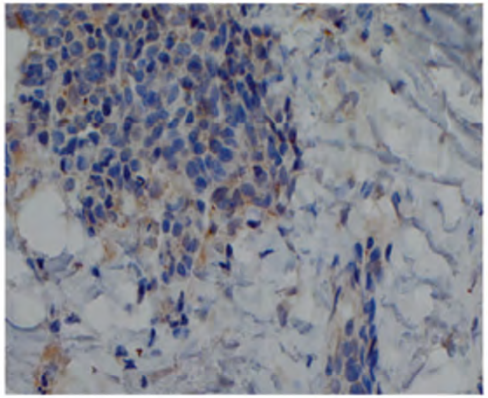
NYU524



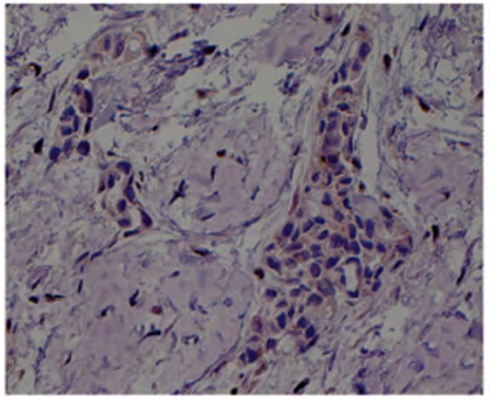
NYU540



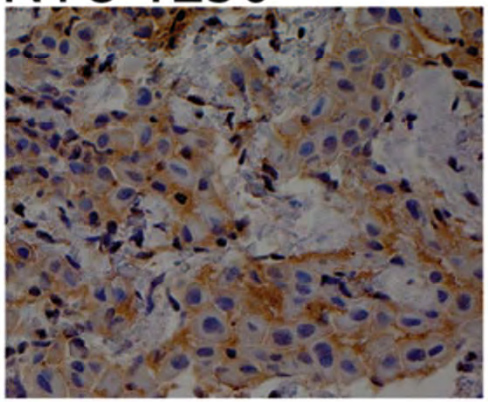
NYU559



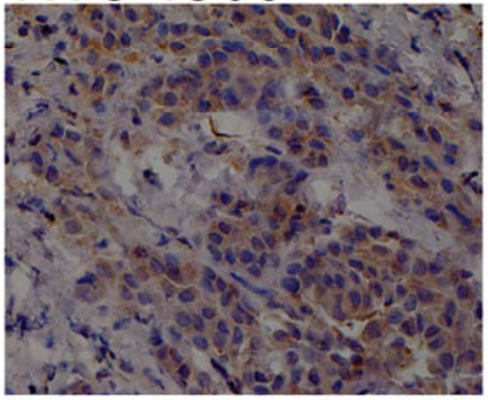
NYU 966



NYU 1250



NYU 1306



Positive nuclear BAP1 immunostaining helps differentiate non-small cell lung carcinomas from malignant mesothelioma.

- Michele Carbone, David Shimizu, Andrea Napolitano, Mika Tanji, Harvey I. Pass, Haining Yang, Sandra Pastorino

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Table. Immunostaining of nuclear BAP1 in malignant mesothelioma and non-small cell lung cancer

Tumor Type	Malignant Mesothelioma				Non-small cell lung cancer		
Histology	Epithelial	Biphasic	Sarcomatoid	Total	Adenocarcinoma	SCC	Total
Sample no.	20	8	7	35	32	13	45
BAP1 Negative	13 (65%)	4 (50%)	5 (71%)	22 (63%)	0	0	0
BAP1 Positive	1 (5%)	1 (13%)	2 (29%)	4 (11%)	30 (94%)	13 (100%)	43 (96%)
BAP1 Focal	6 (30%)	3 (37%)	0	9 (26%)	2 (6%)	0	2 (4%)

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Yoshikawa Y et al., doi: 10.1073/pnas.1612074113 PNAS November 9, 2016

- We found that gene mutations/deletions are frequent in mesothelioma and occur through a variety of DNA alterations.
- We identified new genes implicated in malignant mesothelioma: *SETD2*, *SMARCC1*, *PBRM1*.
- Previous next-generation studies (NGS) underestimated the frequency of genetic alterations in malignant mesothelioma because NGS mainly identifies nucleotide level mutations

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Conclusion

- In the US the incidence of mesothelioma has peaked to about 3200 and has remained stable for the past decade.
- Asbestos deposition induces chronic inflammation driven by HMGB1 and TNF-alpha that over time leads to MM.
- Inherited heterozygous BAP1 mutation cause MM and other cancers. In germline BAP1 mutation carriers cancers are less aggressive than their sporadic counterparts.
- Families with BAP1 mutations should be closely monitored for early cancer detection.
- BAP1 is the most commonly mutated gene in sporadic MM.
- Many mutations are identified in sporadic MM using a combined high density array CGH and target NGS sequencing. Previous studies based only on NGS had underestimated mutation frequency in MM

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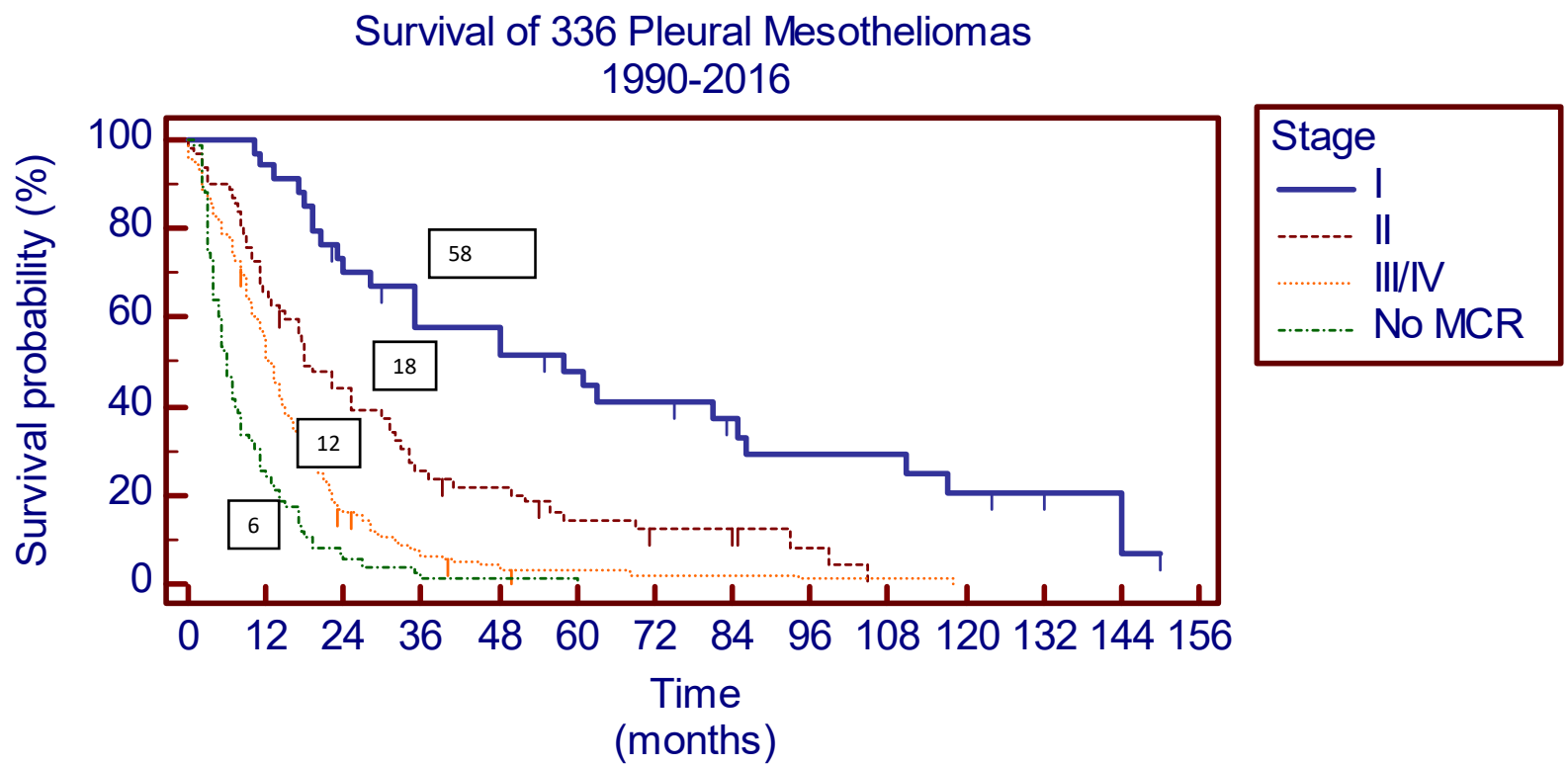
Biomarkers for Pleural Mesothelioma

Harvey I. Pass MD
Stephen E. Banner Professor of Thoracic Oncology
Vice-Chairman, Research
Department of Cardiothoracic Surgery
Director, General Thoracic Surgery

Disclosures

- **Grants**: NCI EDRN,TCGA, DOD, Technion, CDC,
- **Philanthropy**: Rosenwald Foundation, Stephen A. Banner Lung Cancer Foundation, Belluck and Fox, Levi, Phillips and Konigsberg, Simmons Foundation, Baron and Budd, multiple patients who shall remain anonymous
- **Industry: Fujirebio**, 20/20 Gene, MesoScale Diagnostics, Cynvezio, Source MDX, Celera, OPKO, SomaLogic, Genentech, Integrated Diagnostics, Transgenomics, Rosetta Genomics, Calithera, Pinpoint Genomics, Cizzle, emeraldLogic, HTG,
- **Patents** (no money): osteopontin for diagnosis and prognosis of MPM; fibulin 3 for diagnosis and prognosis of MPM; mir-29c* for prognosis of MPM; mir-31 for diagnosis of MPM, HMGB1 for diagnosis of MPM

IASLC



Number at risk

Group: I													
34	32	23	18	16	14	12	9	7	7	5	3	1	0
Group: II													
61	41	26	15	12	7	5	4	2	0	0	0	0	0
Group: III/IV													
166	86	27	10	4	3	2	2	1	1	0	0	0	0
Group: No MCR													
75	18	4	1	1	0	0	0	0	0	0	0	0	0

"SCREENING" for Mesothelioma

- How do patients present in the US?
  - 91% have an exposure to asbestos
  - 90% of pleural patients present with an effusion
  - 77% of abdominal patients present with ascites
    - ***Effusions do NOT OCCUR OVERNIGHT***
- Screening is done in ***asymptomatic patients with a history of exposure to asbestos***
  - Therefore, you are attempting to define plasma biomarker changes which could reflect the development of an asymptomatic effusion or some "perturbation of mesothelial physiology" over time.
- *A change in marker indices could lead to a CT of the chest/abdomen*

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Biomarker Discovery

- **Markers of Exposure** (HMGB1 and isoforms)
  - Non-exposed vs Exposed
  - Matched for age, sex, smoking history
- **Markers of Mesothelioma (Osteopontin, Fibulin 3, Soma 13)**
  - Asymptomatic, asbestos exposed vs MPM
  - Refinement of Specificity
    - Asymptomatic, asbestos exposed vs benign respiratory disease vs other malignancies (preferably presenting as effusions) vs MPM
- **Prognostic Markers** (Osteopontin, SMRP, Soma 13)
  - Who needs further therapy?
  - Who should receive aggressive, potentially toxic therapy?

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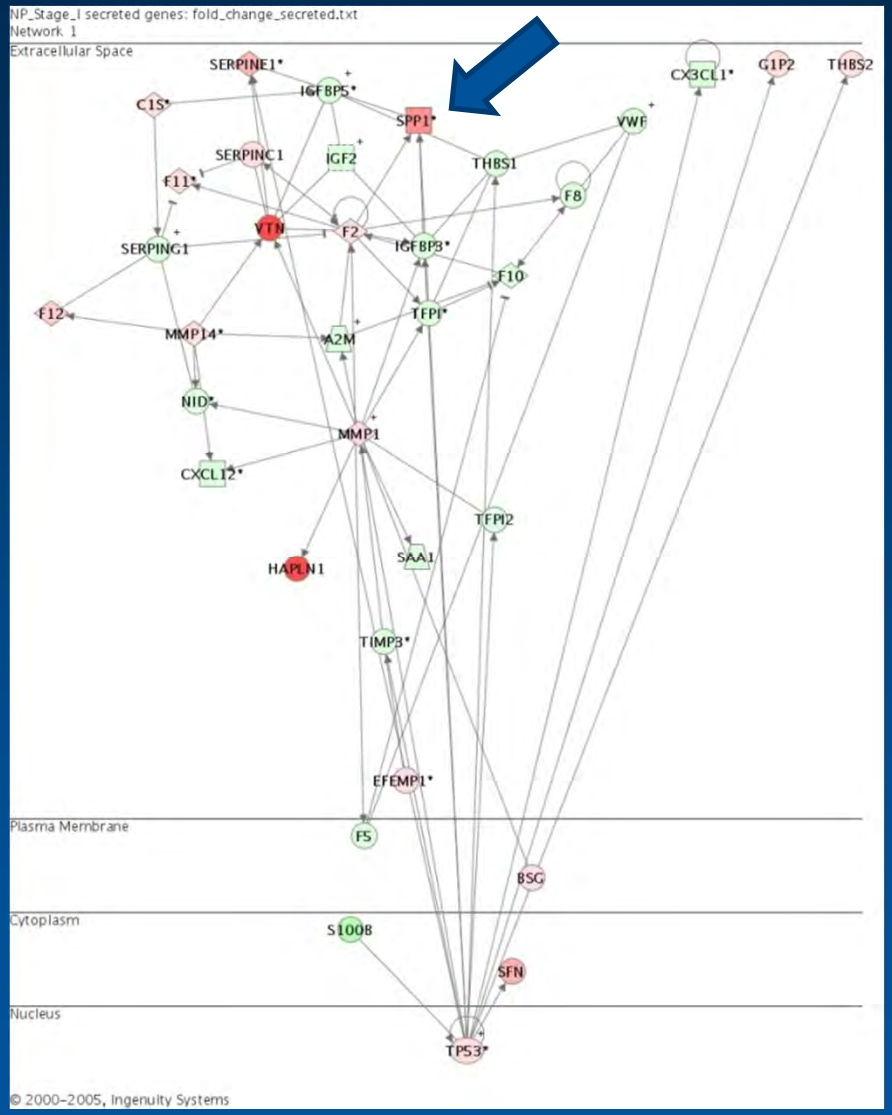
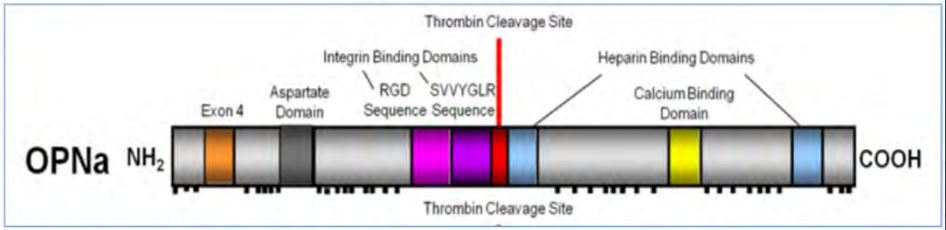
2004: use U133A arrays to compare 7 MPMs to 3 normal peritoneum (mesothelium)…14,500 genes

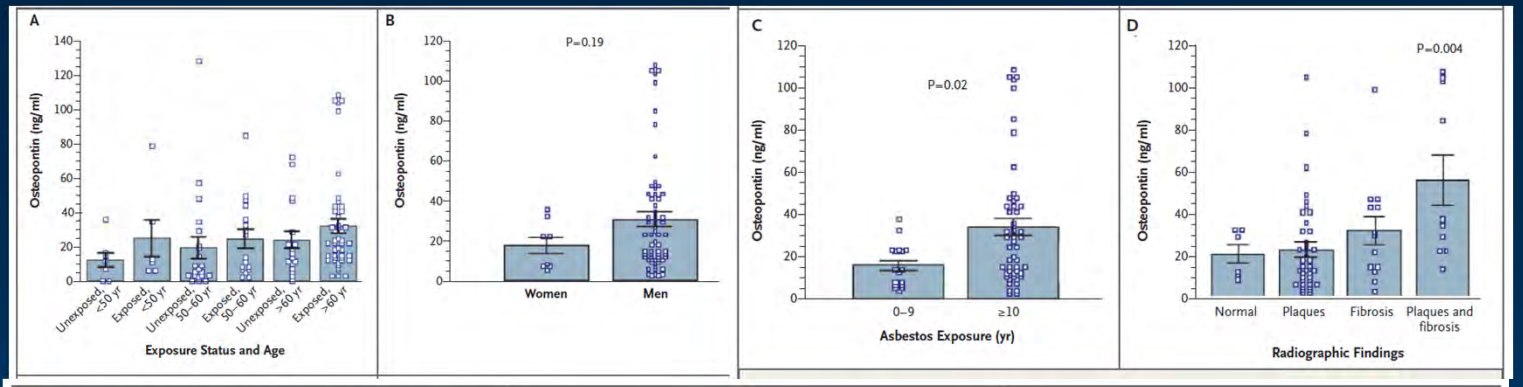


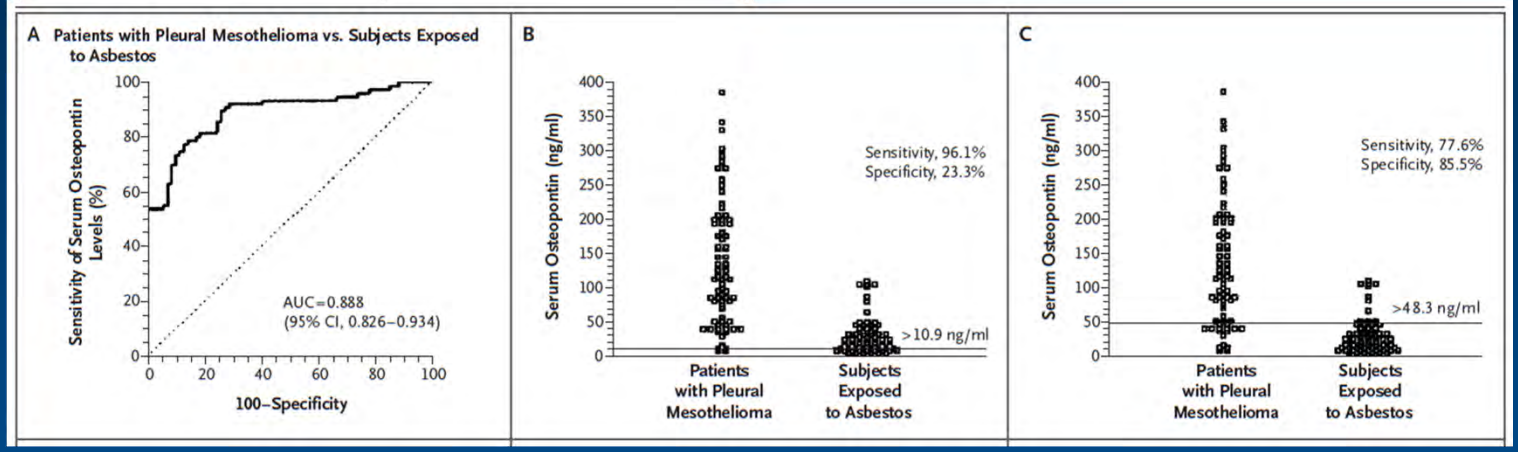
Osteopontin

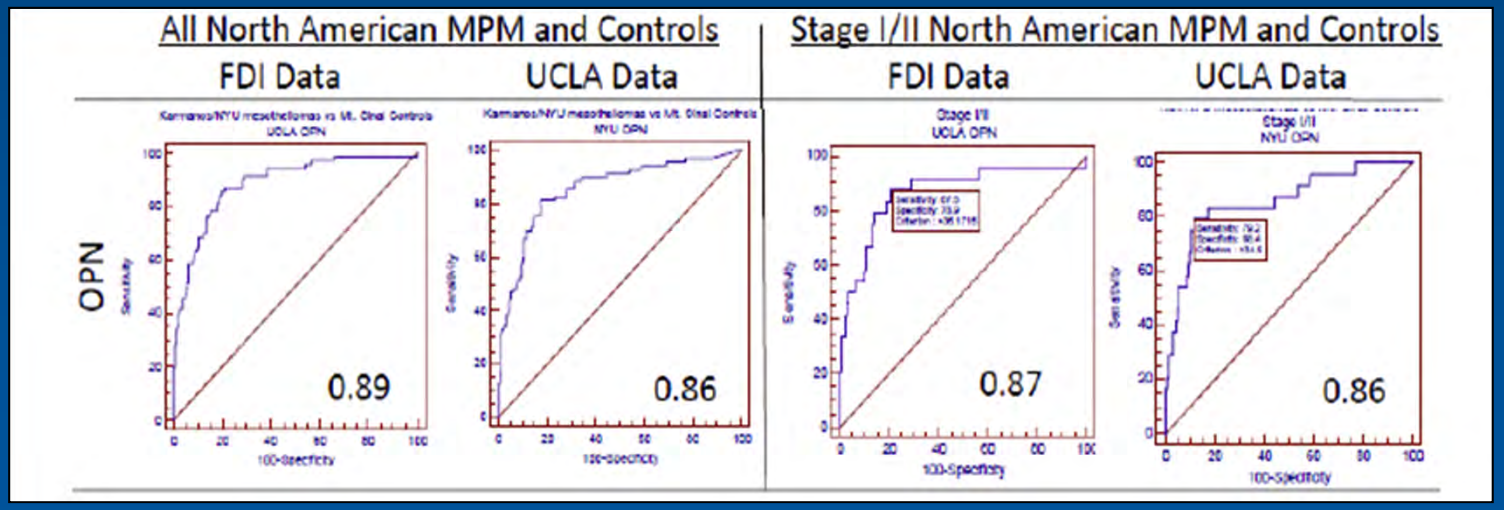


- Multi-functional extracellular phosphoprotein
  - SIBLING family of proteins
  - regulate cell adhesion, migration, invasion, chemotaxis and cell survival by binding to integrins and other cell surface receptors
- Tumor invasion and metastasis formation
- Mechanism by which cancer cells elude apoptosis when under stress due to hypoxia, starvation or chemotherapy
- ***Tissue*** levels are prognostic for MPM
- Stimulates preneoplastic cell proliferation through activation of MAP kinases.

N Engl J Med. 2005 Oct 13;353(15):1564-73.

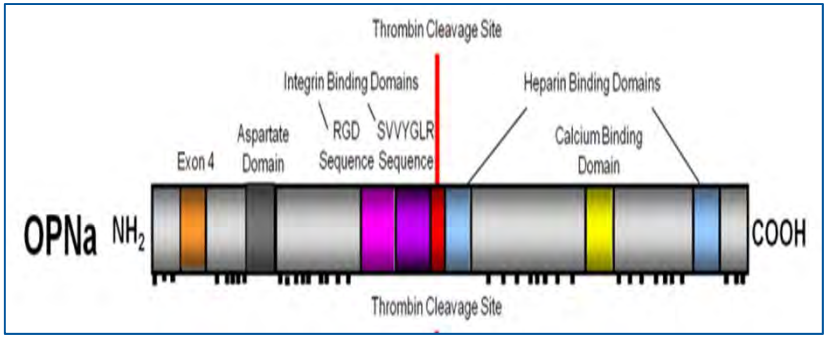






N Engl J Med. 2005 Oct 13;353(15):1564-73.

- Resulted in a whirlwind of controversy
  - Failure to validate in Australian Cohort or CARET
- Problems
  - Thrombin Cleavage Site
  - The ELISA being used
  - Different populations for controls ***not reflecting a high risk screening population***



Publication	#MPM	Notes
Cristaudo A,. J Thorac Oncol. 2011 Sep;6(9):1587-93	31	Plasma AUC=0.8
Creaney J, Lung Cancer. 2011 Mar 11	66	Plasma AUC=0.76
Cristaudo A, Int J Biol Markers. 2010 Jul-Sep;25(3):164-7	32	Plasma AUC=0.78
Rai AJ. Clin Chem Lab Med. 2010 Feb;48(2):271-8	205	Serum AUC=0.68
Paleari L. Int J Biol Markers. 2009 Apr-Jun;24(2):112-7	24	Plasma AUC=0.6
Grigoriu BD, Clin Cancer Res. 2007 May 15;13(10):2928-35	94	Serum AUC=0.724
Pass HI, N Engl J Med. 2005 Oct 13;353(15):1564-73	76	Serum AUC=0.88

Issues:
1. Was the ELISA for OPN satisfactory
2. Is plasma important?

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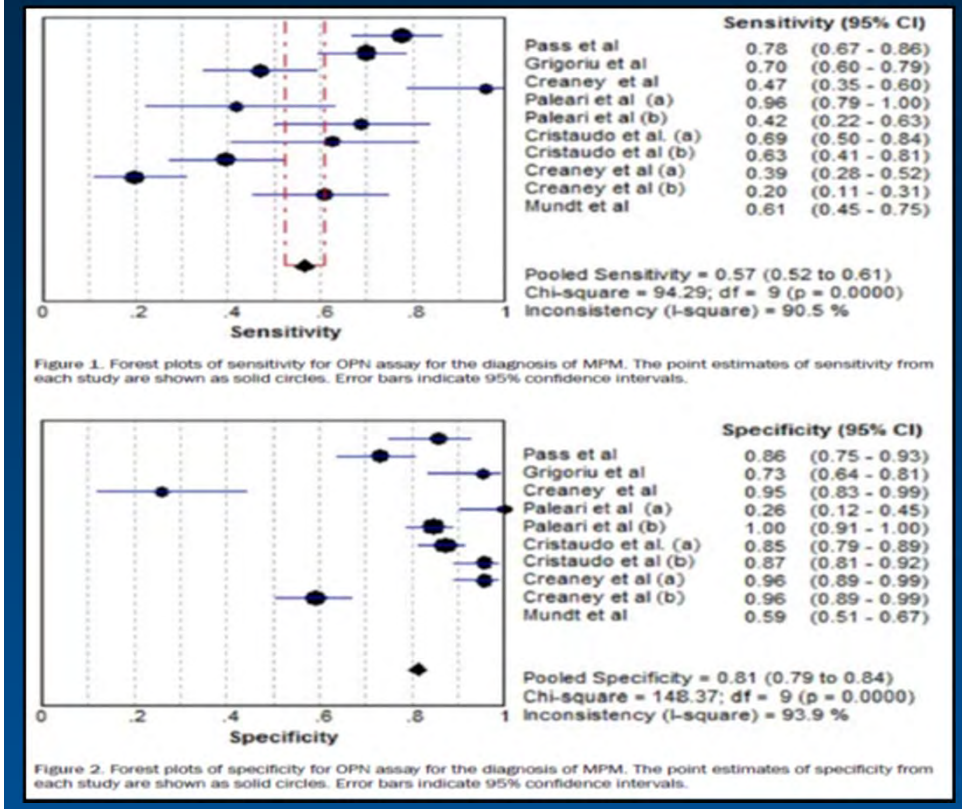
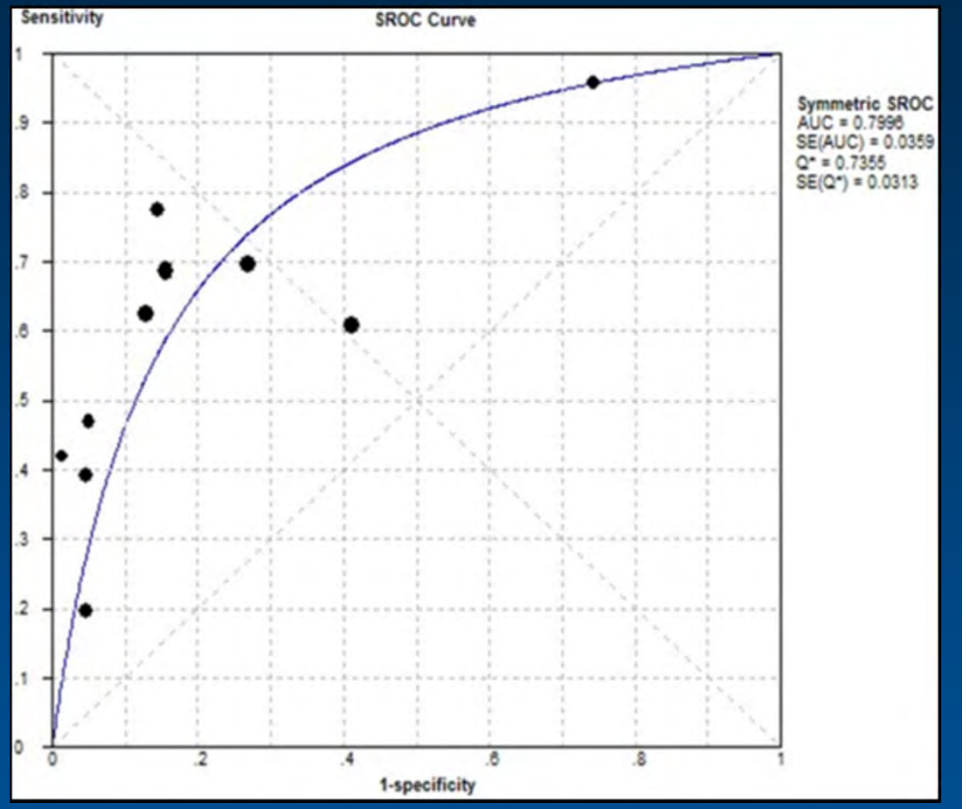


Figure 1. Forest plots of sensitivity for OPN assay for the diagnosis of MPM. The point estimates of sensitivity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

Figure 2. Forest plots of specificity for OPN assay for the diagnosis of MPM. The point estimates of specificity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

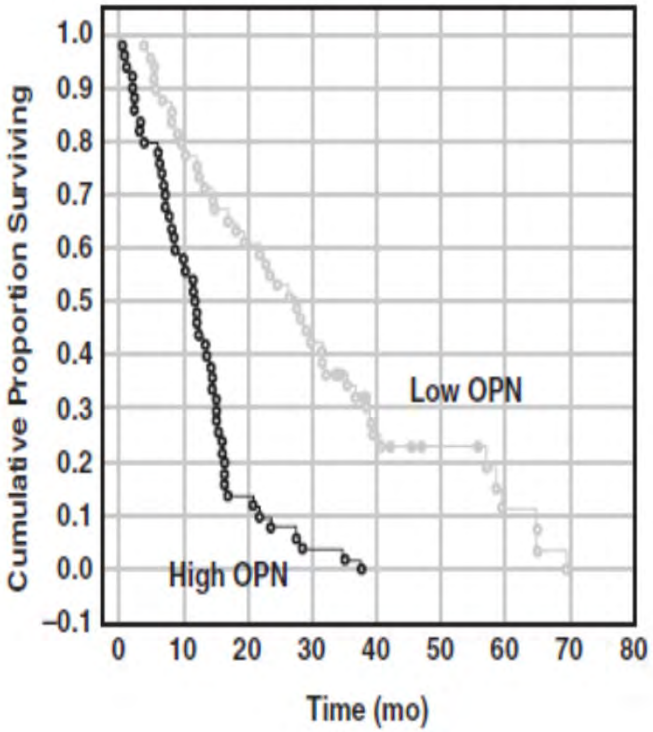


Int J Clin Exp Med. 2014 May 15;7(5):1289-96.

MPM, OPN, and Prognosis

Prognostic Role of Osteopontin Expression in Malignant Pleural Mesothelioma

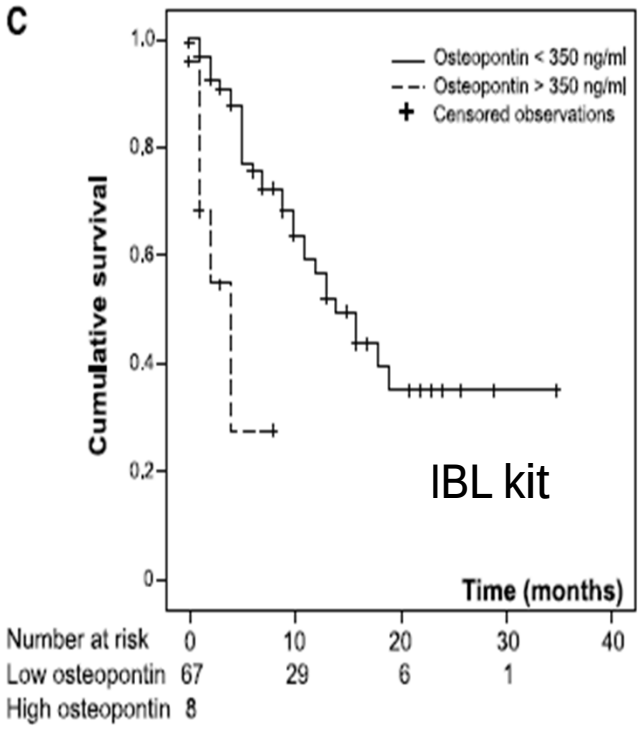
Susanna Cappia,[1] Luisella Righi, MD, PhD,[1] Dario Mirabelli, MD,[2] Paolo Ceppi,[1] Elisa Bacillo,[1] Francesco Ardissone, MD,[1] Luca Molinaro, MD,[1] Giorgio V. Scagliotti, MD,[1] and Mauro Papotti, MD[1]



Am J Clin Pathol 2008;130:58-64

Utility of Osteopontin and Serum Mesothelin in Malignant Pleural Mesothelioma Diagnosis and Prognosis Assessment

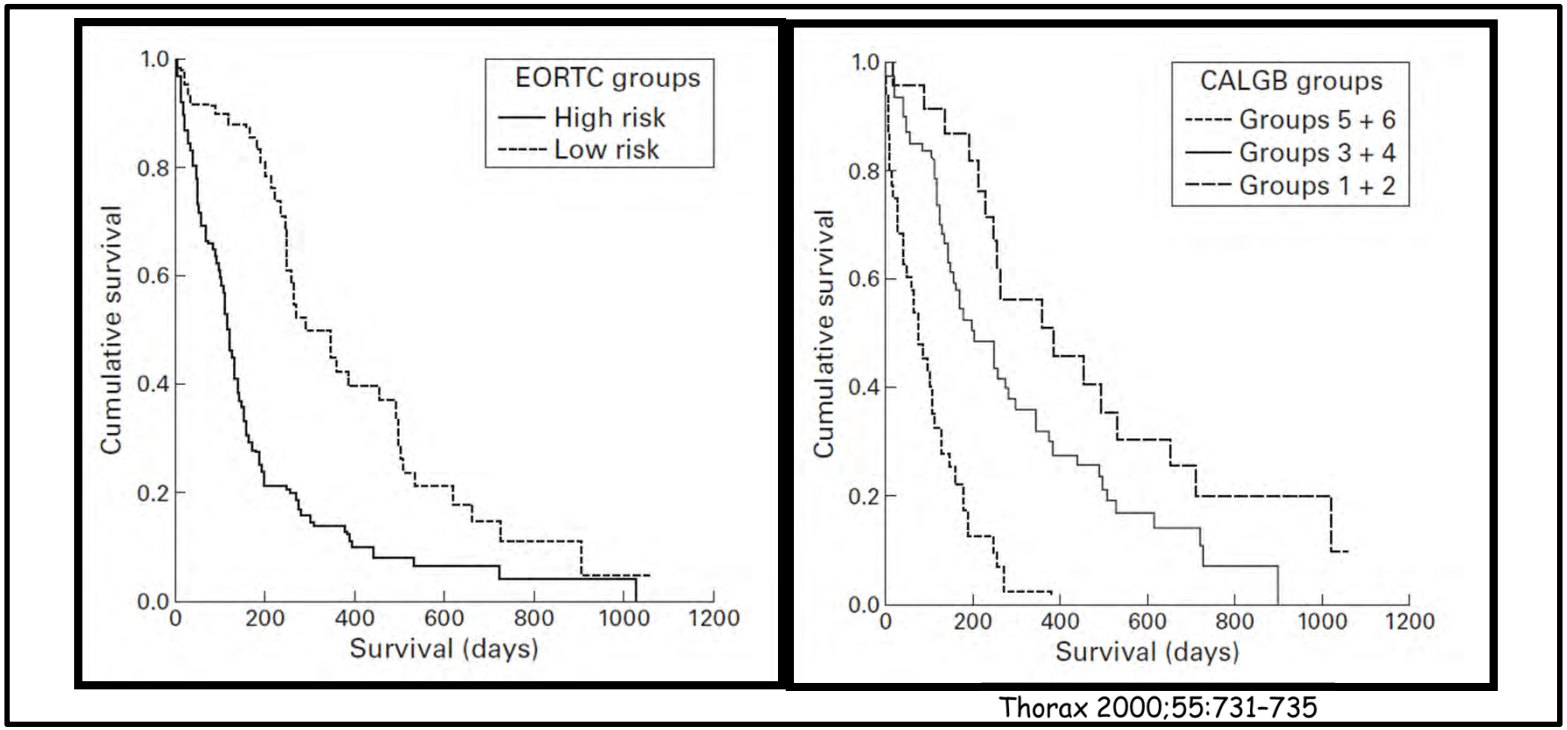
Bogdan-Dragos Grigoriu,[1,6] Arnaud Scherpereel,[1,2] Patrick Devos,[5] Bachar Chahine,[2] Marc Letourneux,[7] Pierre Lebailly,[8] Marc Grégoire,[9] Henri Porte,[3] Marie-Christine Copin,[4] and Philippe Lassalle[1]



Clin Cancer Res 2007;13(10) May 15, 2007

Can Plasma Biomarkers "add value" to already established Clinical Prognostic Indices?

- EORTC and CALGB Prognostic Indices are already an established clinical Prognostic Index for MPM



- ***Can any of the Biomarkers we have talked about add value to the EORTC Prognostic Index?***
  - Take the most relevant biomarkers in the literature and investigate that…..
- SMRP, Fibulin-3, Osteopontin
  - Discovery Set: 83 MPMs from NYU and Wayne State University
  - Blinded Validation Set: 111 MPMs from Princess Margaret Hospital

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Cohort	Variable	Adjusted for EORTC CPI HR (95% CI)	Adjusted for EORTC CPI *p* Value	Adjusted for CALGB CPI HR (95% CI)	Adjusted for CALGB CPI *p* Value
NYU/KCI (N=83)	log-osteopontin	2.70 (1.8-4.0)	<0.001	2.71 (1.8-4.1)	<0.001
	log-mesothelin	1.94 (1.4-2.8)	<0.001	1.63 (1.1-2.4)	0.009
PMCC (N=111)	log-osteopontin	3.53 (2.6-4.9)	<0.001	4.05 (2.9-5.6)	<0.001
	log-mesothelin	1.27 (1.1-1.5)	<0.001	1.40 (1.2-1.7)	<0.001

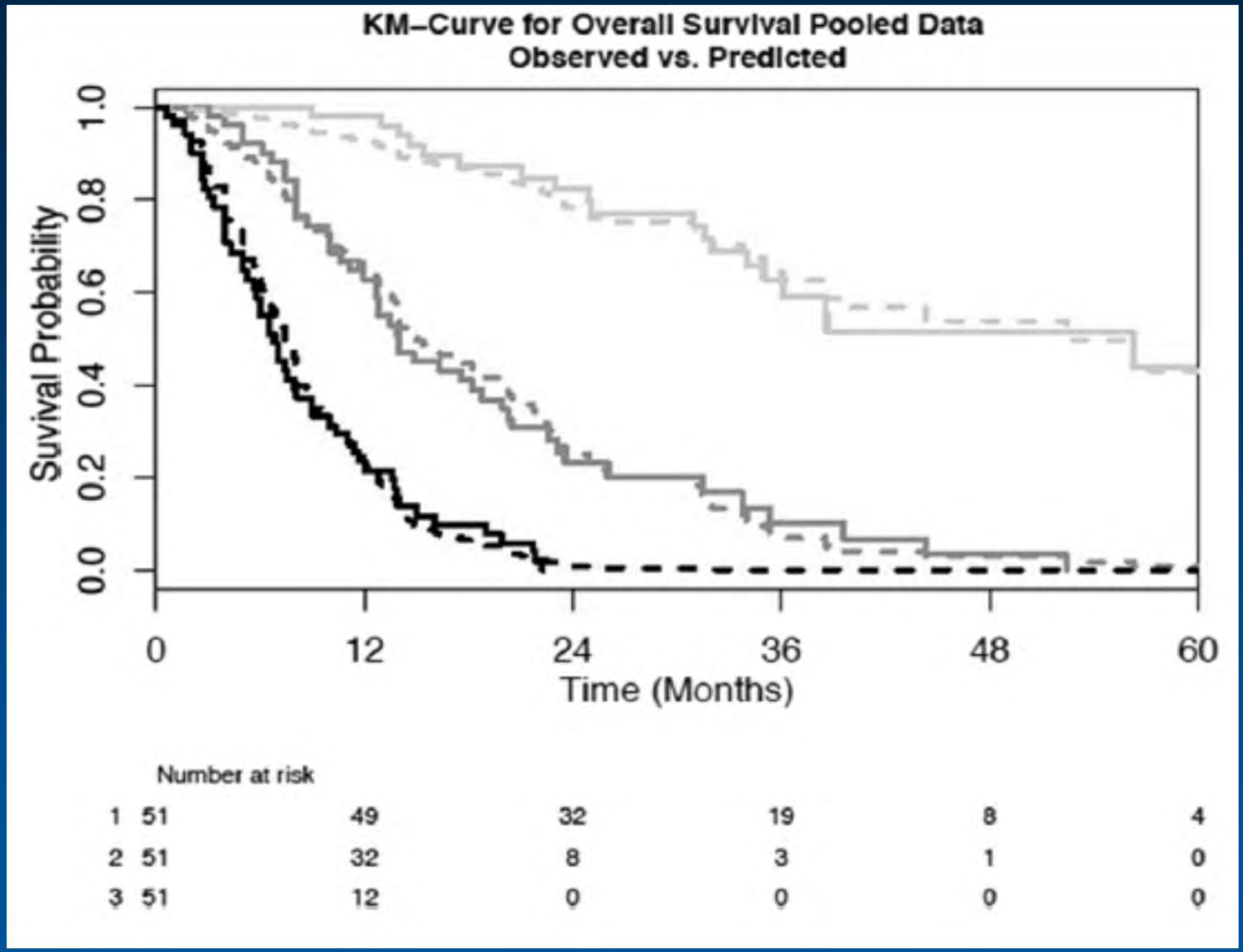
Discovery (NYU/KCI) Cohort

Prognostic Variables	EORTC CPI	CALGB CPI
CPI alone (for log-osteopontin analysis),[a] C-index (95% CI)	0.649 (0.59-0.70)	0.641 (0.59-0.69)
CPI alone (for log-mesothelin analysis),[a] C-index (95% CI)	0.645 (0.59-0.70)	0.640 (0.59-0.69)
CPI + log-osteopontin, C-index (95% CI)	0.767 (0.71-0.82)	0.763 (0.71-0.81)
CPI + log-mesothelin, C-index (95% CI)	0.692 (0.63-0.76)	0.724 (0.66-0.79)
Improvement in Harrell's C-indices when adding log-osteopontin[b]	0.118 (0.10-0.18)	0.122 (0.11-0.18)
Improvement in Harrell's C-indices when adding log-mesothelin[b]	0.045 (0.03-0.11)	0.084 (0.06-0.13)

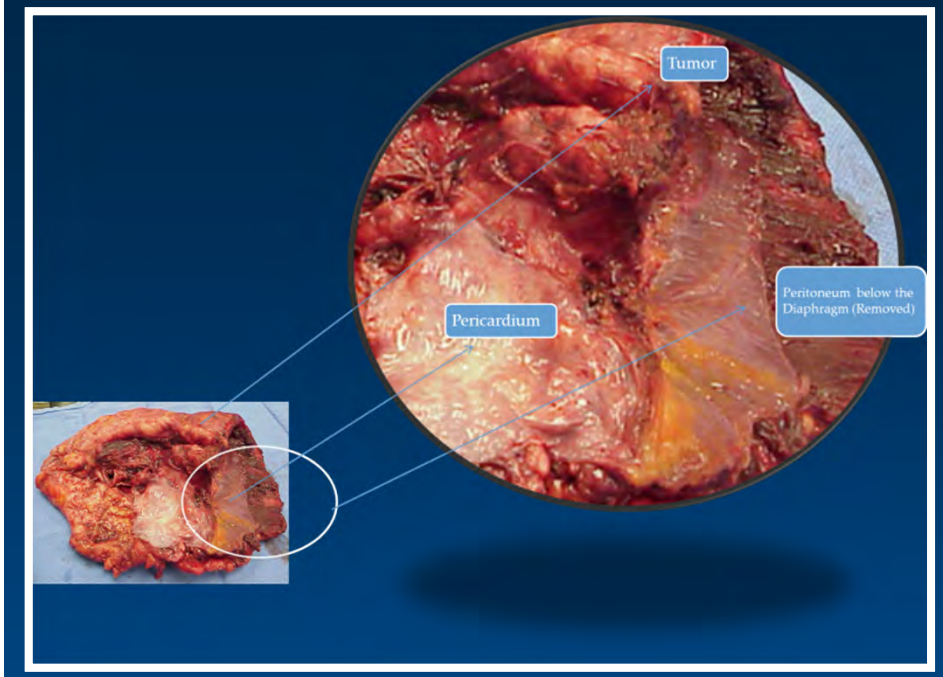
Validation (PMCC) Cohort

Prognostic Variables	EORTC CPI	CALGB CPI
CPI alone, C-index (95% CI)	0.596 (0.55-0.64)	0.602 (0.54-0.66)
CPI + log-osteopontin, C-index (95% CI)	0.811 (0.76-0.86)	0.781 (0.73-0.83)
CPI + log-mesothelin, C-index (95% CI)	0.650 (0.58-0.72)	0.649 (0.58-0.71)
Improvement in Harrell's C-indices when adding log-osteopontin[b]	0.216 (0.20-0.26)	0.179 (0.16-0.23)
Improvement in Harrell's C-indices when adding log-mesothelin[b]	0.054 (0.03-0.12)	0.047 (0.03-0.10)

Journal of Thoracic Oncology 2016: 6: 900-909



Journal of Thoracic Oncology 2016: 6: 900-909



37matched Peritonea and MPMs

RNA extraction

HG 1.0 ST Arrays
28,869 genes
• Candidate Genes for Secreted Proteins

DISCOVERY

Inquire GEO profiles

IN SILICO VALIDATION

ELISA determination in Plasma

FIRST ORDER VALIDATION

58 NYU MPM
96 NY Asbestos Exposed
30 "other" NYU Effusions

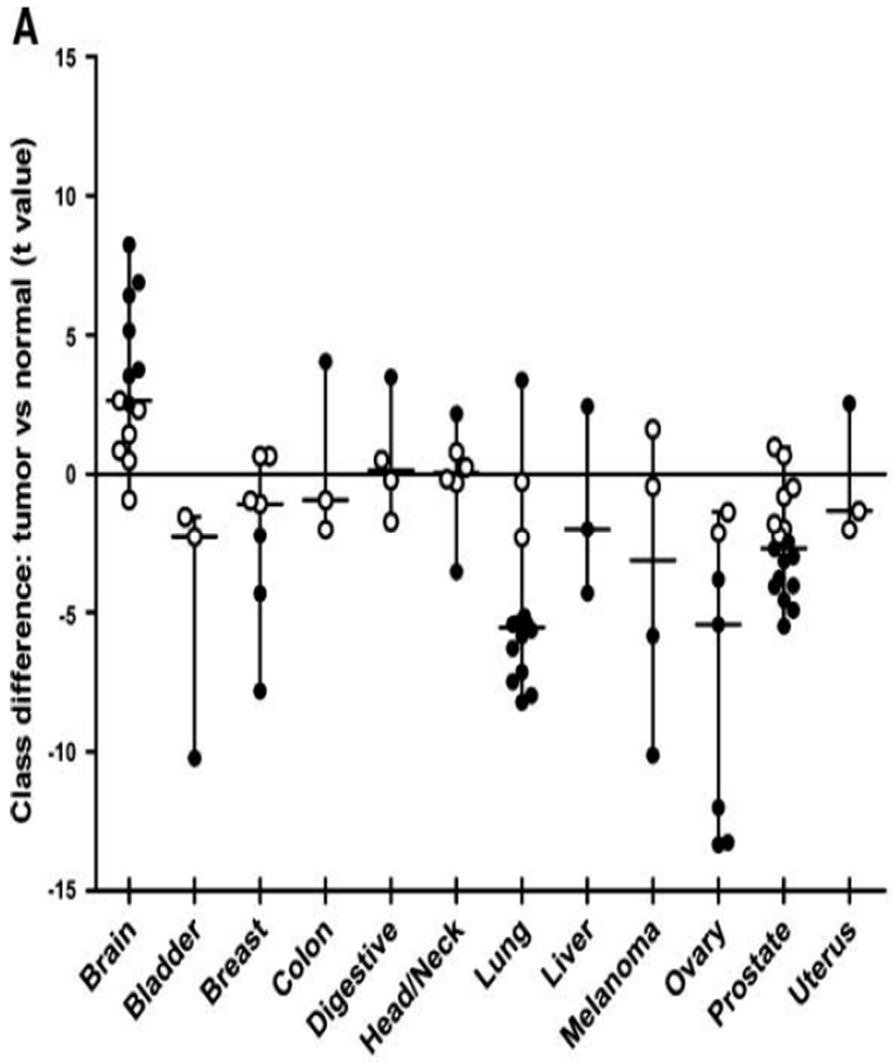
#/32,321	probe_id	symbols	annotation	ttest.paired.fdr	fold.change.paired
1	8178193	HLA-DRA	major histocompatibility complex, class II, DR alpha	4.49E-07	11.7560741
2	7896308	NA	NA	6.65E-08	11.58329688
3	7899480	SNORA73A	small nucleolar RNA, H/ACA box 73A	1.42E-09	10.8688601
4	7896561	NA	NA	4.88E-14	10.81826501
5	7895001	NA	NA	3.37E-13	10.33878988
6	7896258	NA	NA	2.55E-11	10.27347585
7	7894315	NA	NA	2.57E-09	10.22125339
8	7895101	NA	NA	6.47E-11	9.946499931
9	7892514	NA	NA	1.75E-11	9.499949191
10	7893543	NA	NA	9.36E-07	9.285996806
11	8096301	SPP1	secreted phosphoprotein 1	1.92E-13	9.191609924
12	7893424	NA	NA	2.98E-07	9.024945572
13	7892639	NA	NA	5.63E-10	8.992779777
14	7894264	NA	NA	1.86E-09	8.653358226
15	7895873	NA	NA	4.83E-11	8.482593475
16	8058765	FN1	fibronectin 1	9.94E-14	8.452420124
17	7892599	NA	NA	3.55E-10	8.332134431
18	7893103	NA	NA	2.65E-07	8.318946229
19	7895299	NA	NA	5.40E-10	8.227536834
20	7893173	NA	NA	2.43E-09	8.175192493
21	7896542	NA	NA	1.98E-12	8.148581397
22	7894516	NA	NA	2.07E-10	8.126757075
23	7894074	NA	NA	7.44E-10	8.096863972
24	7892972	NA	NA	1.02E-06	8.047826351
25	7895334	NA	NA	3.88E-10	7.989057851
26	7895012	NA	NA	9.76E-07	7.864289572
27	7895907	NA	NA	2.67E-10	7.846854849
28	7893782	NA	NA	4.29E-11	7.806424167
29	7894798	NA	NA	5.64E-09	7.805304933
30	7895985	NA	NA	6.39E-09	7.782686318
31	8091283	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	1.12E-14	7.760882762
32	7894044	NA	NA	3.08E-09	7.5976604
33	7943160	SCARNA9	small Cajal body-specific RNA 9	8.75E-11	7.557312113
34	8130867	THBS2	thrombospondin 2	7.47E-12	7.557021973
35	7894512	NA	NA	2.46E-08	7.512051025
36	8019762	NA	NA	9.75E-15	7.505448533
37	8052355	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	1.32E-09	7.357396759

Fibulin-3 (EFEMP1)

- One of the “short” fibulin members
- 2p16
- Extracellular glycoprotein
- Knockouts associated with early aging
- Missense mutation is the cause of *autosomal dominant macular degeneration*.
- Functional ligand of EGFR activating ***Akt- and mitogen-activated protein kinase (MAPK)-signal transduction.***

IASLC

Fibulin-3 Is Uniquely Upregulated in Malignant Gliomas and Promotes Tumor Cell Motility and Invasion



- Promotes invasion, adhesion, and migration
- Has a predominant isoform

Mol Cancer Res 2009;7(11):1756–70

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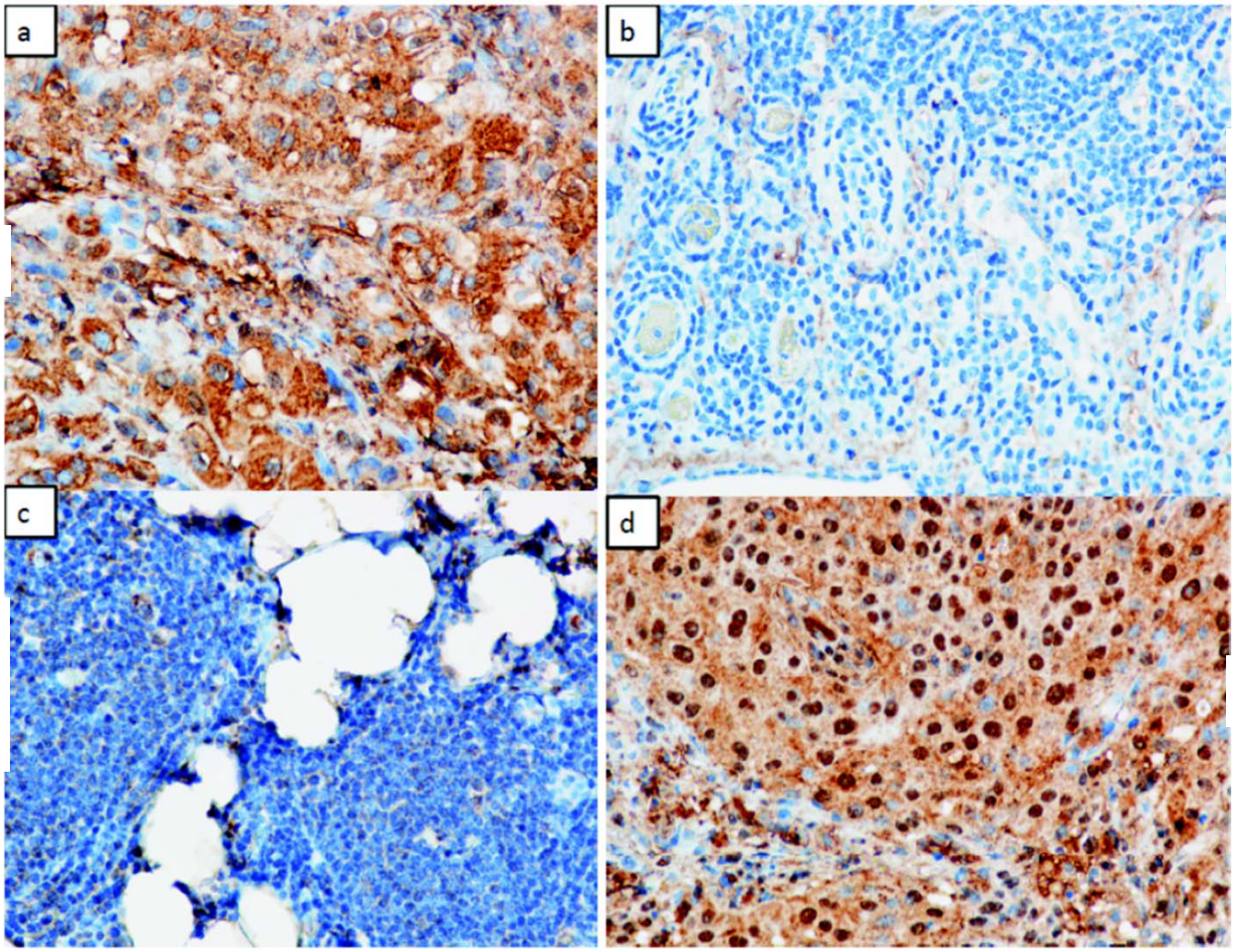
FBLN3 Immunohistochemistry

Epithelial MPM

Mesothelial/ Submesothelia Tissue



Mesothelial/ Submesothelia Tissue

Epithelial MPM

N Engl J Med 2012 Oct 11;367(15):1417-27.

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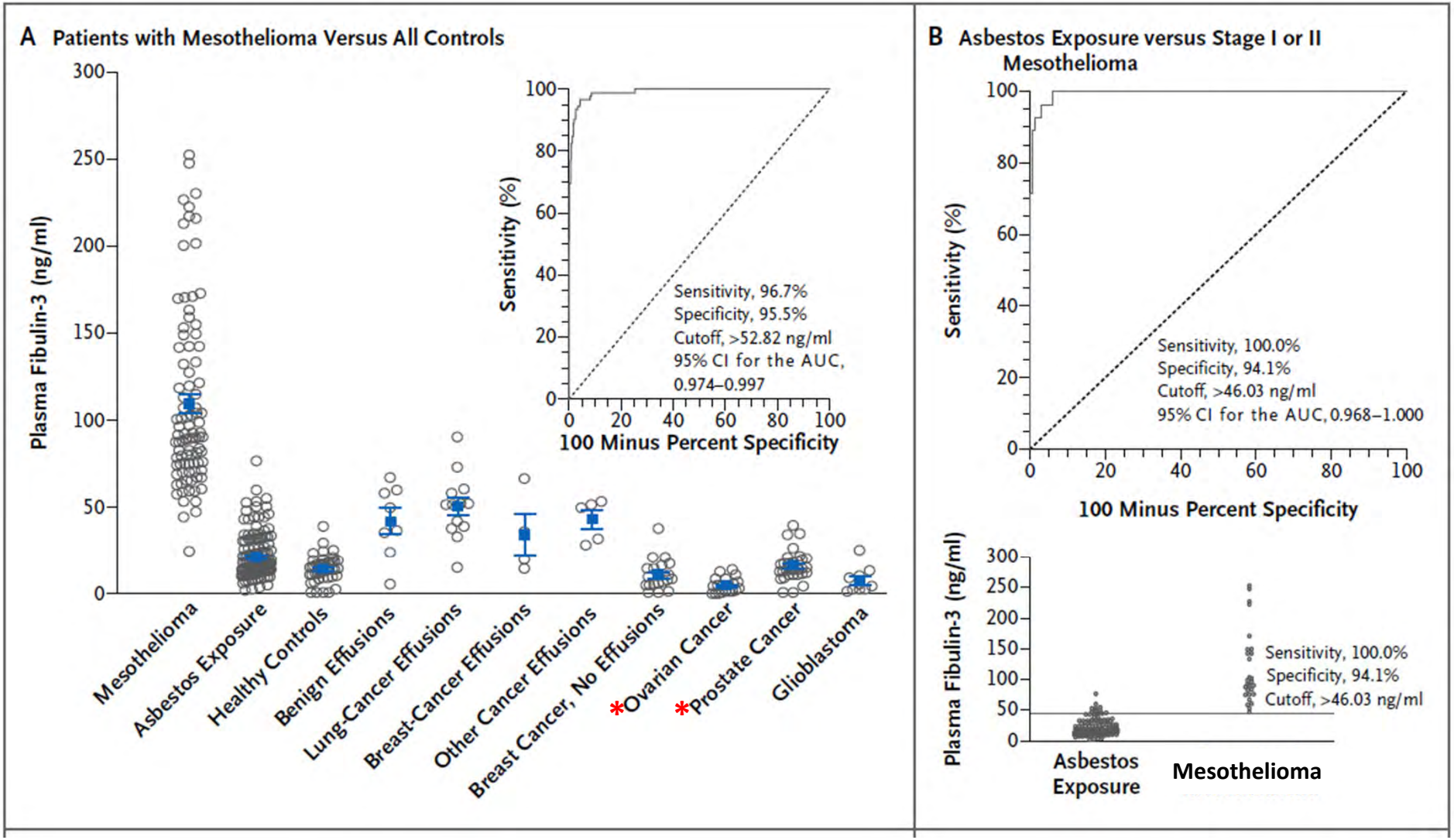
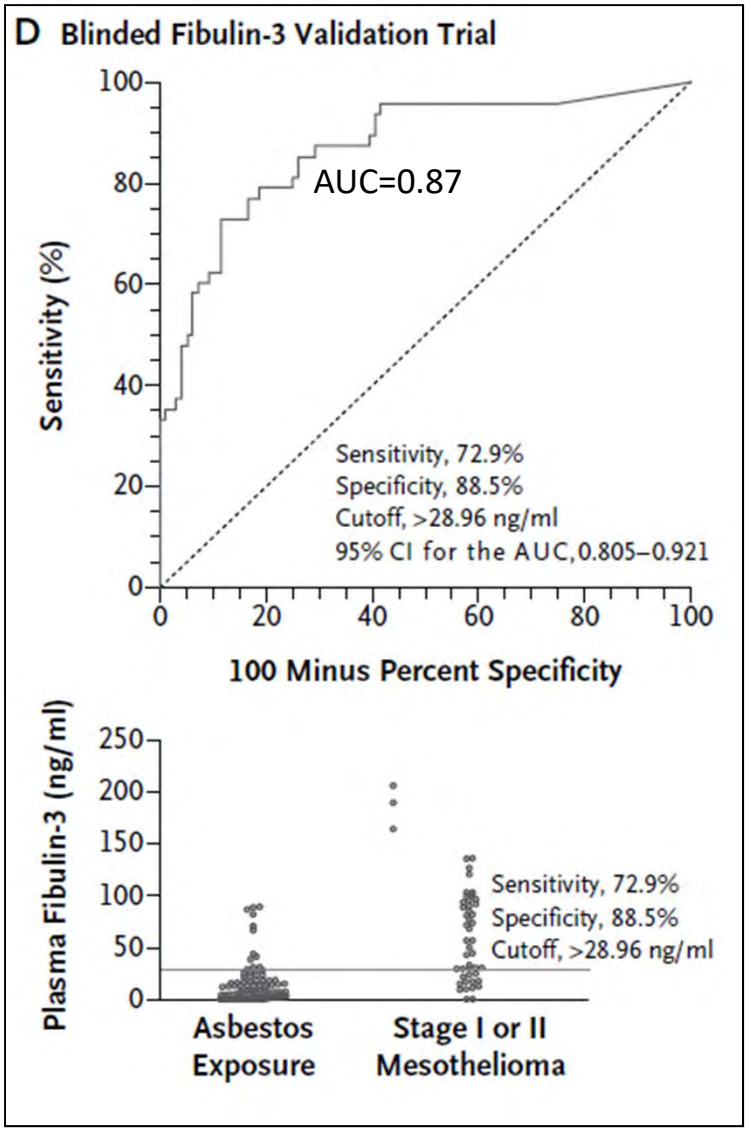
Plasma FBLN3 Can Discriminate MPM From Other Conditions And Is Elevated In Early Stage MPM



N Engl J Med 2012 Oct 11;367(15):1417-27.

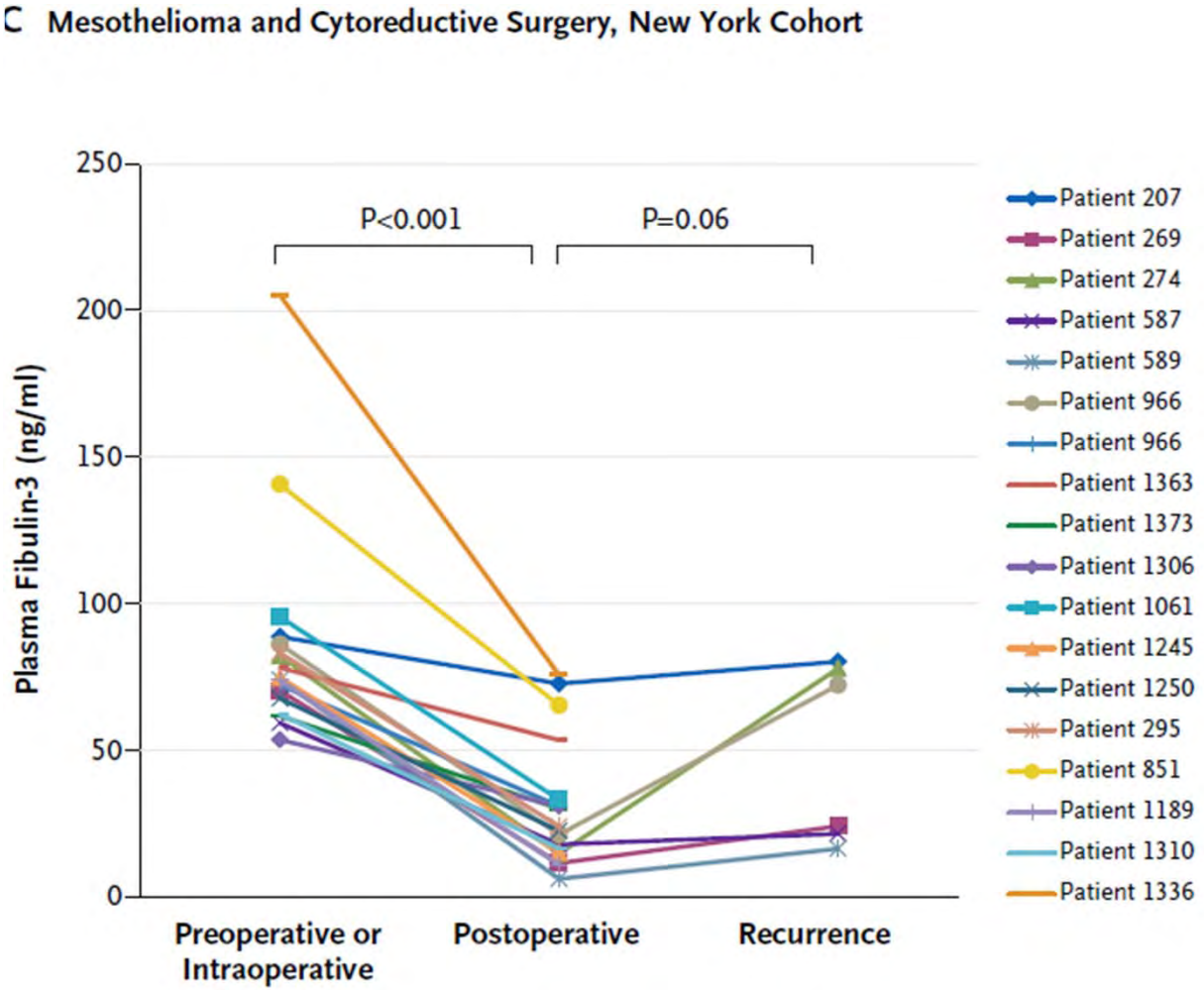
Plasma FBLN3 Blinded Validation: The Princess Margaret Cohort

Variable	Toronto Cohort	
	Patients with Mesothelioma (N=48)	Asbestos-Exposed Persons (N=96)
Demographic and clinical characteristics		
Age — yr	64±1	65±1
Sex — no.		
Male	37	94
Female	11	2
Race — no.†		
White	NA	NA
Other	NA	NA
Asbestos exposure — no. (%)	32 (67)	96 (100)
Current or previous smoker — no.		
Yes	24	62
No	24	34
Fibulin-3 level		
Plasma fibulin-3 — ng/ml	66.4±7.2	13.9±2.1



N Engl J Med 2012 Oct 11;367(15):1417-27.

Plasma FBLN3 Falls After MPM Cytoreduction and Rises at Recurrence



N Engl J Med 2012 Oct 11;367(15):1417-27.

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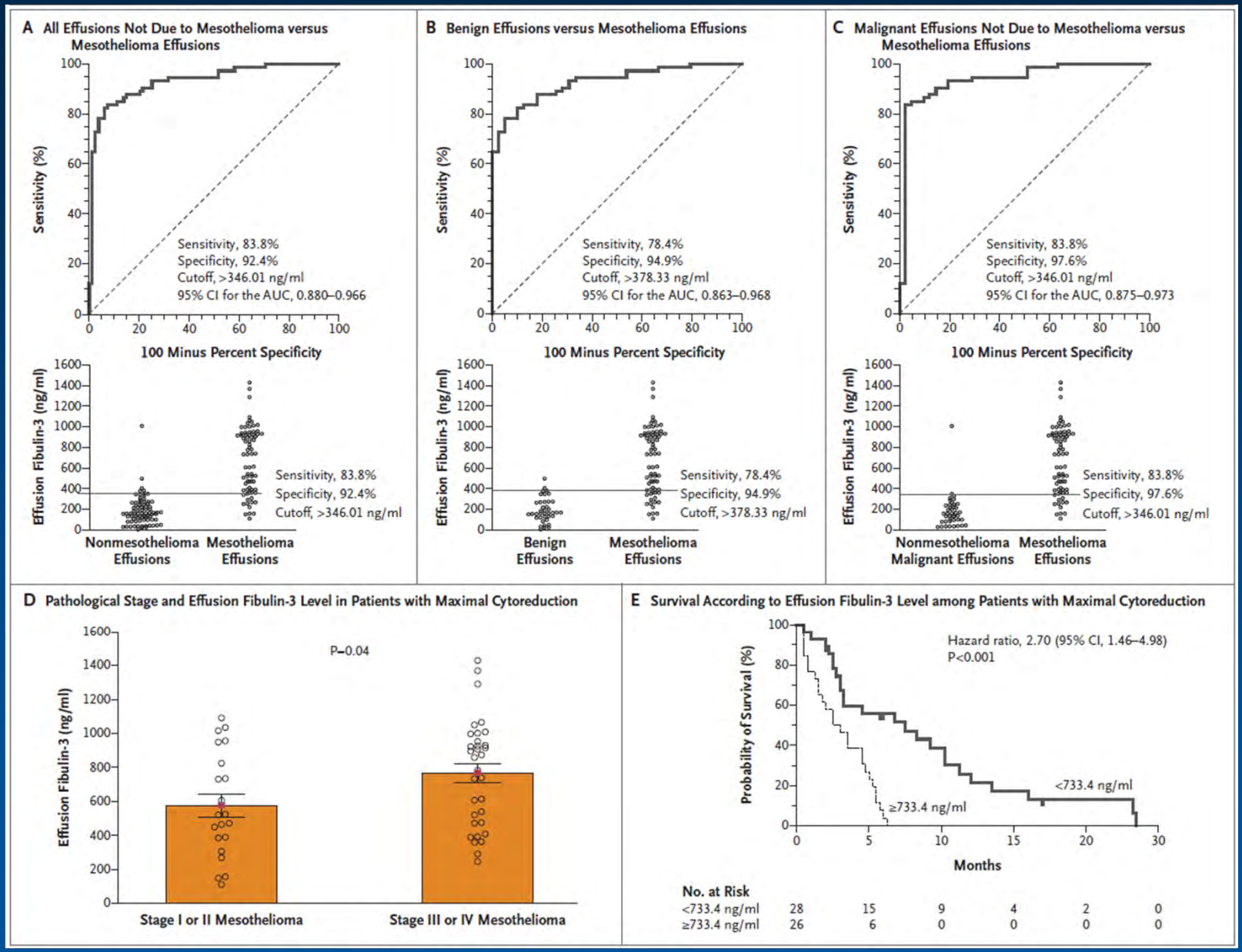
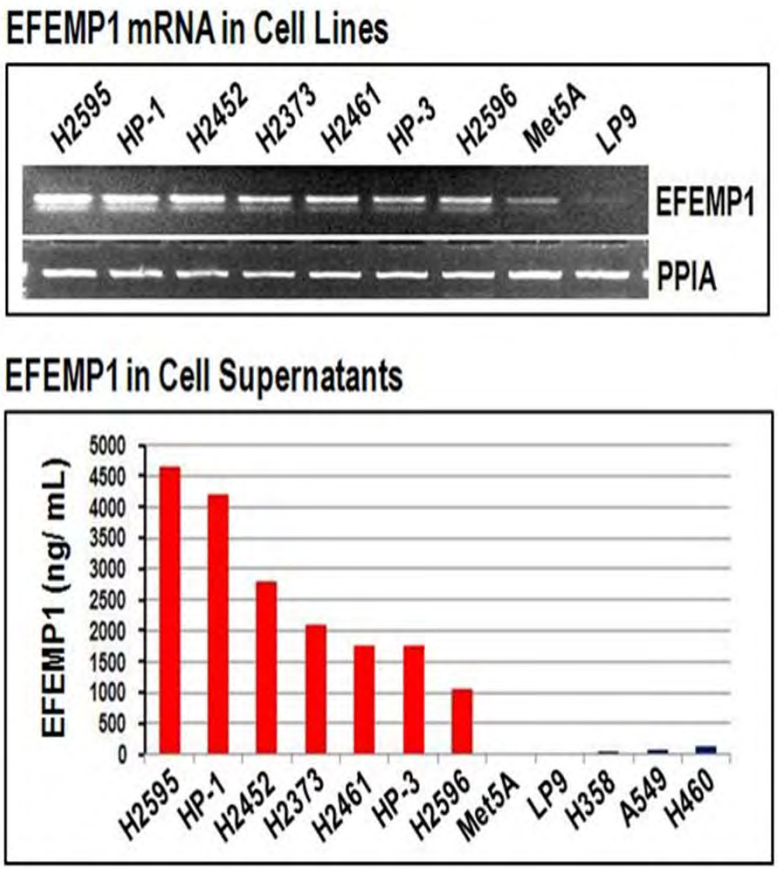
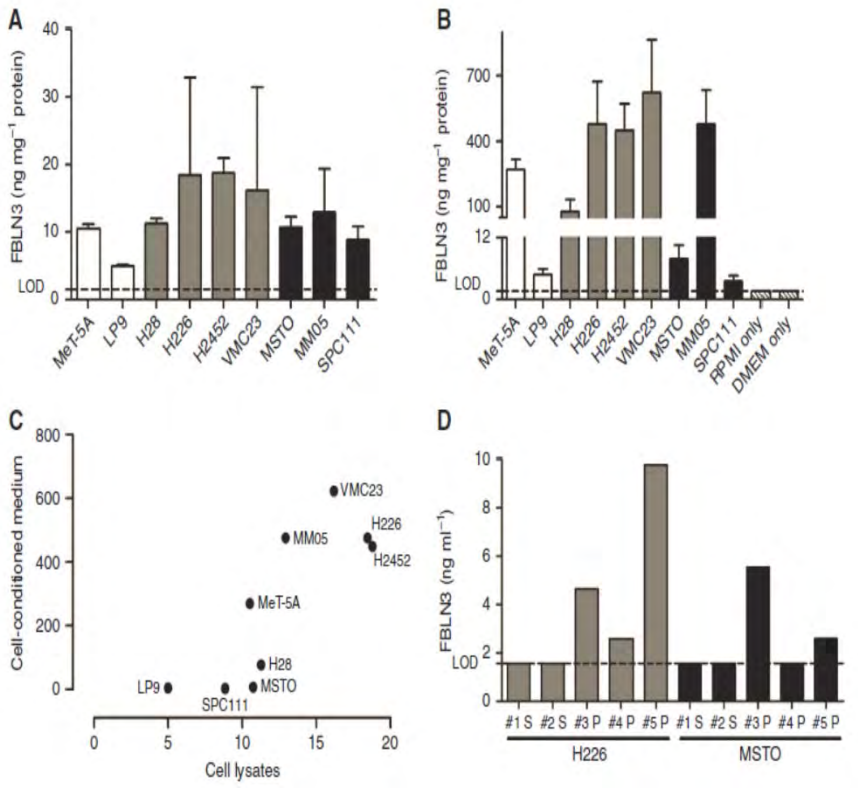
What about Effusion Fibulin-3 Levels?



N Engl J Med 2012 Oct 11;367(15):1417-27.

EFEMP1 Message/Media Protein is present in all MPM cell lines and not in Tag/Tert Transformed mesothelial cell lines or lung cancer cell lines





British Journal of Cancer (2015), 1–7 | doi: 10.1038/bjc.2015.286

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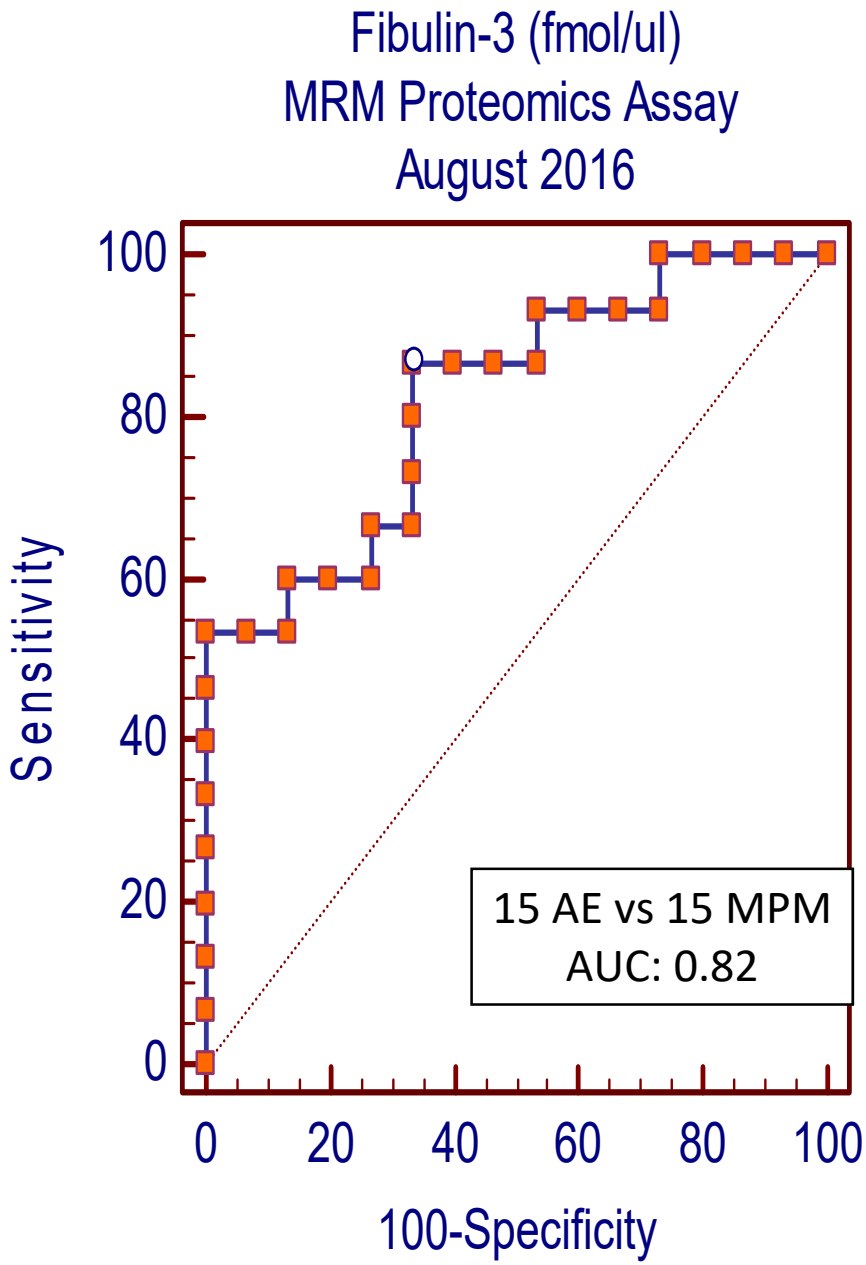
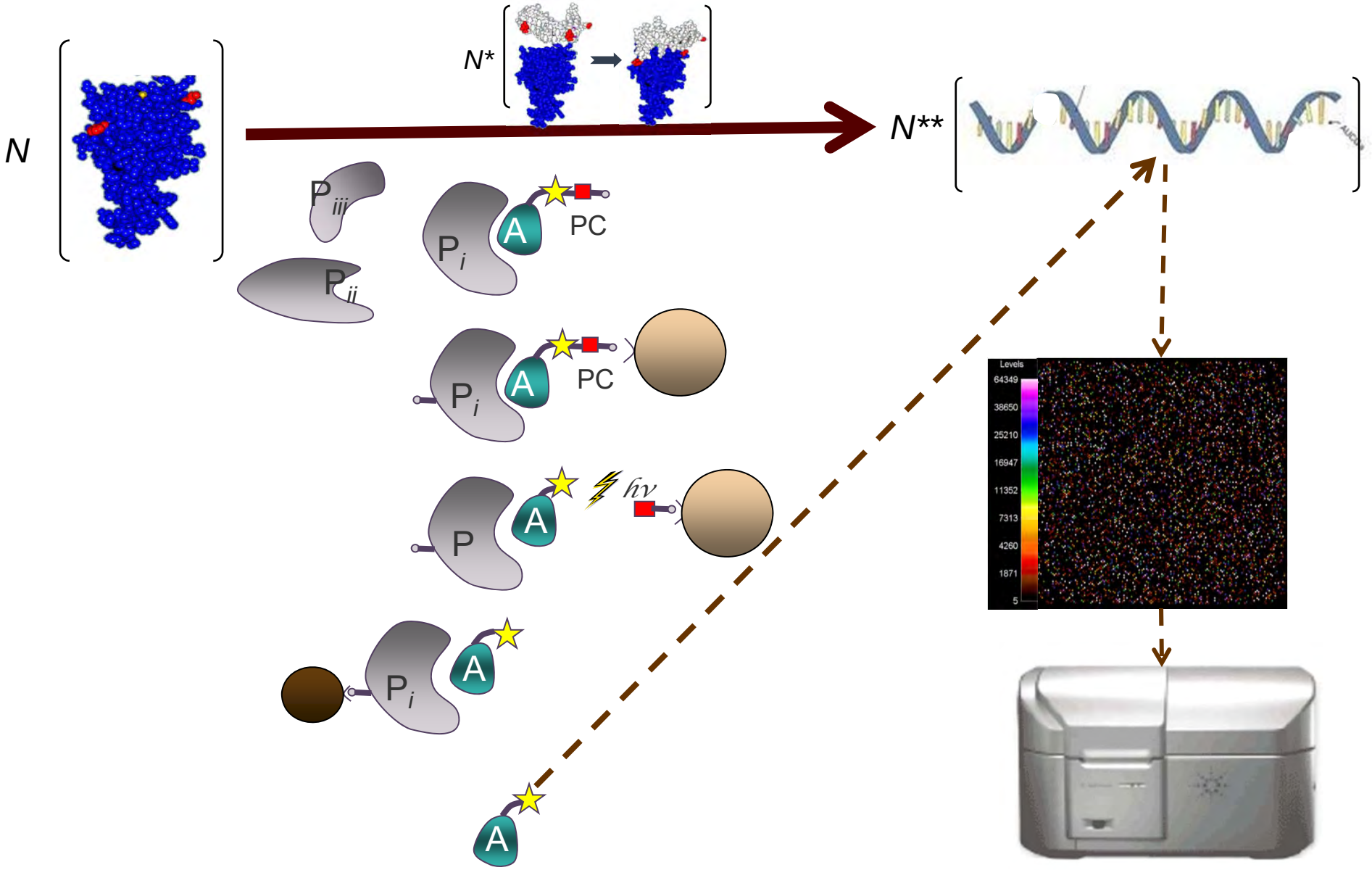
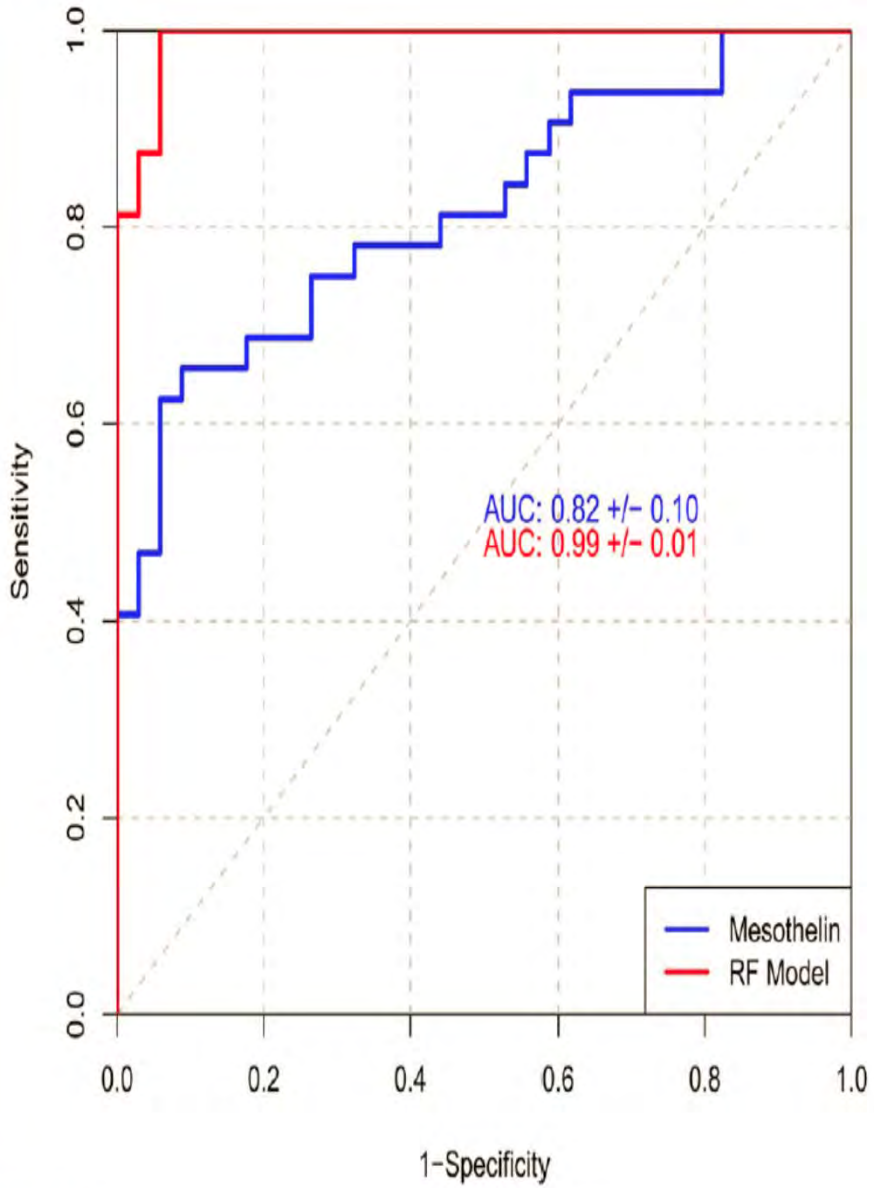
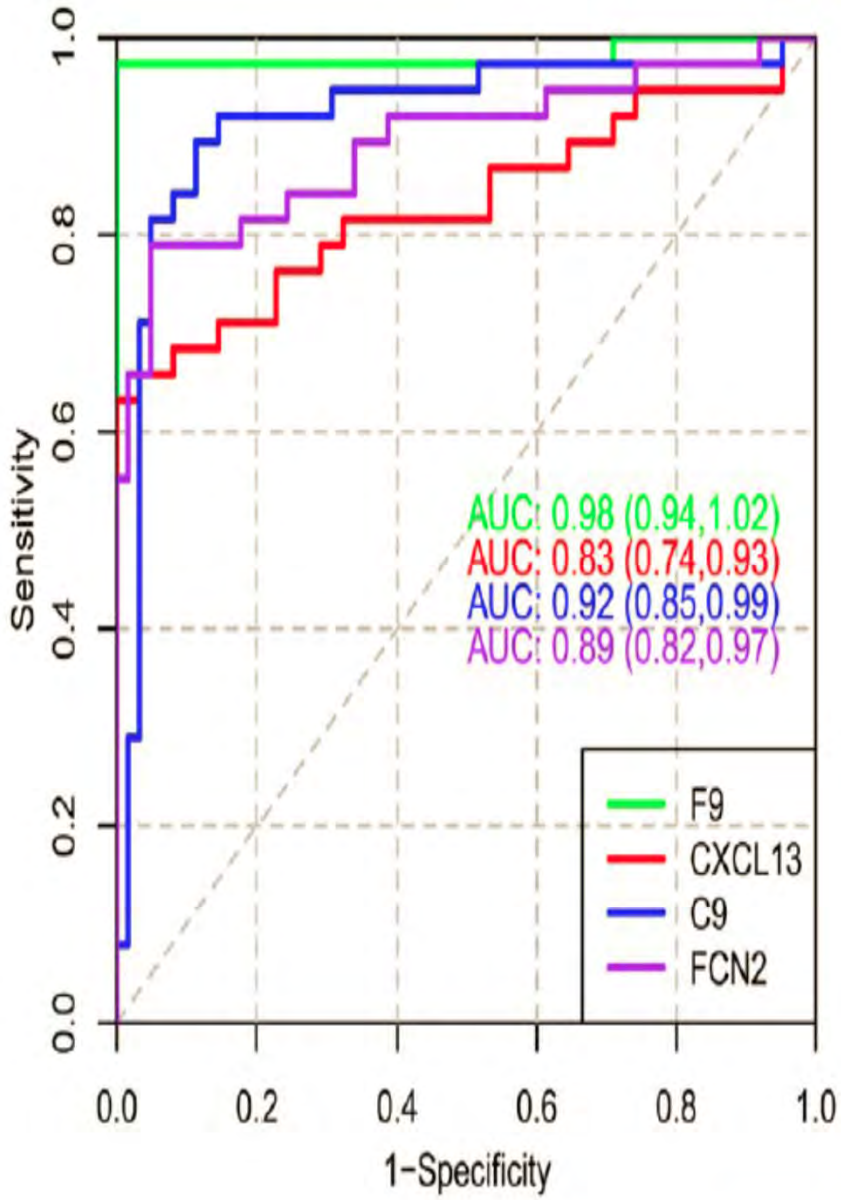

Fibulin-3 (fmol/ul)
MRM Proteomics Assay
August 2016
Sensitivity
100
80
60
40
20
0
0
20
40
60
80
100
100-Specificity
15 AE vs 15 MPM
AUC: 0.82

Biomarker Discovery with SomaLogic Slow Off Rate Modified Aptamers Platform

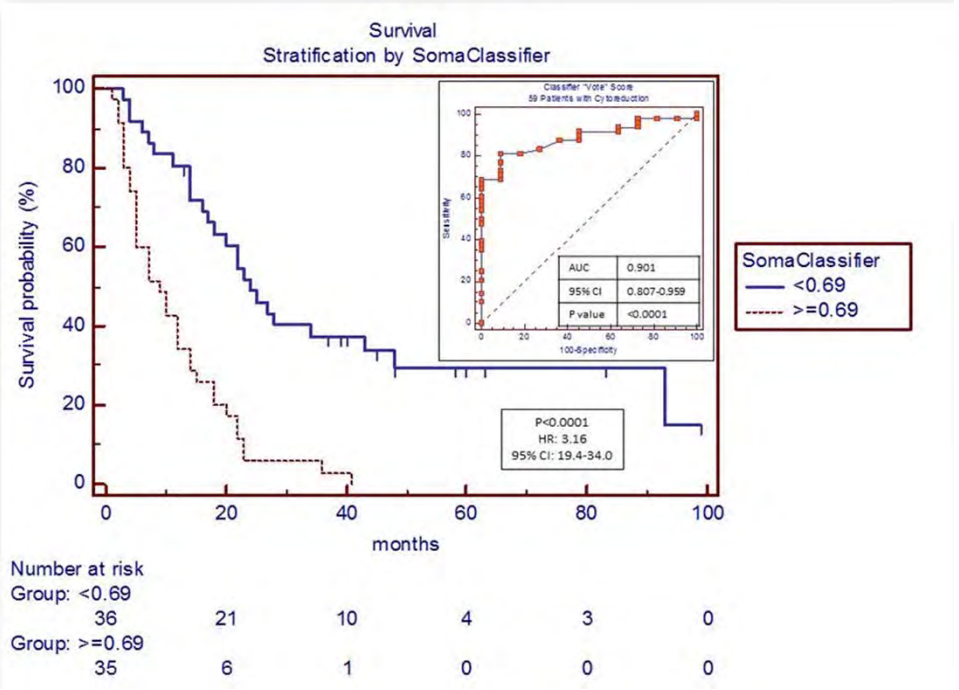



Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUC: 0.82 +/- 0.10
AUC: 0.99 +/- 0.01
Mesothelin
RF Model


Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
AUC: 0.98 (0.94,1.02)
AUC: 0.83 (0.74,0.93)
AUC: 0.92 (0.85,0.99)
AUC: 0.89 (0.82,0.97)
F9
CXCL13
C9
FCN2

Future Plans: SomaLogic

- EDRN Competetive Renewal
  - Develop a luminex based SomaMer 13 assay in the NYU Laboratory for further validation
  - Combine the SomaMer 13 with a novel Fibulin 3 SomaMer to create a more specific SomaMer 14 assay



  - Validate the SomaMer 13 assay for prognostic potential

Biomarkers of Asbestos Exposure

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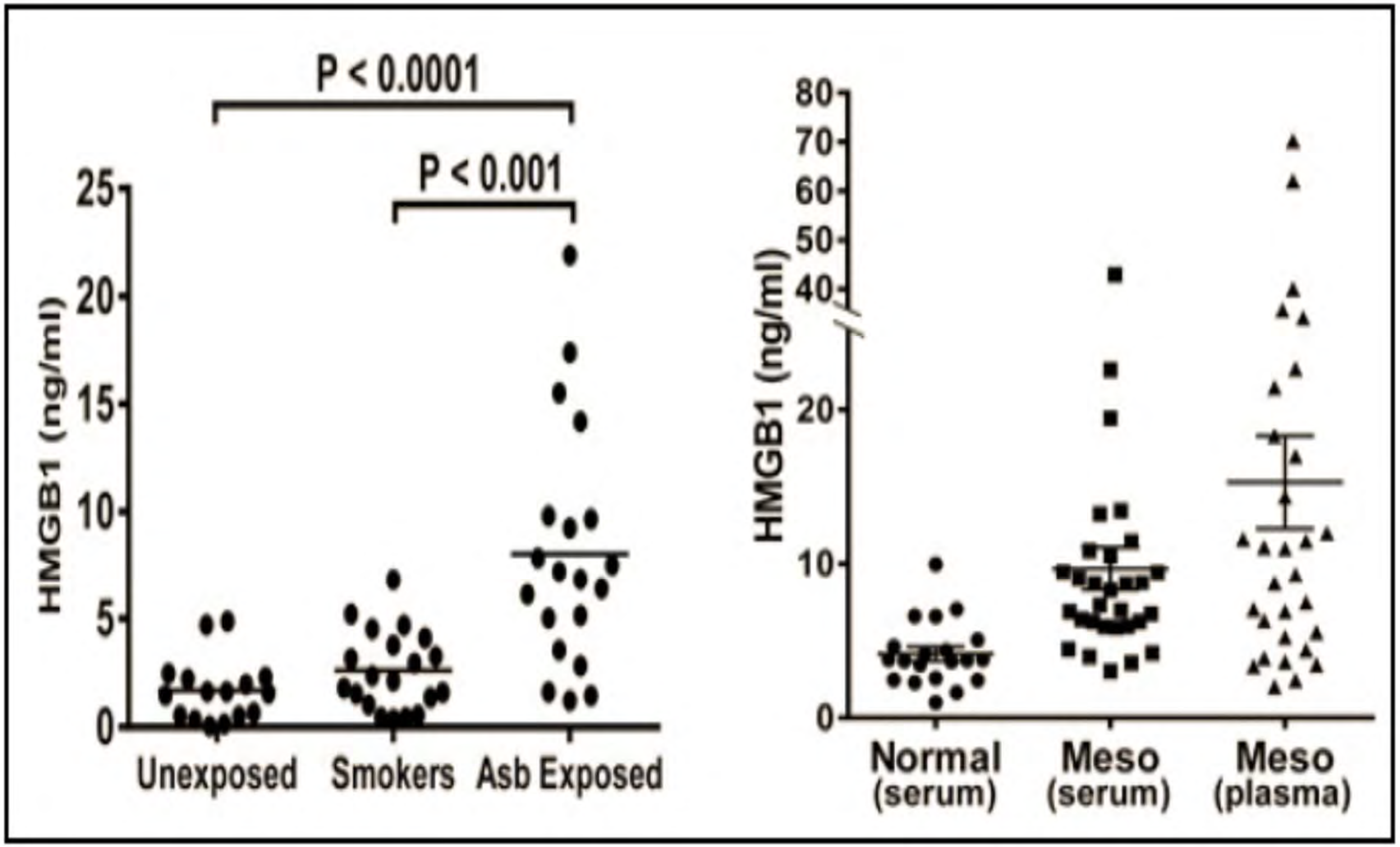
HMGB1, Asbestos Exposure, and MPM



Proc Natl Acad Sci U S A. 2010 Jul 13;107(28):12611

Other HMGB1 Studies…..

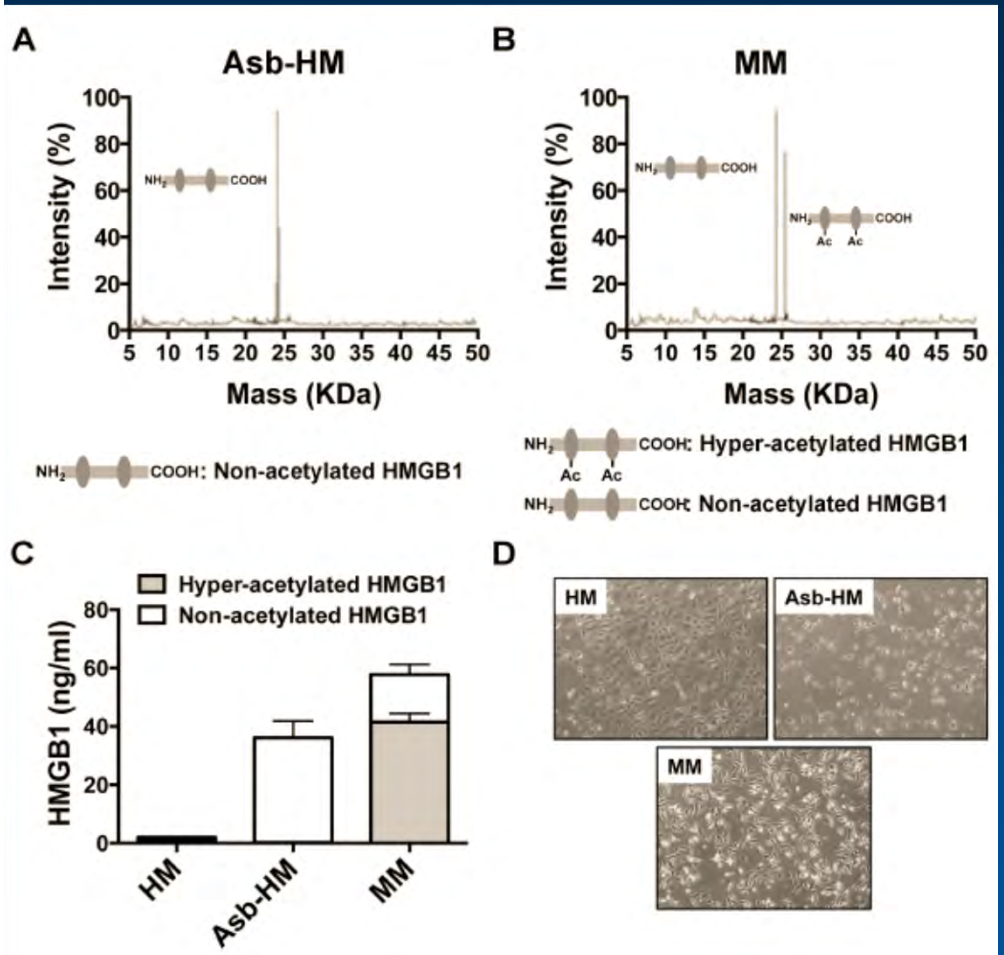
JEM

Brief Definitive Report

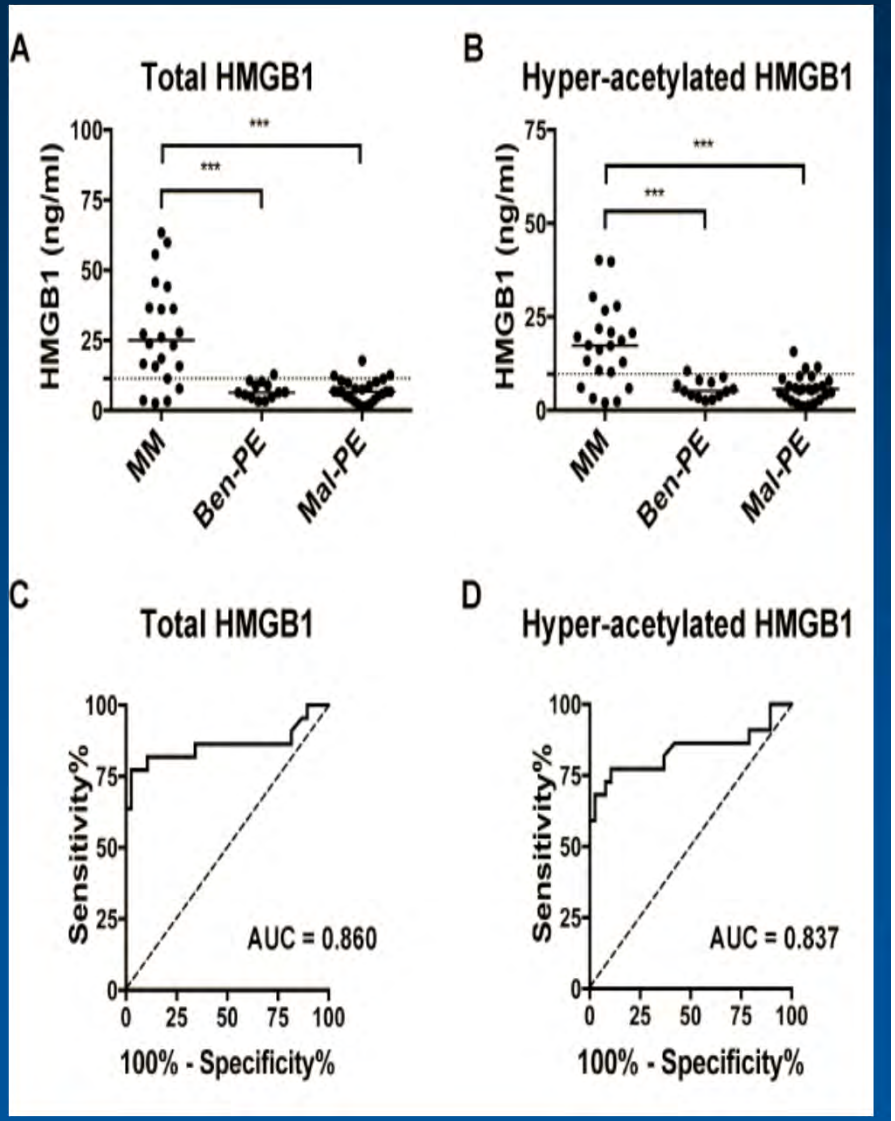
Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release

Emilie Venereau,[1] Maura Casalgrandi,[2] Milena Schiraldi,[3] Daniel J. Antoine,[4] Angela Cattaneo,[1] Francesco De Marchis,[1] Jaron Liu,[5] Antonella Antonelli,[5] Alessandro Preti,[2] Lorenzo Raeli,[3] Sara Samadi Shams,[5] Huan Yang,[6] Luca Varani,[3] Ulf Andersson,[7] Kevin J. Tracey,[6] Angela Bachi,[1] Mariagrazia Uguccioni,[3] and Marco E. Bianchi[1,5]

HMGB1 Isoforms are Different Between asbestos-exposed Mesothelial cells and Mesothelioma



HMGB1 Isoforms are Different Between asbestos-exposed pipe fitters and Mesothelioma



Conclusions

- Exploration of blood based biomarkers may lead to novel biomarkers of asbestos exposure as well as the development of mesothelioma.
- Blood based biomarkers may also help in determining which pleural mesotheliomas are most aggressive, altering therapeutic decisions.
- Validation of these markers is necessary before their use in the clinic.

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Thanks to…

- NYU Thoracic Lab
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  - Joe Levin BS
  - Nathalie Hirsch BA
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  - Stephen Levin MD
- DMCC
  - Mark Thornquist PhD
- Carbone Laboratory, University of Hawaii
  - Michele Carbone MD, PhD
  - Haining Yang, PhD
- Antoine Laboratory, University of Liverpool
- University of Toronto
  - Ming-Sound Tsao MD
  - Geoffrey Liu MD
- NCI Early Detection Research Network
- CDC National Mesothelioma Virtual Bank
- NCI TCGA Mesothelioma
- Department of Defense CDMRP
- SomaLogic
  - Rachel Ostroff PhD

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QUESTIONS