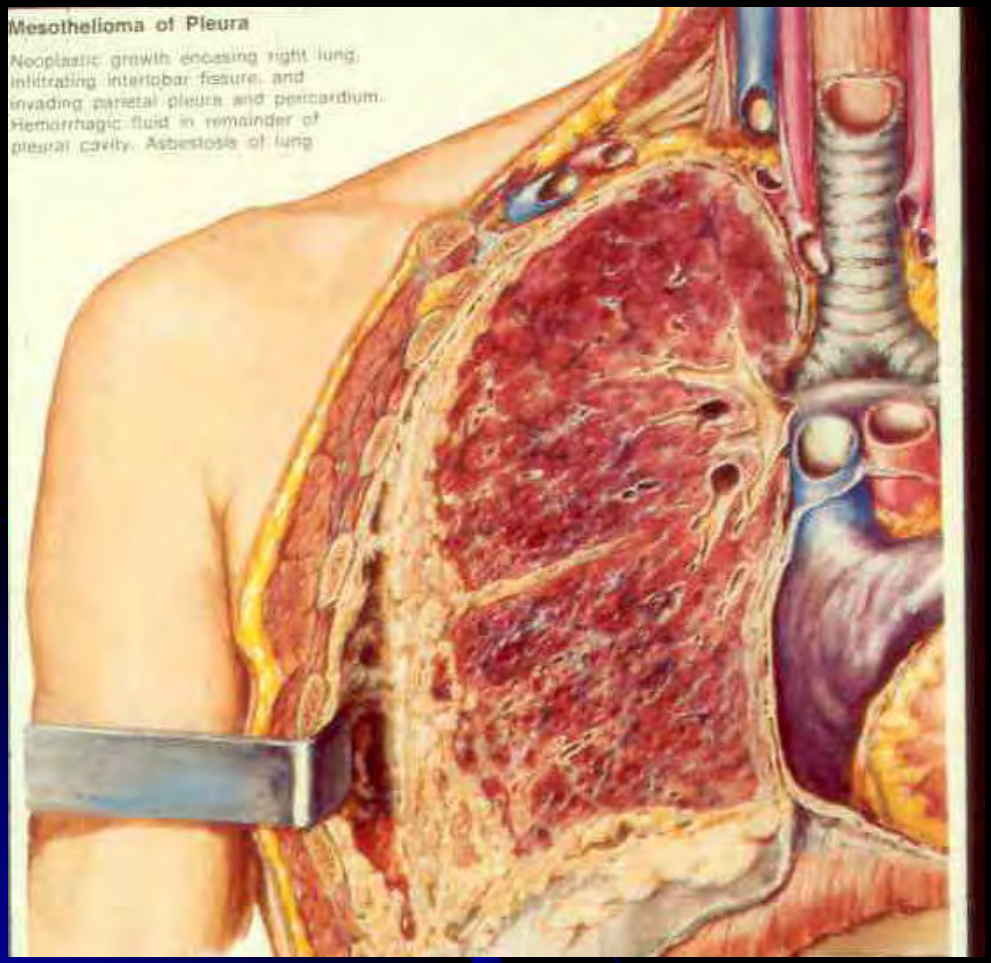
Advances in Treatment of Malignant Pleural Mesothelioma: *A Reason for Hope*

Daniel H. Sterman, M.D.
Associate Professor of Medicine and Surgery
Co-Director, PENN Mesothelioma and Pleural Program
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania
USA

Action Mesothelioma Day
Liverpool, UK
July 5, 2013

Malignant Mesothelioma:



- Tumor of Serosal Surfaces of Pleura (80%), Peritoneum, Pericardium, Tunica Vaginalis
- Median Survival Varies Depending on Cell Type
- Morbidity Related To Local Invasion Of Vital Structures, Not Metastatic Disease

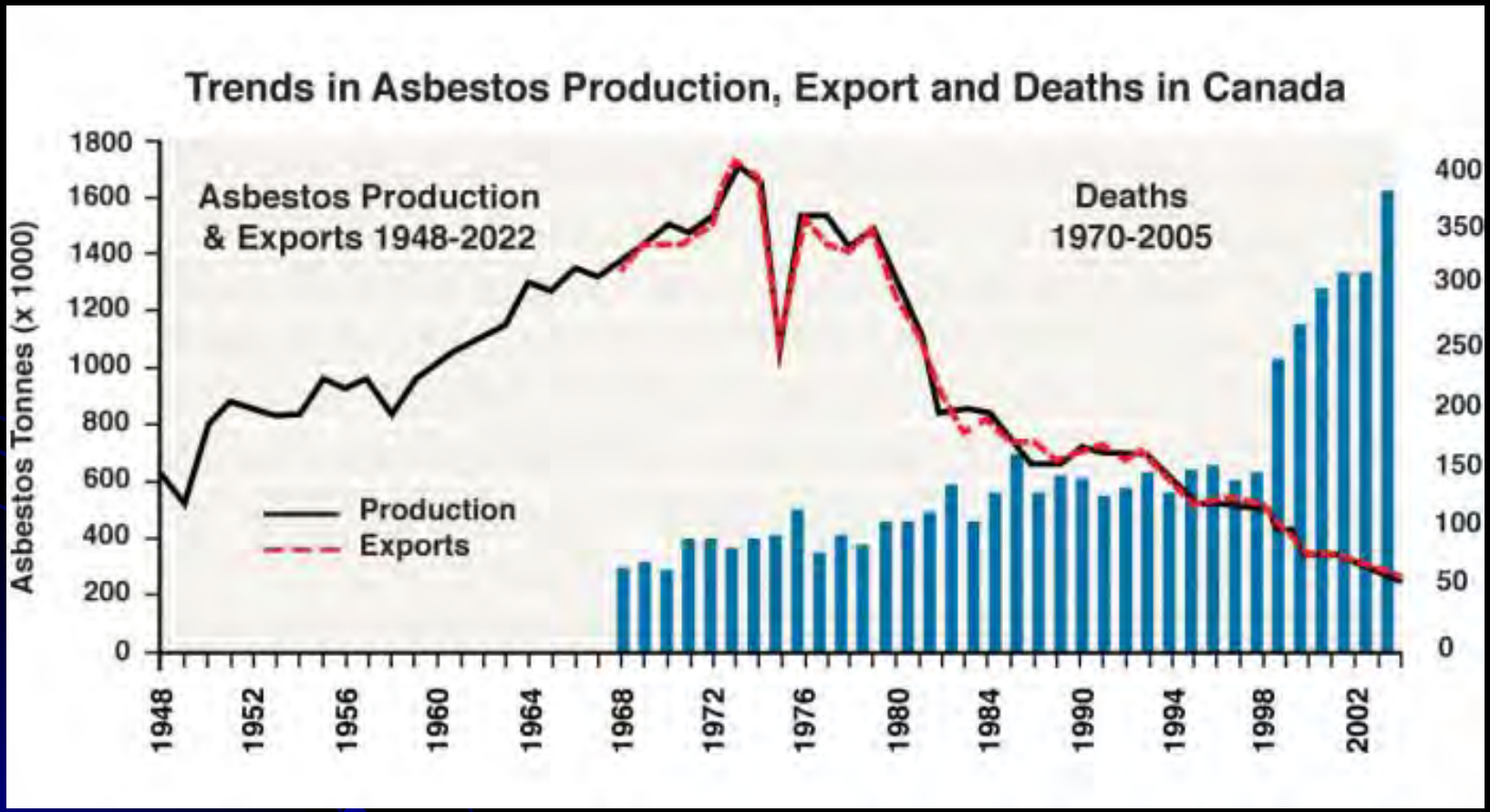
Mesothelioma Pathogenesis:

~80% of Pleural Mesotheliomas Are Associated With A Known Exposure To Asbestos

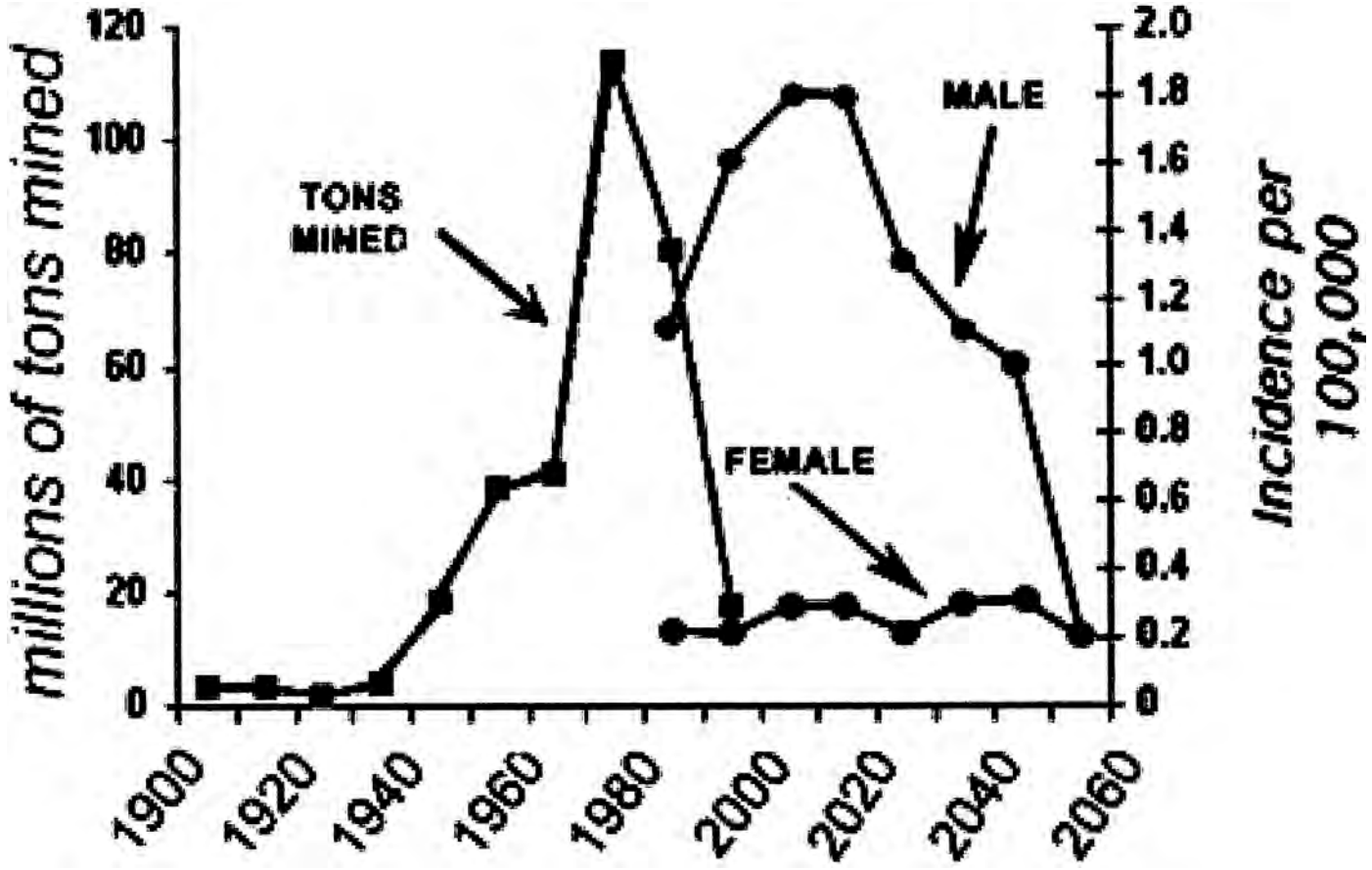
Occupational and Environmental Exposures

- Most exposures occupational: Asbestos mining, processing; Pipefitting /insulation; shipbuilding; brake repair; construction; plumbing
- Other exposures: Environmental (near asbestos site); Contact with clothes from exposed workers; Contaminated buildings.

Mesothelioma and Asbestos in North America



Asbestos production and mesothelioma incidence: asbestos production in the United States in the last century and mesothelioma incidence from 1980 projected to 2055

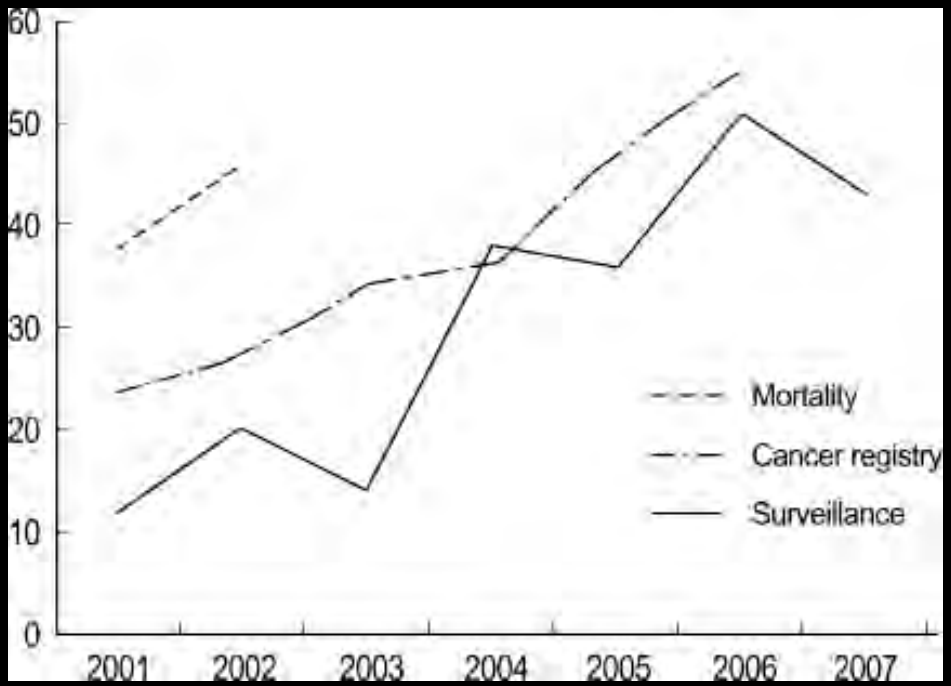


Cugell, D. W. et al. Chest 2004;125:1103-1117

CHEST
The Cardiopulmonary and Critical Care Journal

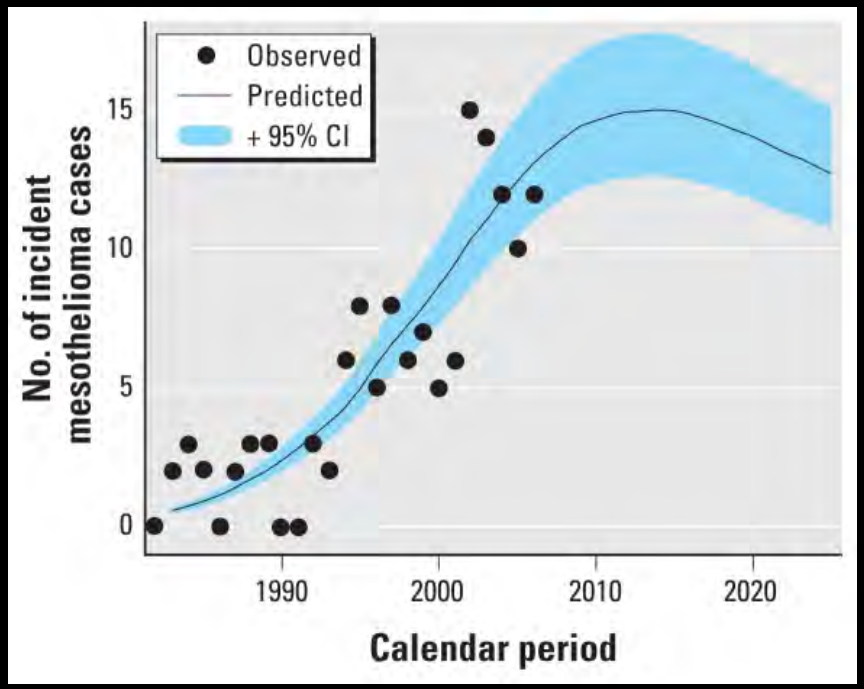
Increases in Mesothelioma in Asia

Trends of Malignant Mesothelioma Incidence in Korea



J Korean Med Sci. 2009; 24(3): 363–367.

Projected Mesothelioma cases – Hong Kong males 2002–2027



Environ Health Perspect. 2010; 118(3): 382–386.

Genes Have Been Identified That Predispose Individuals To Develop Mesothelioma

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]

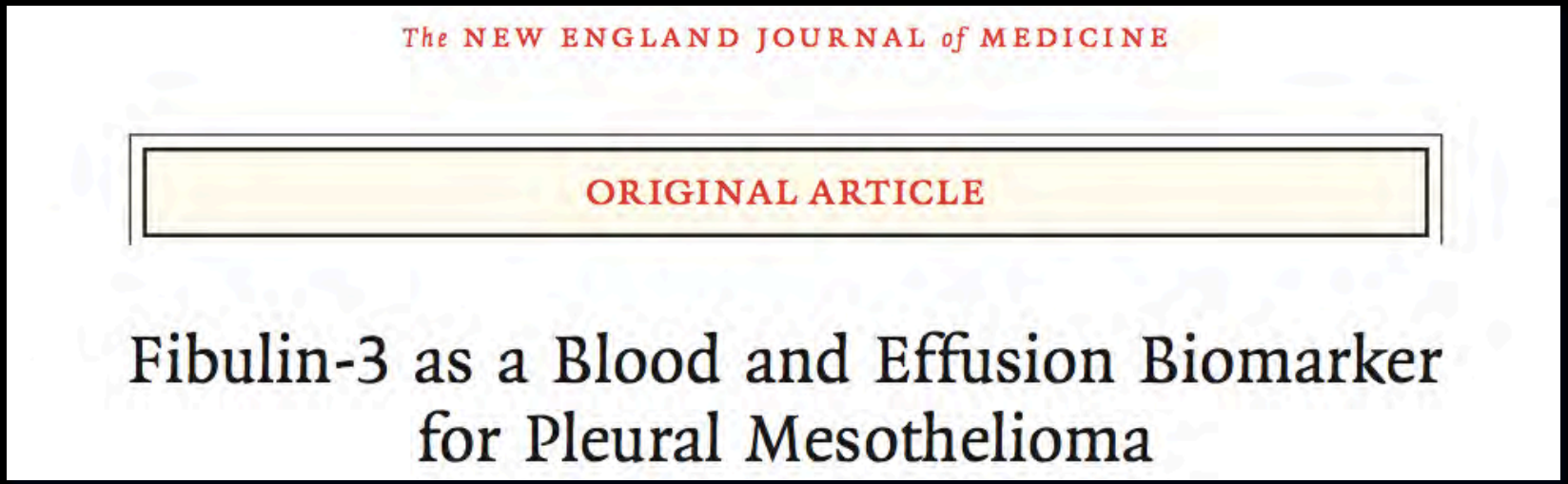
The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma

Matthew Bott[1,2], Marie Brevet[1], Barry S Taylor[3], Shigeki Shimizu[1], Tatsuo Ito[1], Lu Wang[1], Jenette Creaney[4], Richard A Lake[4], Maureen F Zakowski[1], Boris Reva[3], Chris Sander[3], Robert Delsite[5], Simon Powell[5], Qin Zhou[6], Ronglai Shen[6], Adam Olshen[6], Valerie Rusch[2] & Marc Ladanyi[1,7]

Nature Genetics, 2011

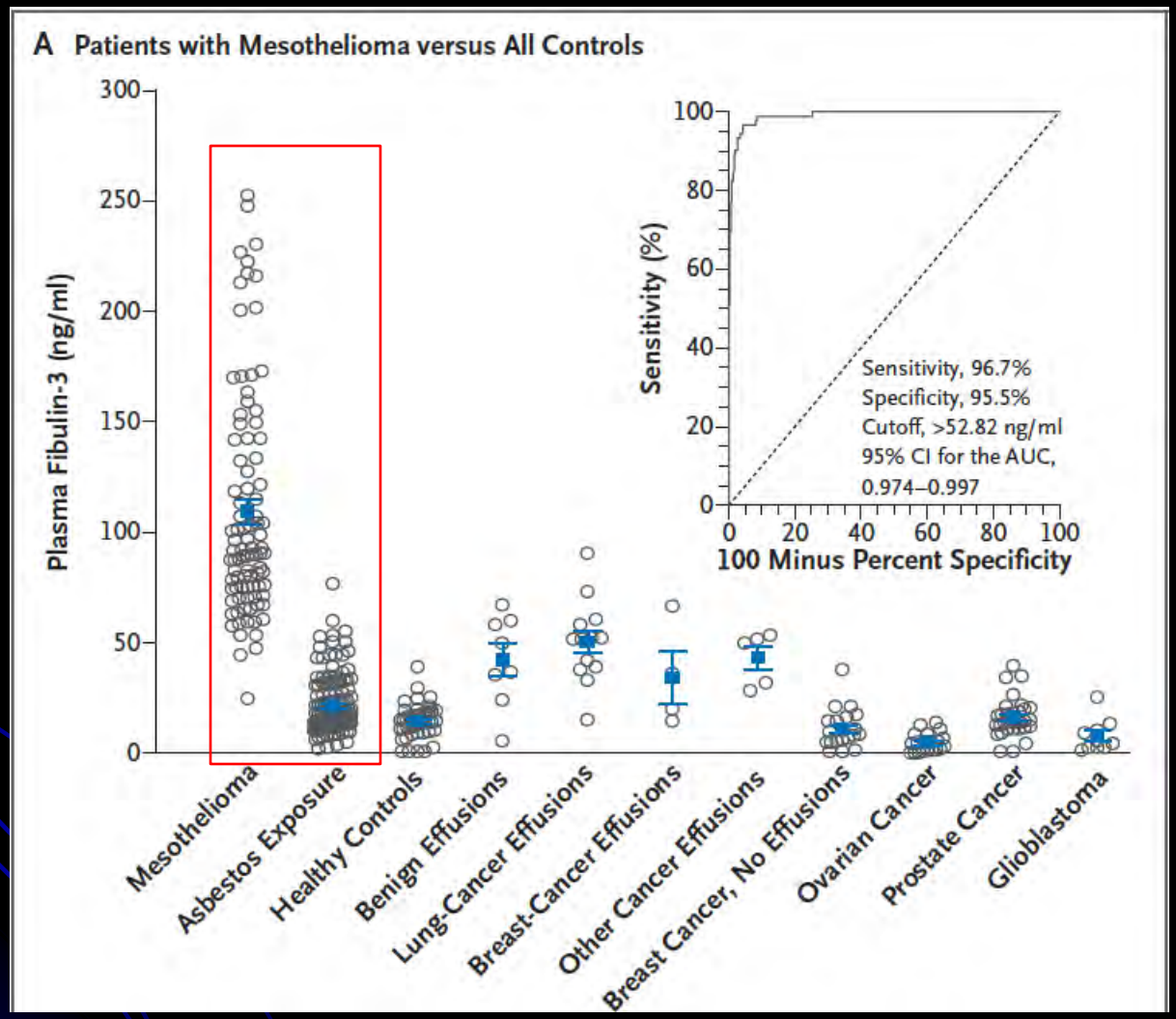
Advances in Early Detection of Mesothelioma

(New York University, Mount Sinai, Univ. of Hawaii, Univ. of Toronto)

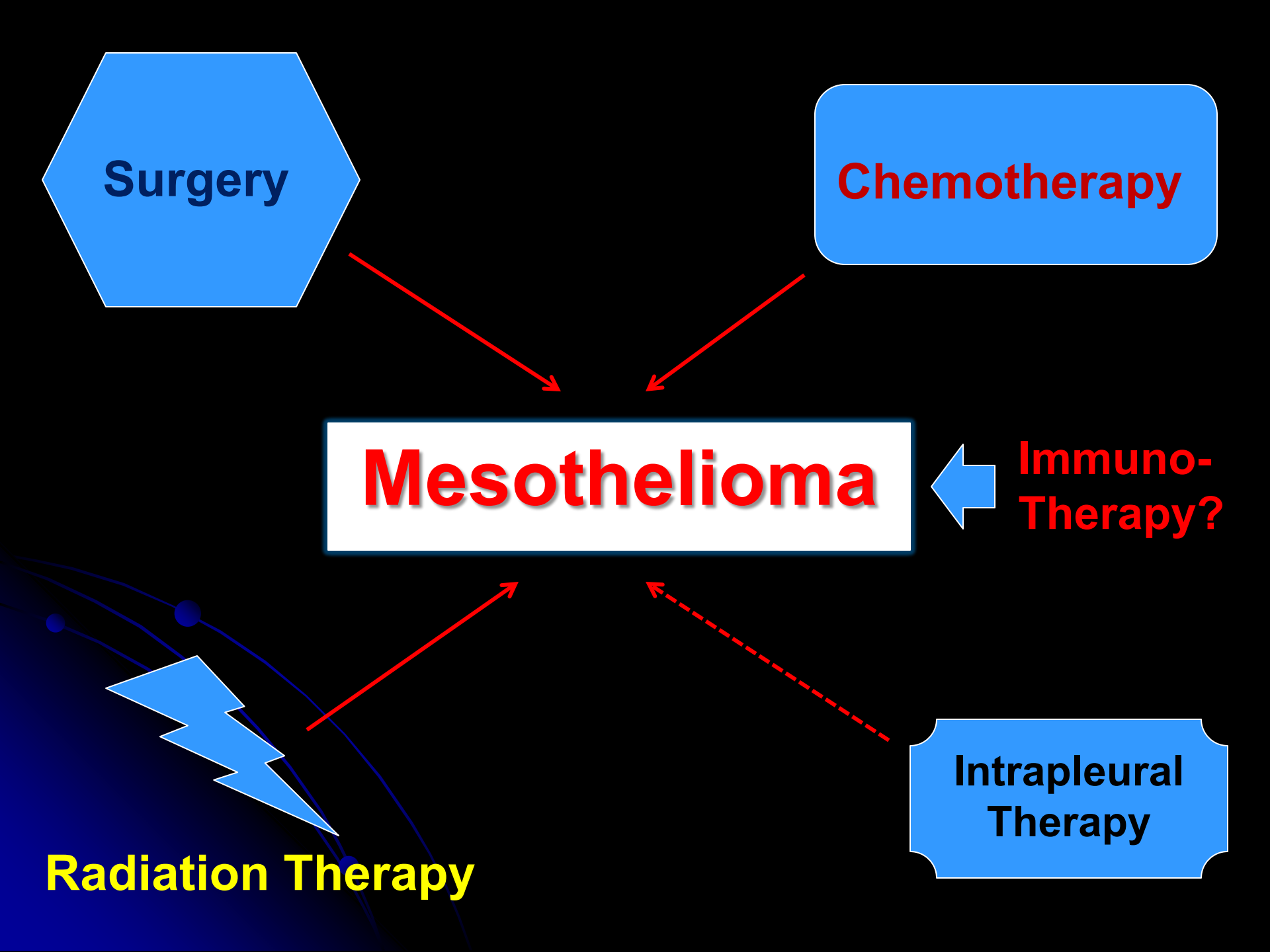


- We may be getting closer to a blood test for the diagnosis of malignant mesothelioma.
- Ultimately, this may be a means to screen people at risk to allow for early detection and even prevention of mesothelioma.

Advances in Early Detection of Mesothelioma

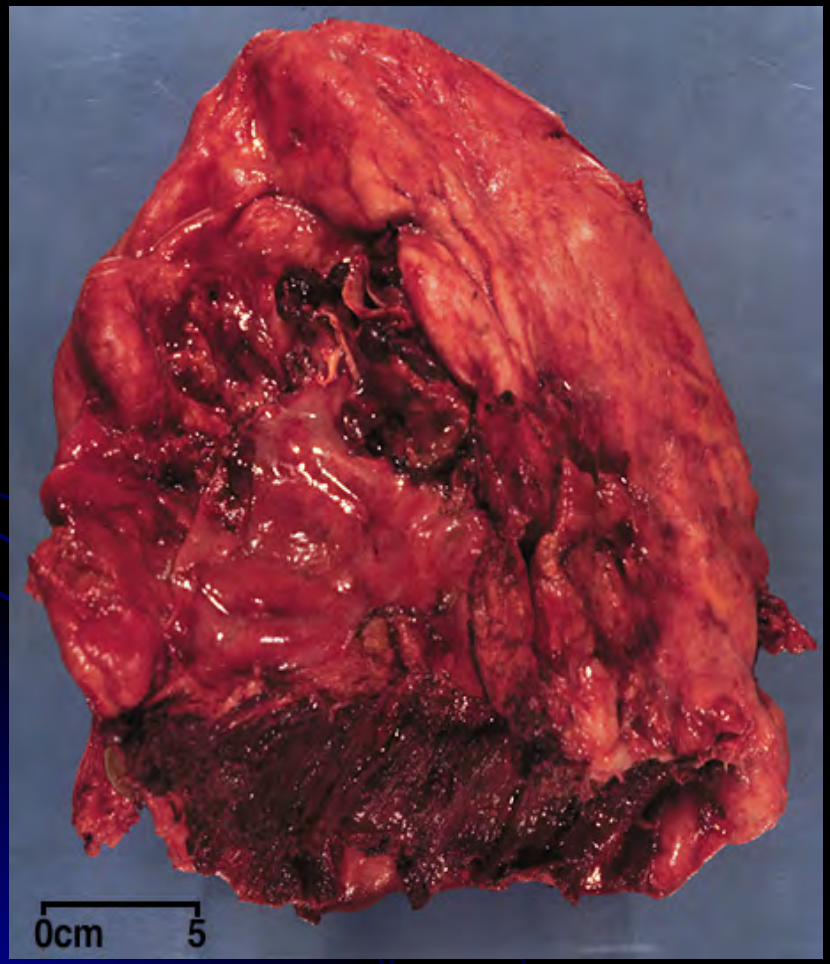


Pass, et al, NEJM 2013


Surgery
Chemotherapy
Mesothelioma
Immuno-
Therapy?
Intrapleural
Therapy
Radiation Therapy

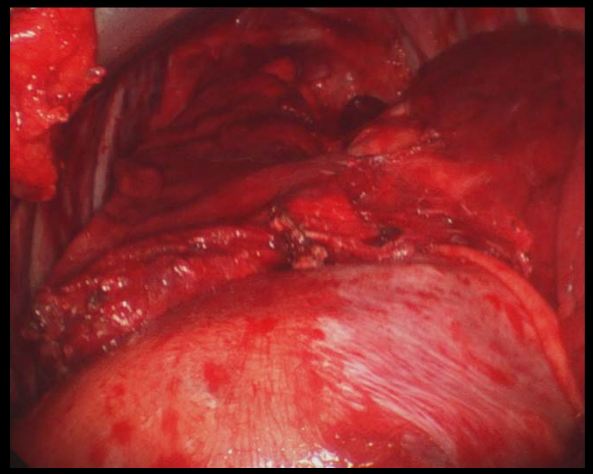
Advances in Surgery for Mesothelioma:

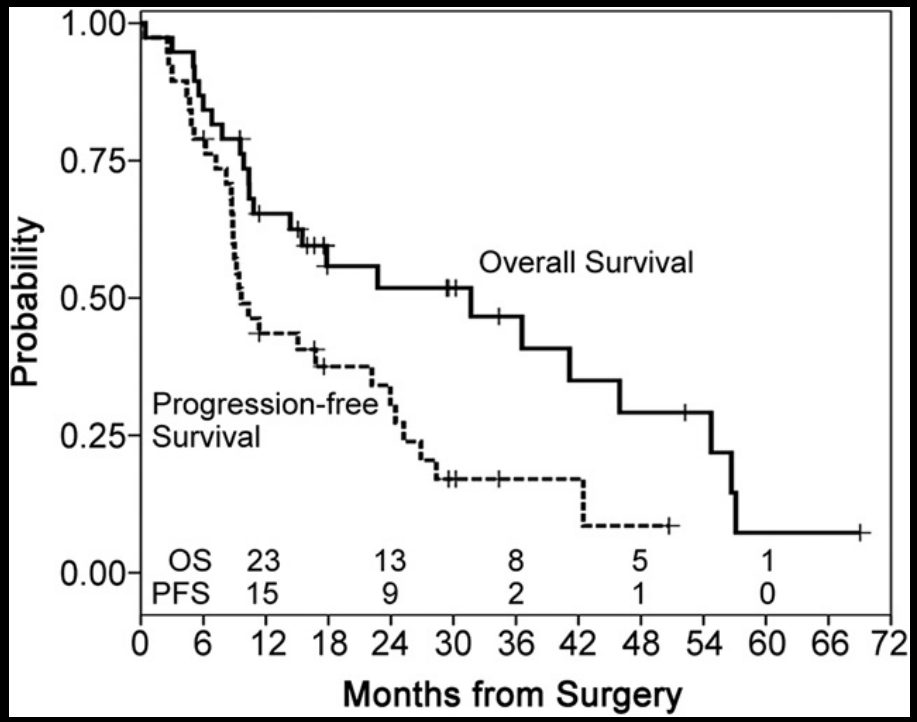
Shift Towards "Lung-Sparing" Approaches



→

Advances in "Lung-Sparing" Surgery:
Improved Survival in Advanced Stages

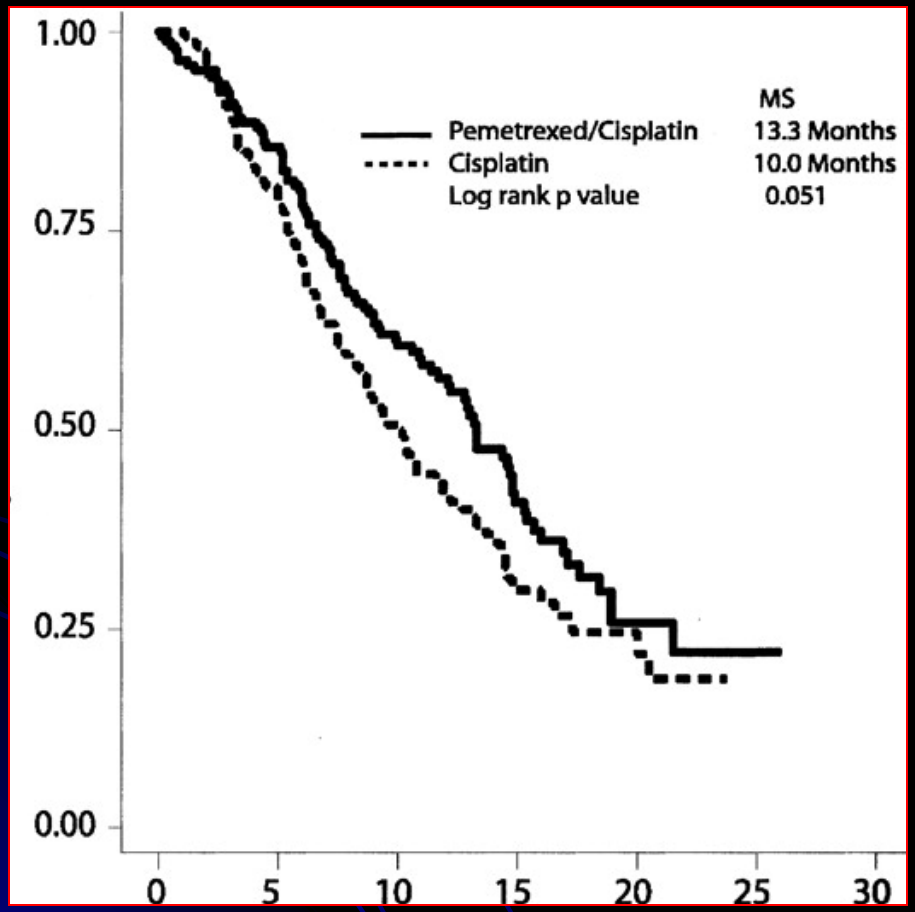


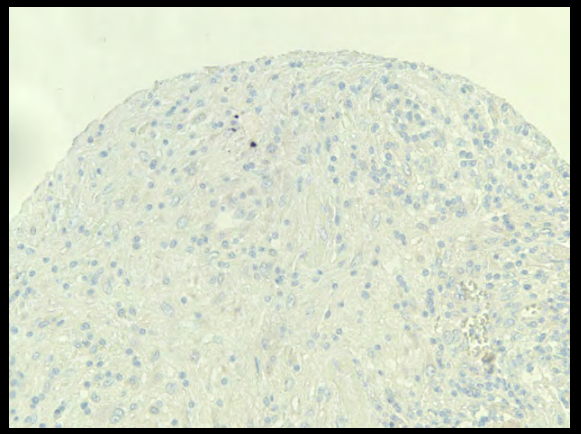


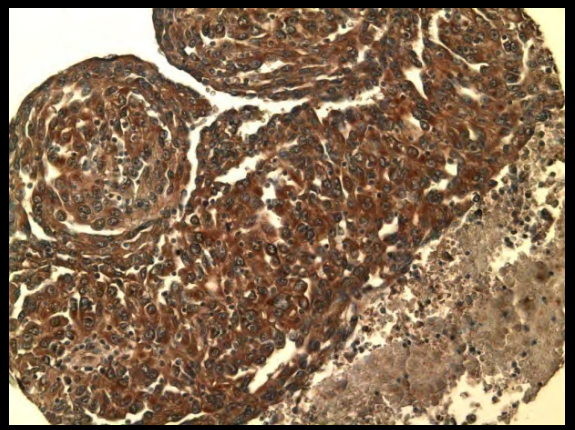
Photos Courtesy of Dr. Joseph Friedberg, M.D.
University of Pennsylvania, Philadelphia, USA

Advances in Chemotherapy:

"*Personalized" Medicine and Targeted Therapies*



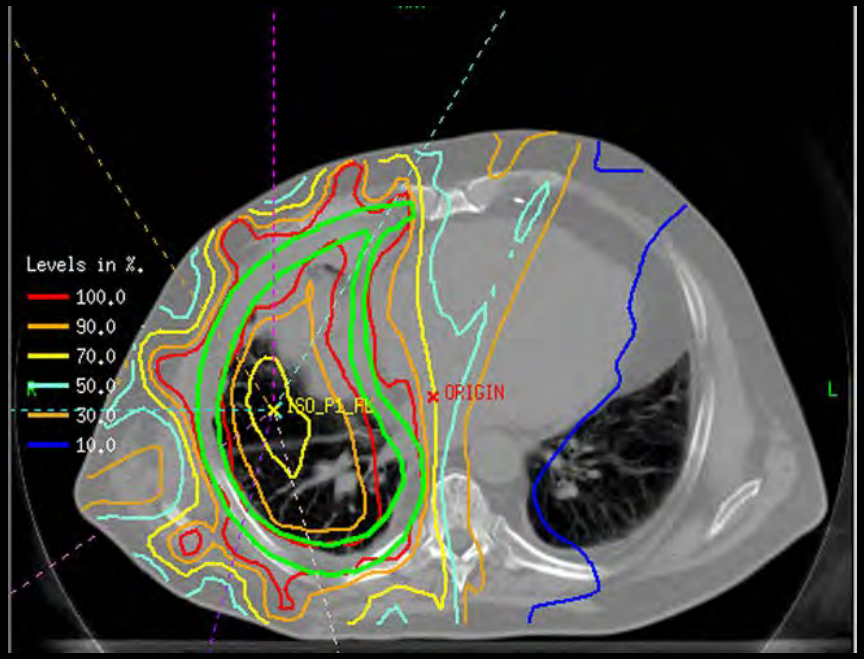


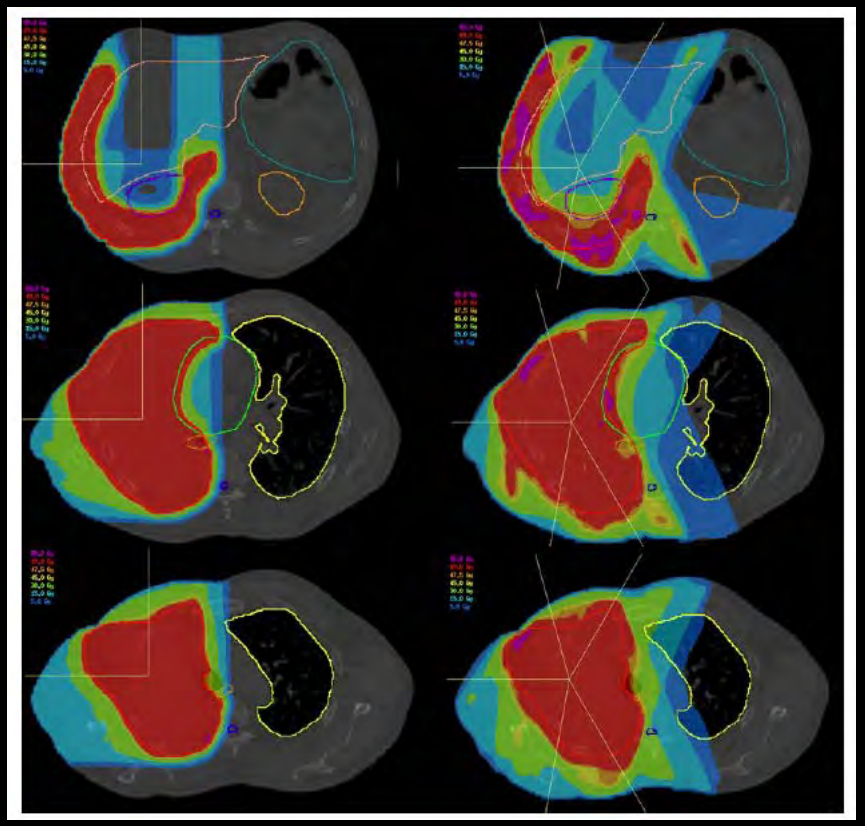


Vogelzang, JCO, 2003

Advances in Radiation for Mesothelioma:

More Precise Tumor Targeting and Less Collateral Damage





Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. 1278e1283, 2012

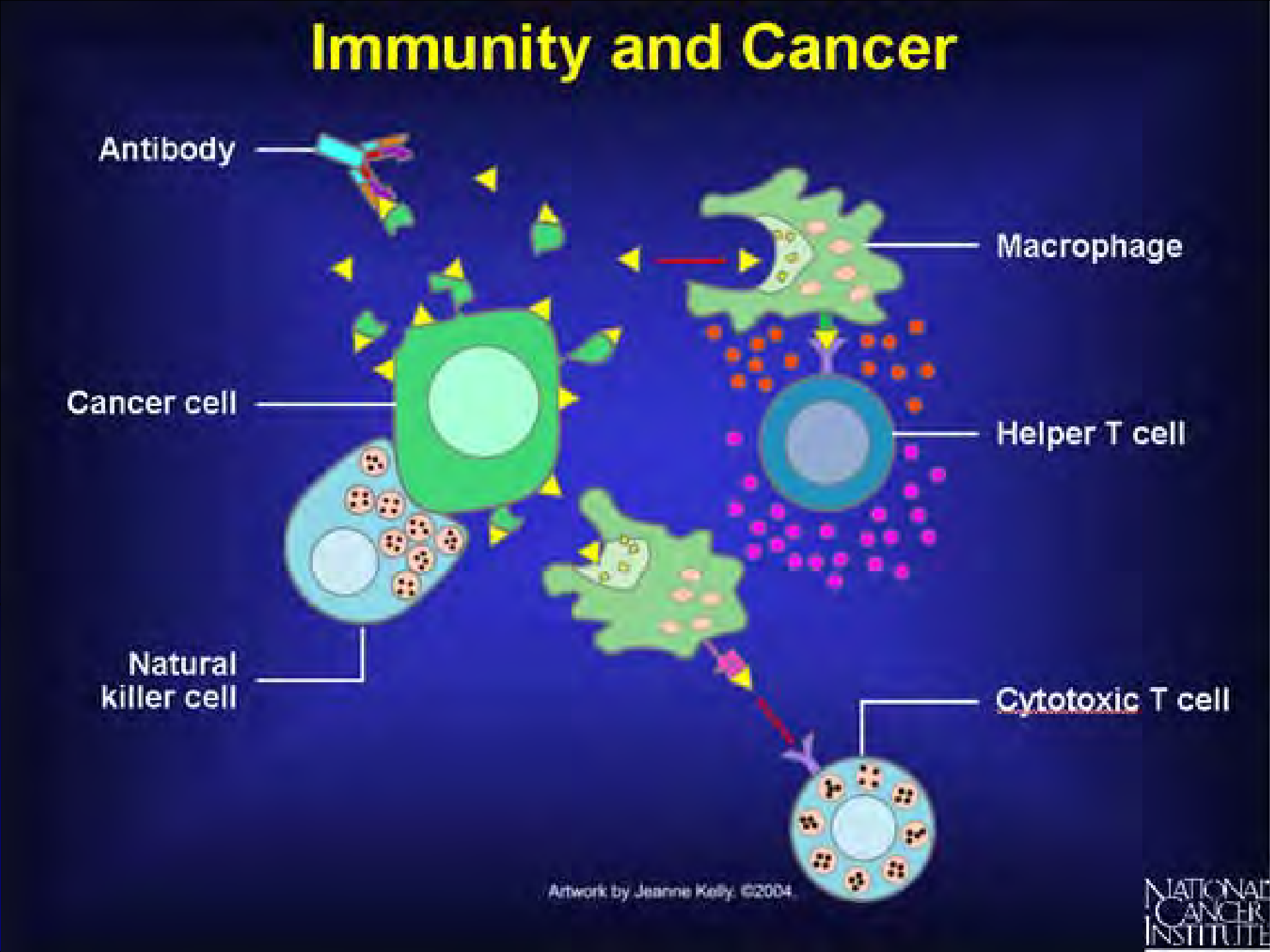
Proton Beam Therapy

Principals of Cancer Immunotherapy

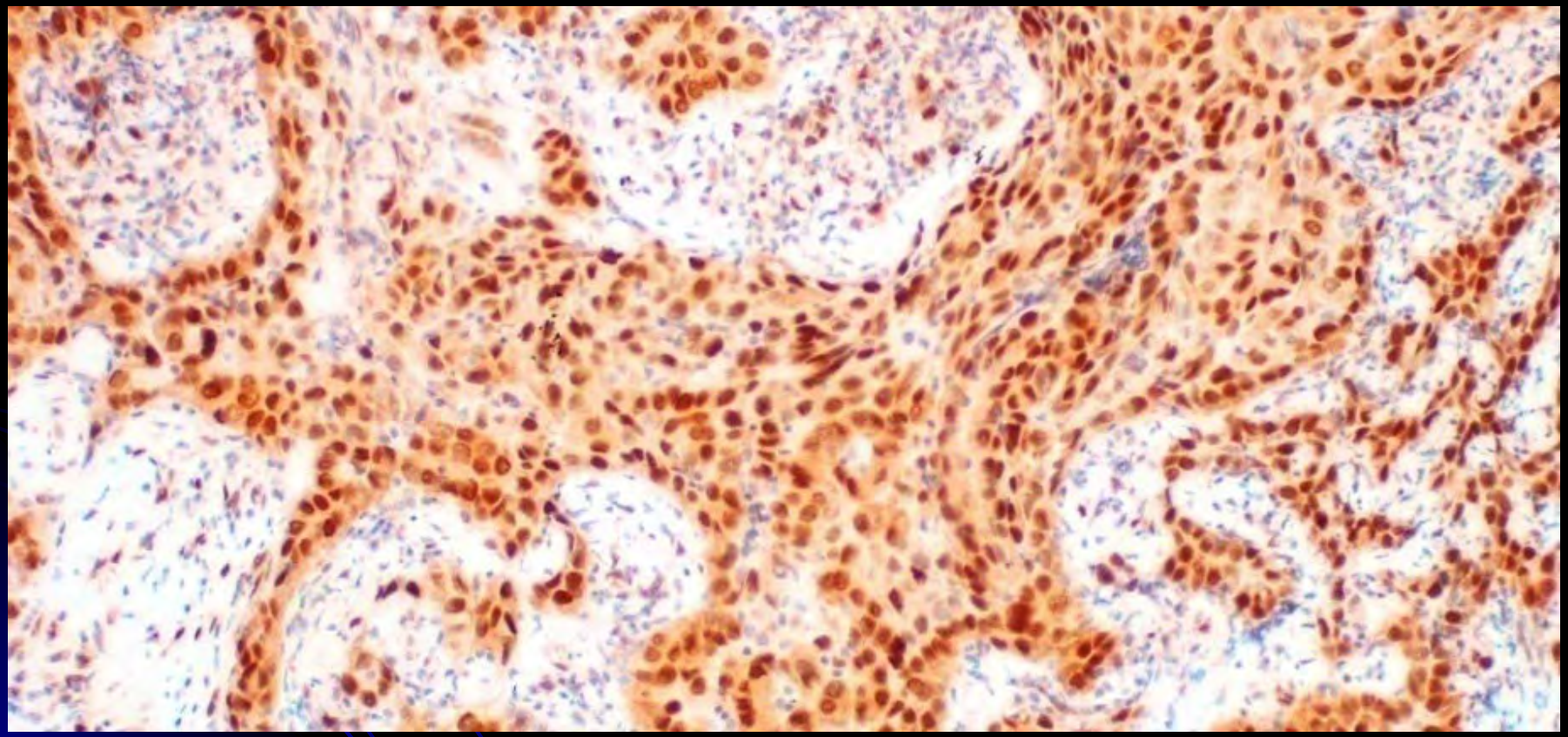
- There are differences in the composition of tumors that allow the immune system to recognize tumor cells as “foreign” and kill them.

- Tumors have “evaded” or “overwhelmed” this system and require a stimulus to enable the immune system to eliminate the tumor cells.

Immunity and Cancer



Wilms' Tumor-1 (WT-1) Vaccine for Malignant Mesothelioma



Oka, et al. Current Opinion in Immunology. 2008 20 (2)

WT-1 Peptide Vaccine Trials

Memorial Sloan-Kettering and M.D. Anderson Cancer Centers

- Malignant Mesothelioma
- WT-1 positive
- 4-12 weeks post surgery & chemotherapy

RANDOMIZE

WT-1 vaccine / Adjuvant

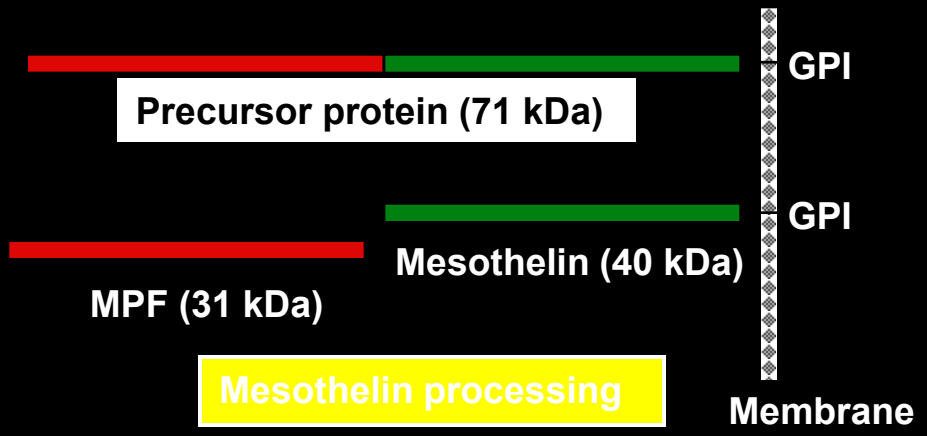
Vs.

Adjuvant alone

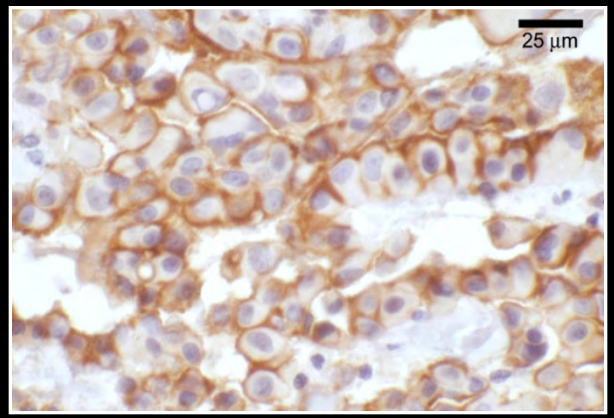
Aim is to Improve Survival after Surgery for Mesothelioma

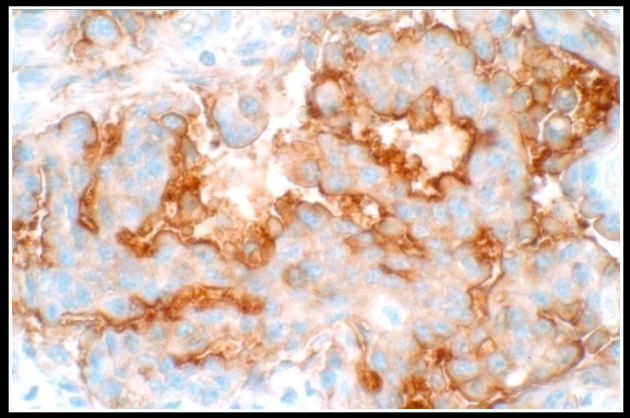
Antibody Therapy: *Mesothelin*

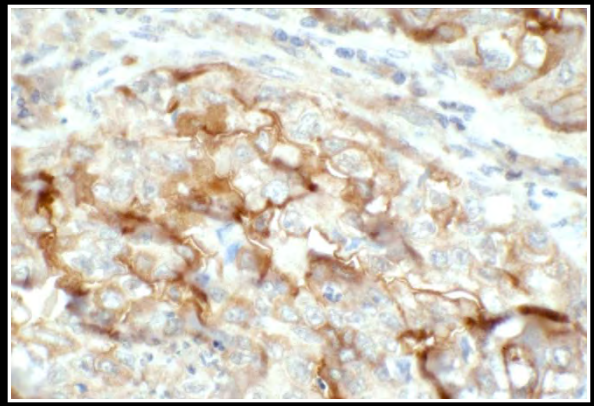
- Cell surface glycoprotein
- Normal expression in human tissues is limited to mesothelial cells of pleura, peritoneum & pericardium



- Mesothelin highly expressed in many cancers, esp. MPM



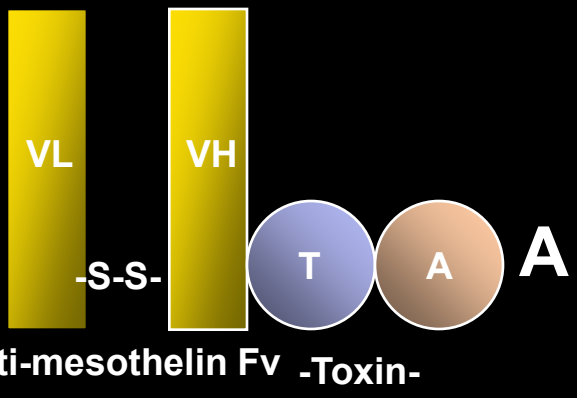




Hassan et al. Clin. Cancer Res., 2004

Targeting Mesothelin For Cancer Therapy

Recombinant immunotoxin



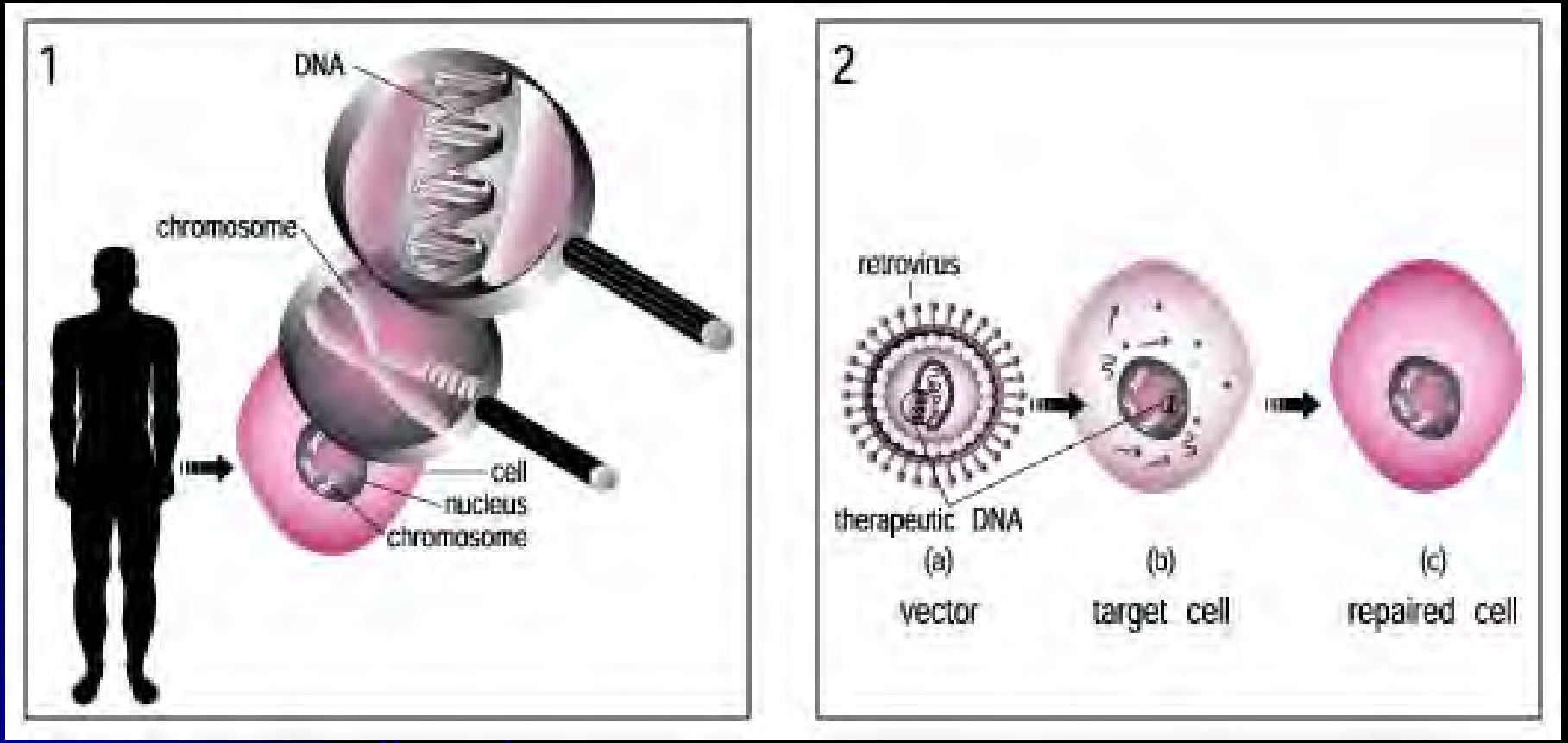
SS1P

Chimeric mAb

MORAb-009

Hassan et al. Cancer Immunity, 2007

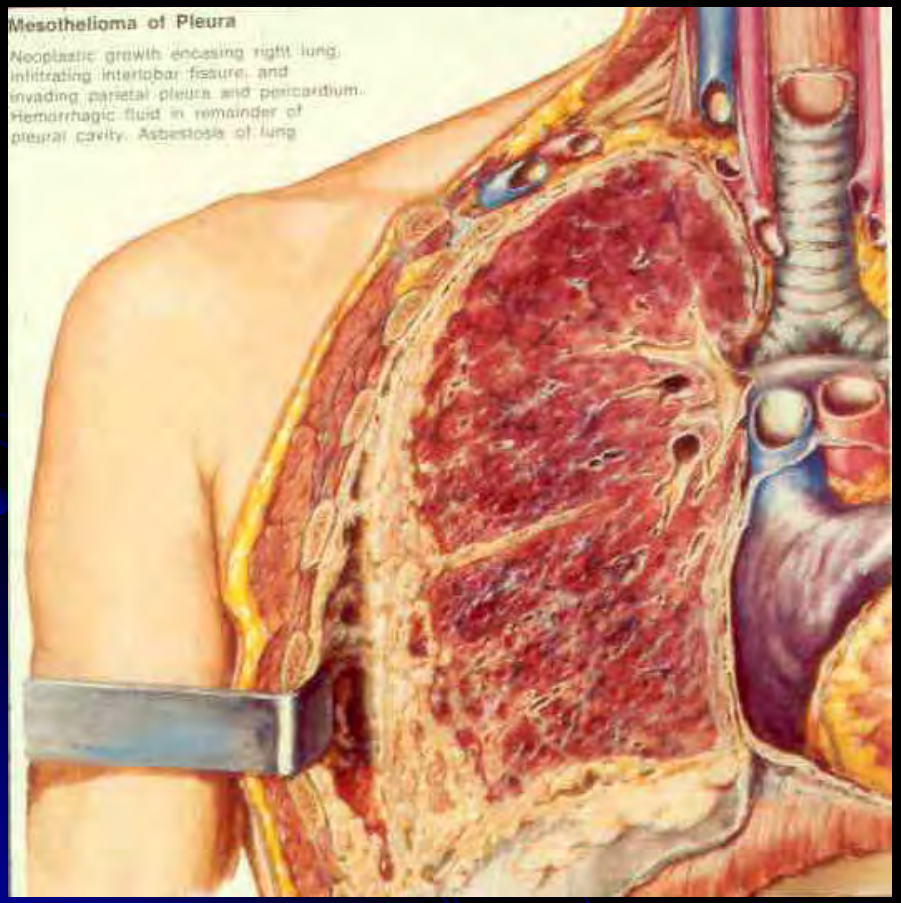
Human Gene Therapy

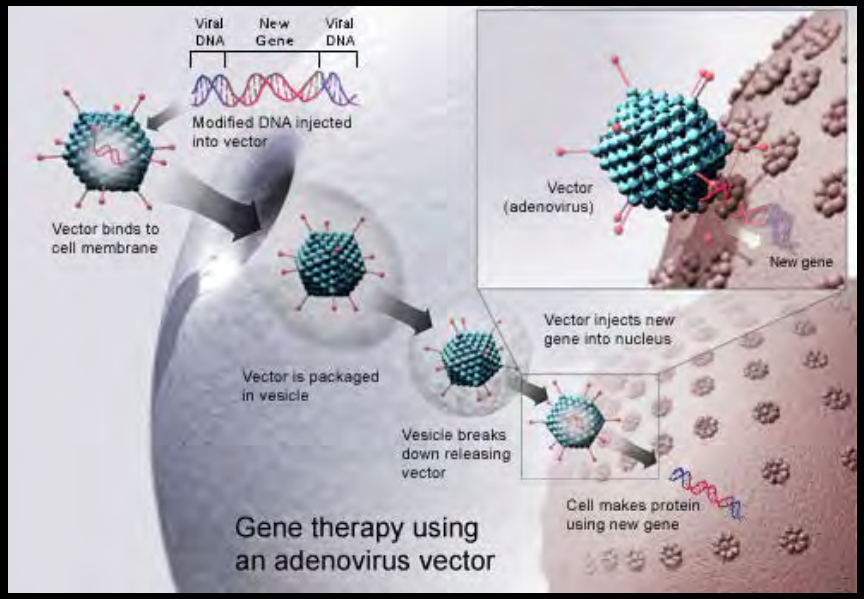


Gene therapy for malignant mesothelioma: beyond the infant years

RG van der Most[1,2], BWS Robinson[1] and DJ Nelson[1,3]

[1]School of Medicine and Pharmacology, University of Western Australia, Nedlands, Western Australia, Australia; [2]Western Australian Institute of Medical Research, Nedlands, Western Australia, Australia and [3]School of Biomedical Sciences, Curtin University, Bentley, Western Australia, Australia

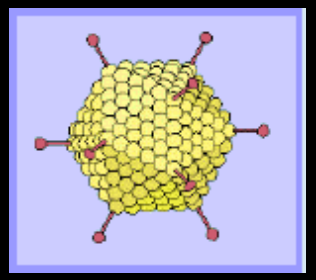




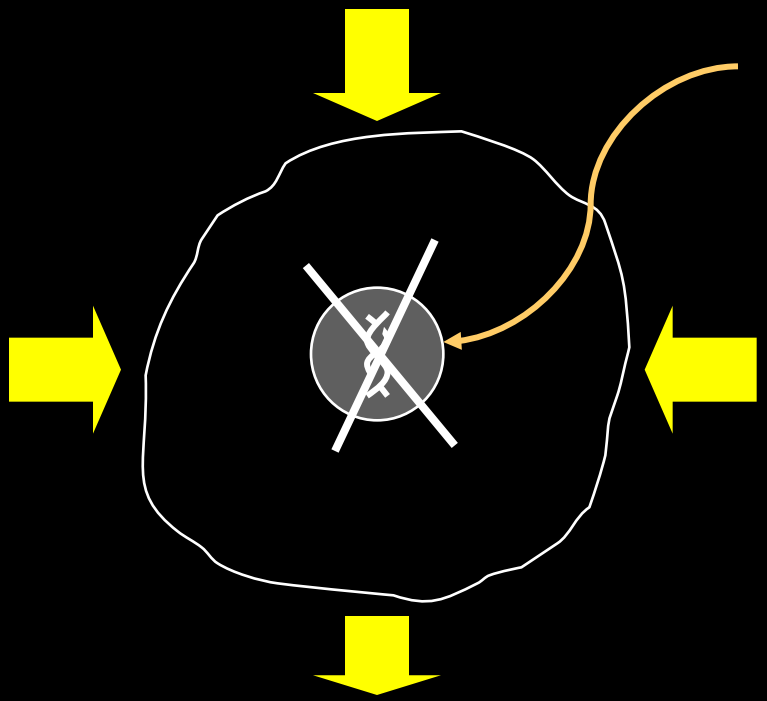
- Localized to chest cavity
- Accessible for local drug delivery
- Current therapies inadequate
- Some response to immunotherapy

Interferon Gene Therapy- Biology

<u>Direct</u> Inhibition of Tumor Cell Growth And Survival



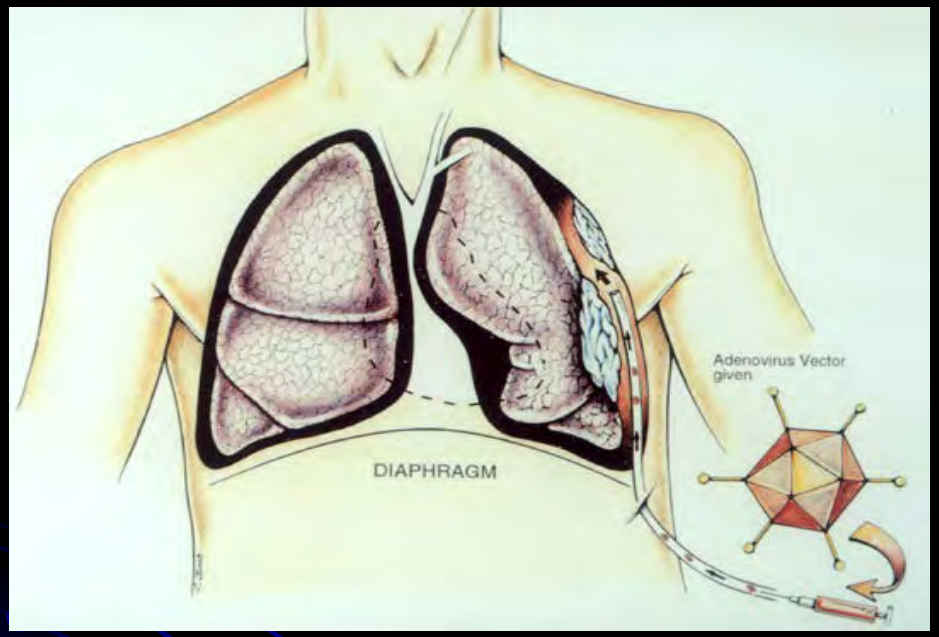
Activation of Anti-tumor Immune Responses

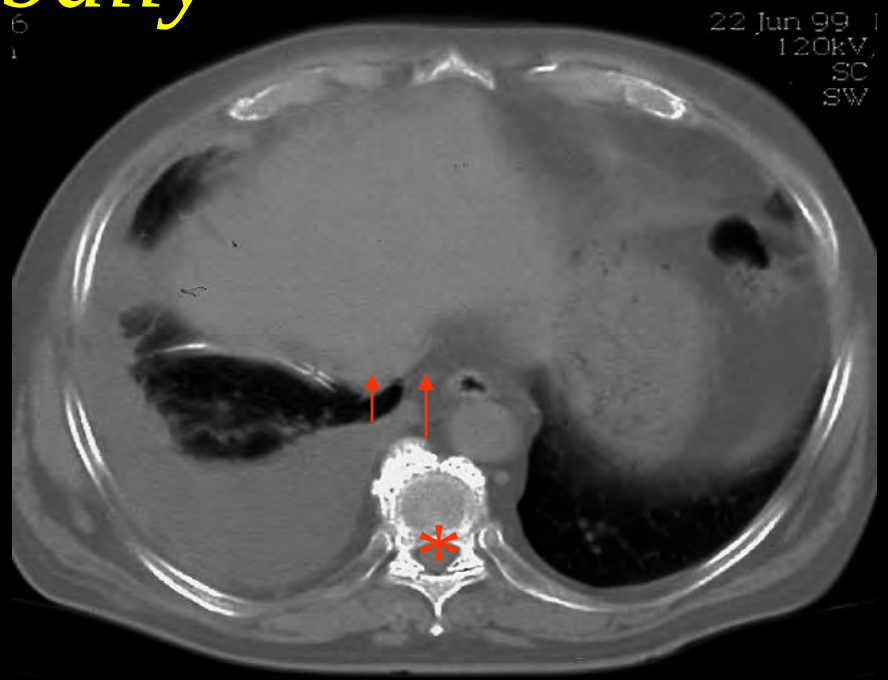


Blockade Of Tumor Blood Supply

Inhibition of Tumor Cell Growth
Tumor Cell Death

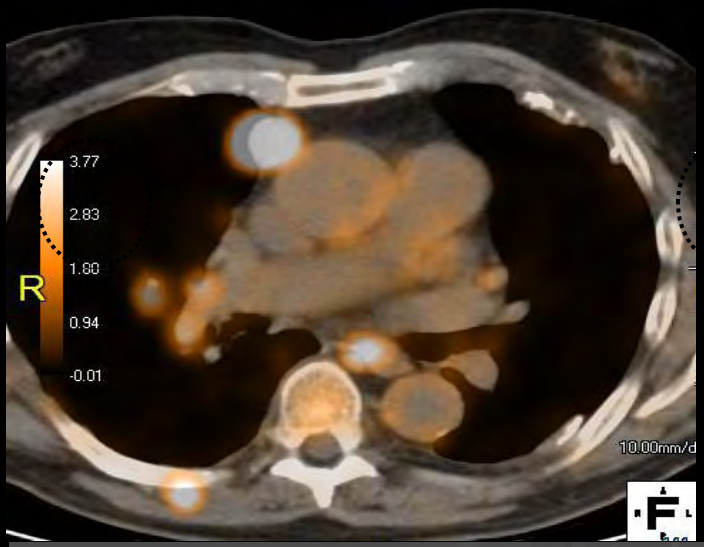
Gene Transfer Schema: *"Inject Locally, Act Globally"*

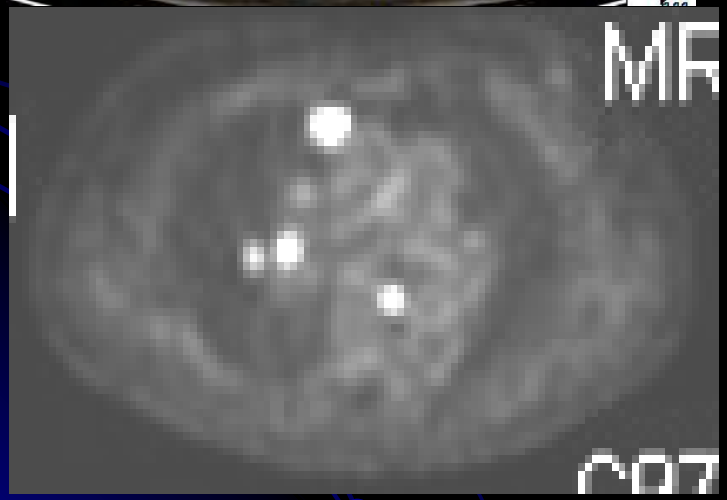




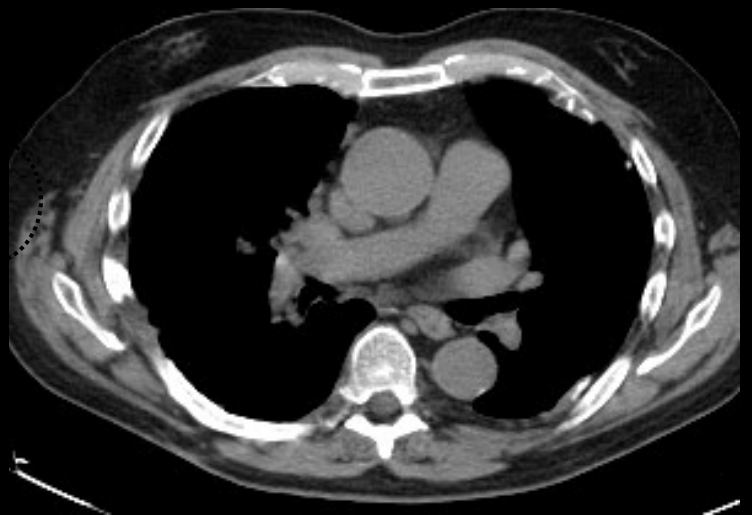
1) Insert tunneled pleural catheter and maximally drain fluid, if present.
2) Infuse adenoviral vector into pleural space
3) Sample pleural fluid to assess gene transfer, etc..

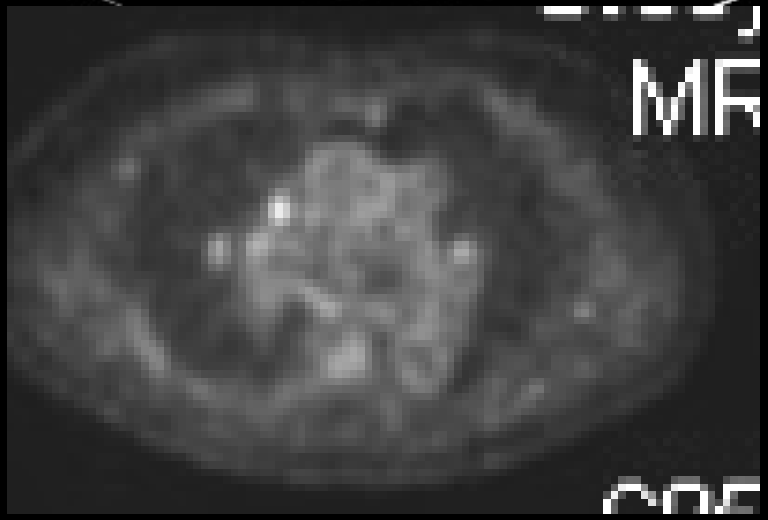
Pt 309 Post Gene Therapy PET Scan





Pre-therapy



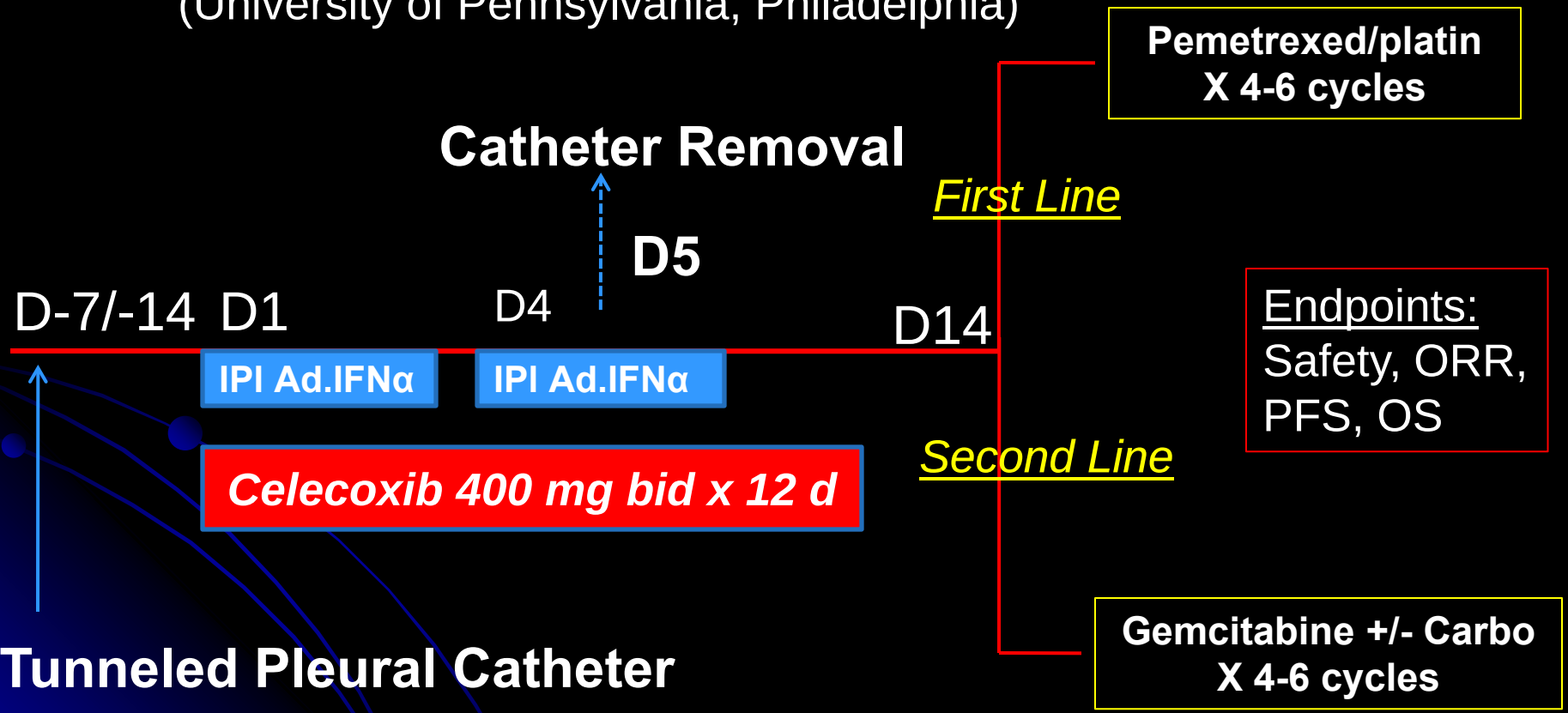


Post-therapy (6 months)

Patient 304 Sailing to Victory in Portsmouth, England April, 2010

Design of Phase I/II Clinical Trial of ImmunoGene Chemo Combination

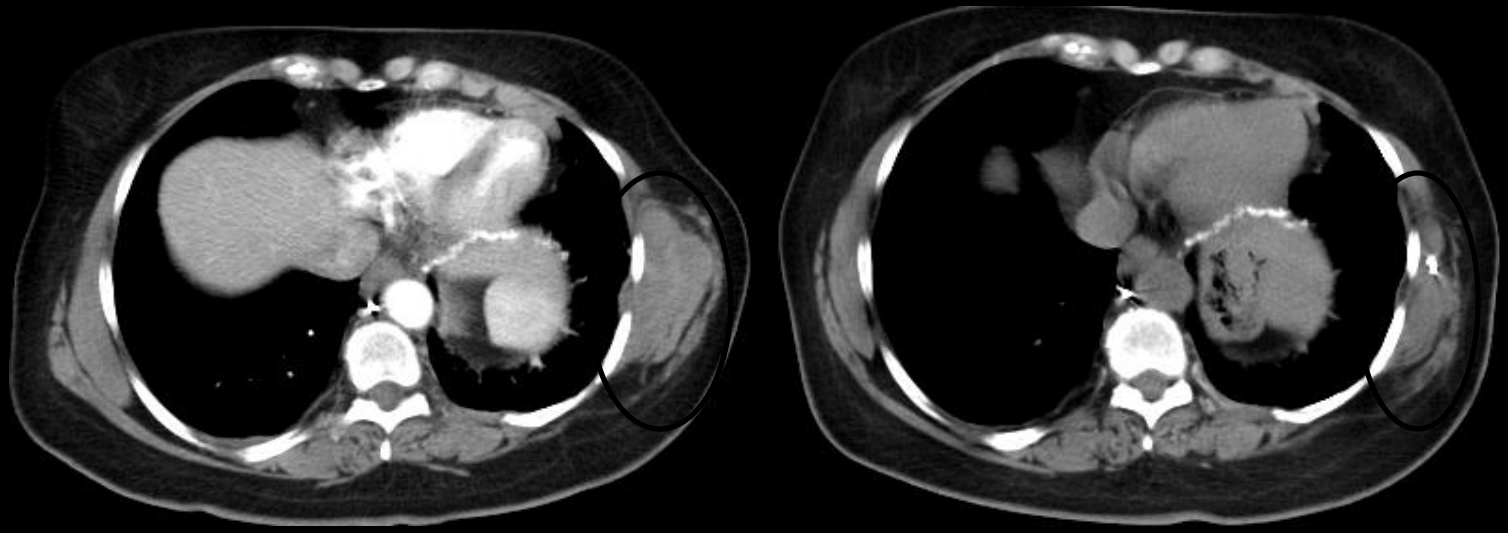
(University of Pennsylvania, Philadelphia)



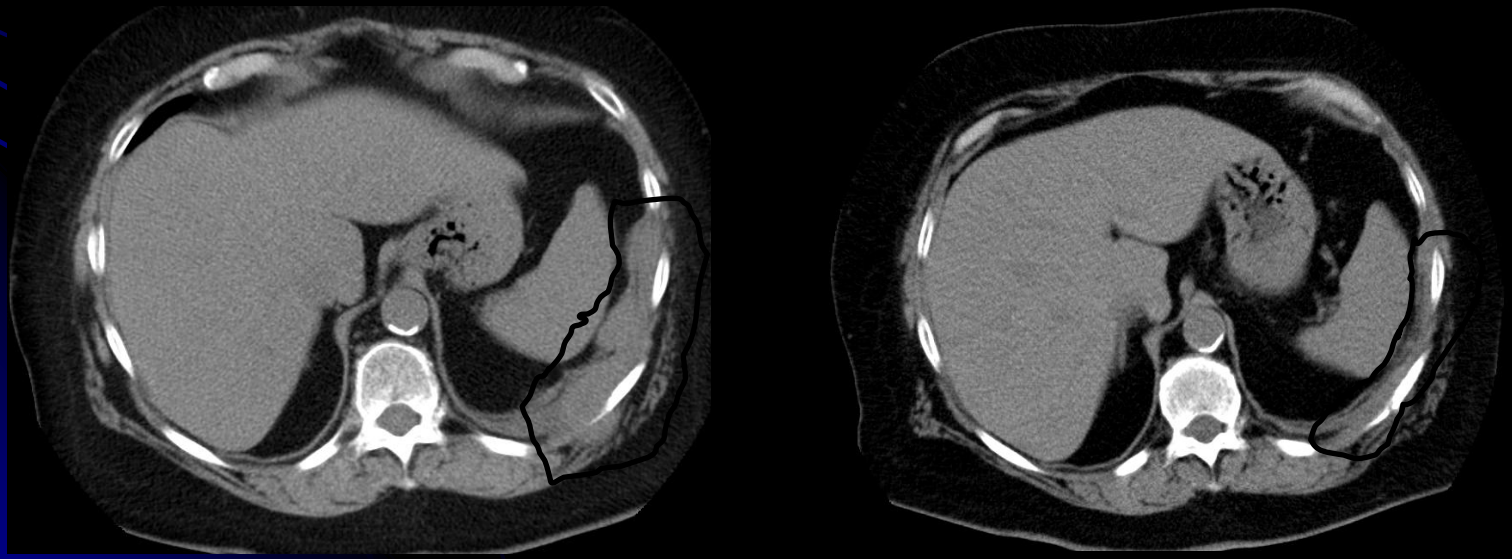
Patient 404

Pre treatment

2 months post

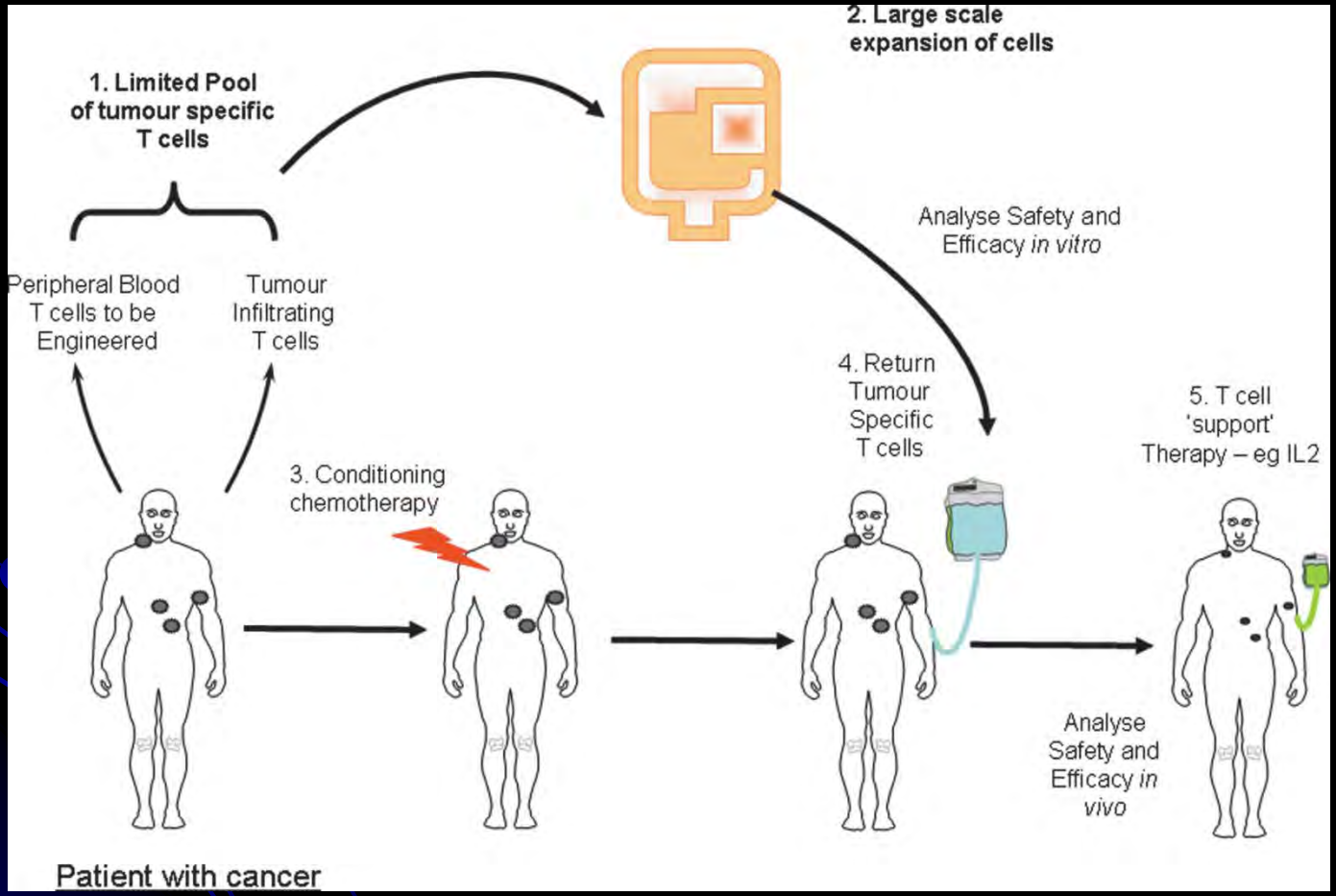


Patient 406



Adoptive T Cell Therapy for Mesothelioma

(Penn, Memorial Sloan-Kettering, NCI)



Hawkins, et al. HUMAN GENE THERAPY 21:665–672 (June 2010)

Regressions Of Massive Melanoma Tumor After Transfer Of Anti-Tumor T Cells

(National Cancer Institute, Bethesda, Maryland, USA)

Advances in Experimental Therapy: *Gene-Modified T Cell Clinical Trial*

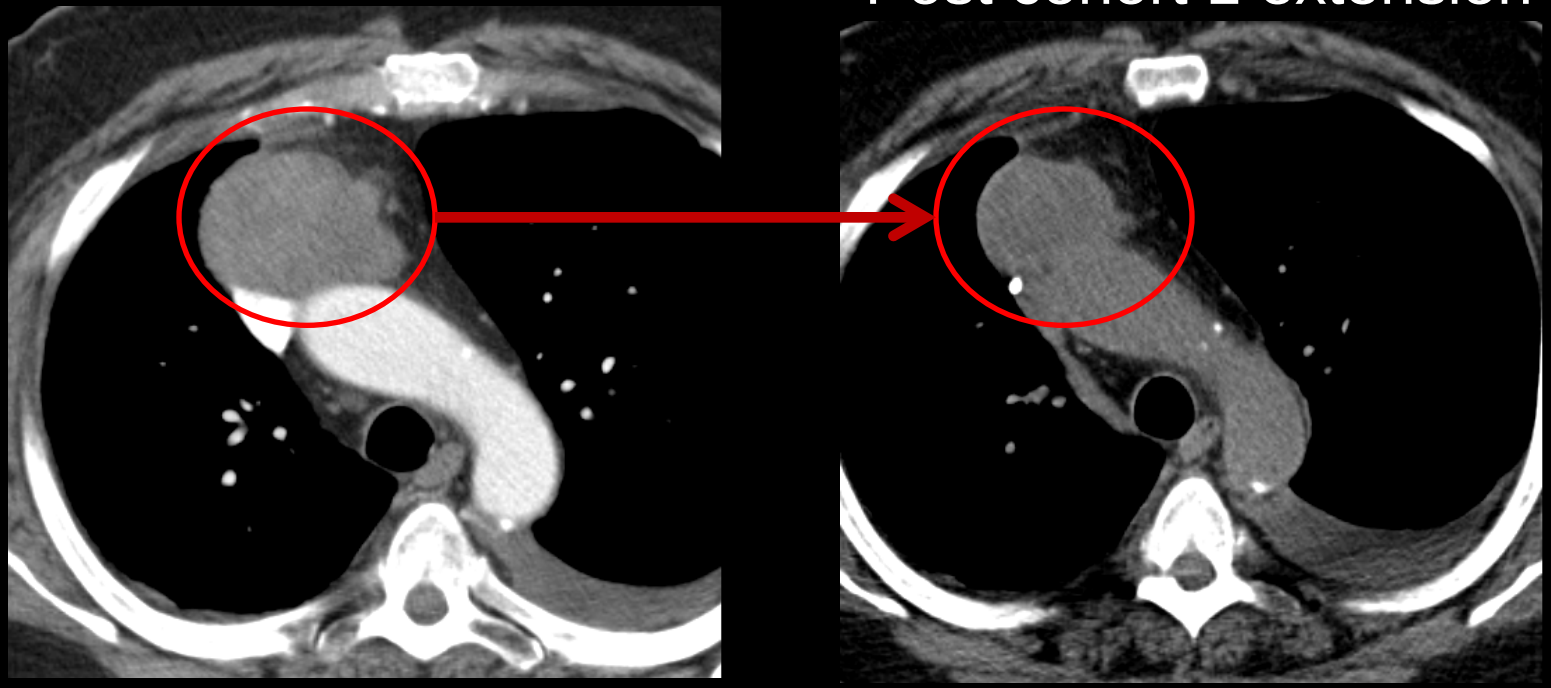
Dr. Haas and T-Cell Recipient

(HIPPA Consent Obtained)

Infusion Bag with 10^8 Mesothelin-CAR T cells

Pre cohort 1 extension

Post cohort 1 extension



Estimated 57% decrease in volume

Phase I Trial of Autologous Redirected RNA Meso-CIR T Cells

UPCC 17510 /
NCT01355965
Abramson Cancer Center of
the University of

Overcoming Hurdles

- Increase federal research funding levels
- Foster inter-institutional consortia to maximize expertise and resources
- Encourage public-private partnerships with pharma and biotech

Together, We Can Work Towards a Cure!