

# Myositis and Cancer: What's the Connection?

Andrew Mammen, MD, PhD

Assistant Professor of Neurology

Co-Director, Johns Hopkins Myositis Center

# Disclosures

- None

# The next 40 minutes

- Review the epidemiology of cancer-associated myositis
- Consider recent data showing the association of specific autoantibodies with cancer
- Discuss cancer screening for patients with myositis
- Discuss a theory which could help explain the correlation between myositis and cancer

# Introduction

- Association between cancer and myositis first described in 2 cases in 1916
- Observations suggesting that the association of cancer and myositis is not coincidental:
  - Improvement in rash and strength after cancer treatment
  - Recurrence of weakness with tumor relapse
  - Development of myositis around the time of cancer diagnosis

# Frequency of Malignancy (%) in PM and DM

<u>Study</u>	<u>DM (%)</u>	<u>PM (%)</u>
Bohan et al	13	10
Callen	26	3
Vesterager et al	50	
Mola et al	20	0
Holden et al	17	0
Henriksson et al	7	6
Hoffman et al	8	7
Goh and Rajan	60	
Tymms and Webb	19	13
Baron and Small	45	18
Banbasset et al	26	14
Manchul et al	32	18
Hidano et al	20	
Lakhanpal et al	22	28
Duncan et al	26	
Cox et al	41	
Bonnetblanc et al	41	
Oddis et al	10	7
Sigurgeirsson et al	15	9
Love et al	11	3
Ario et al	27	7
Maoz et al	45	27

# Looking for an association between cancer and myositis: one good large study

- Hill, CL et al. 2001
  - Pooled analysis of published national data from Sweden (1964-1983), Denmark ( 1977-1989), and Finland (1969-1985)

*Hill, CL et al. Lancet (357); 2001*

# Some Statistics...

## – Standardized Incidence Ratio (SIR)

- The ratio of the observed to the expected new cases of cancer
- For example:
  - Expect 2 new cases of cancer
  - Observe 10 new cases of cancer
  - $\text{SIR} = \text{observed/expected} = 10/2 = 5$
  
  - Expect 2000 new cases of cancer
  - Observe 10,000 new cases of cancer
  - $\text{SIR} = \text{observed/expected} = 10,000/2000 = 5$

# Cancer Increased in Dermatomyositis Patients

- 618 cases of DM
  - Mean age at diagnosis was ~ 55 years
- 198/618 (32%) had cancer
- SIR for all cancer types for DM: 3.0
  - SIR for men: 3.3
  - SIR for women: 2.8
- 115/198 (58%) of cancers developed  
AFTER the diagnosis of DM

*Hill, CL et al. Lancet (357); 2001*

# Cancer Increased in Polymyositis Patients

- 914 cases of PM
  - Mean age at diagnosis was ~ 56 years
- 137/914 (15%) had cancer
- SIR for all cancer types for PM: 1.3
  - SIR for men: 1.4
  - SIR for women: 1.2
- 95/137 (69%) of cancers developed **AFTER** the diagnosis of PM

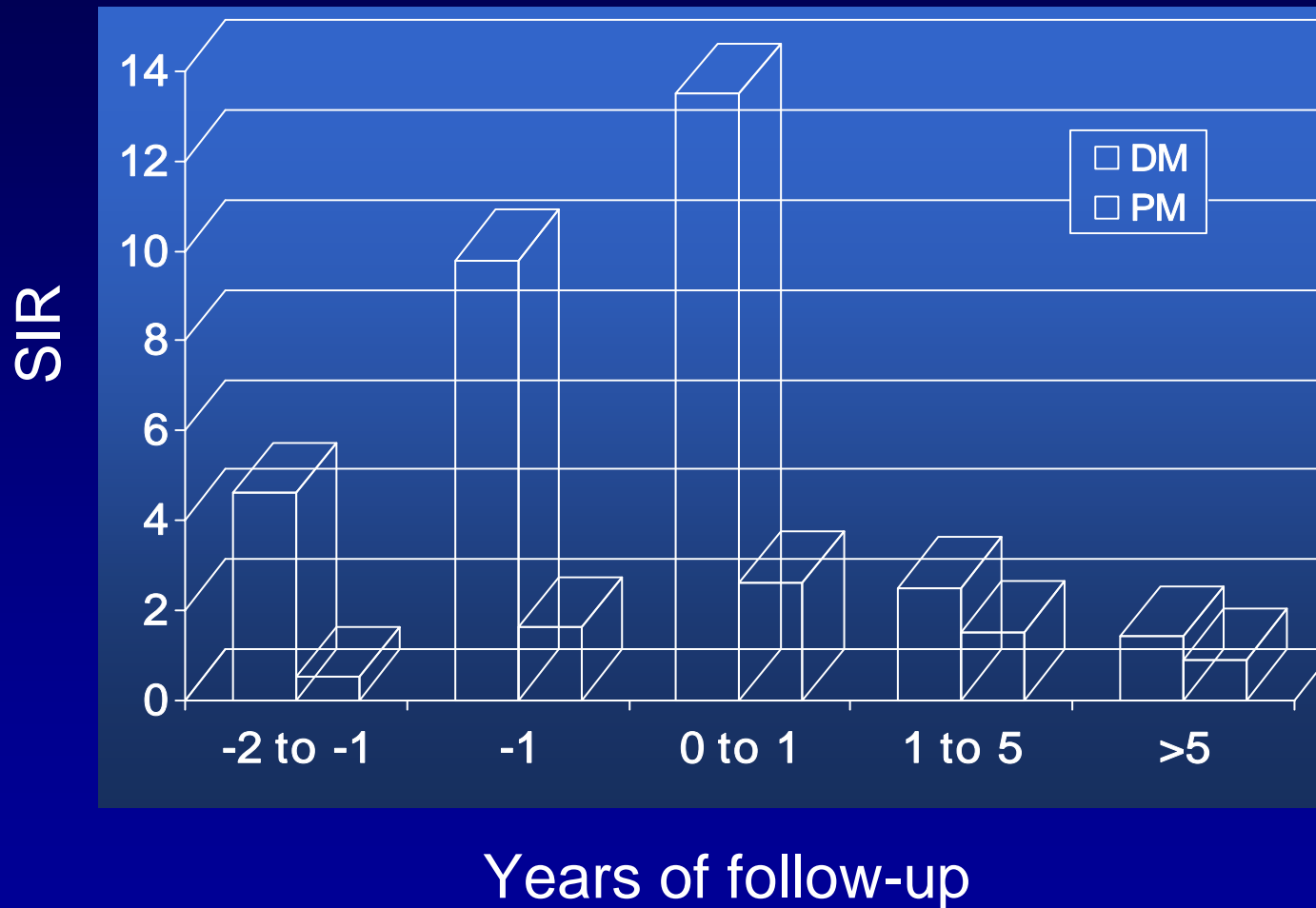
*Hill, CL et al. Lancet (357); 2001*

# Cancers with Greatest Increased Risk

- DM
  - Ovarian (SIR 10.5)
  - Lung (SIR 5.9)
  - Pancreatic (SIR 3.8)
  - Non-Hodgkin Lymphoma (SIR 3.6)
  - Stomach (SIR 3.5)
  - Colorectal (SIR 2.5)
  - Breast (SIR 2.2)
  - Others
- PM
  - Non-Hodgkin lymphoma (SIR 3.7)
  - Lung (SIR 2.8)
  - Bladder (SIR 2.4)
  - Others

*Hill, CL et al. Lancet (357); 2001*

# Temporal association of cancer and myositis



# How Long is Cancer Risk Increased?

- Risk is highest within the first year of diagnosis
- In those with polymyositis, the risk fell to expected rates 5 years after diagnosis
- In those with dermatomyositis, the risk did not fall to expected rates
  - Ovarian, pancreatic, lung remained high up to 5 years
  - Pancreatic and colorectal cancer risks remained elevated past 5 years

# Another study demonstrating increased risk of cancer with myositis:

- Population based, retrospective study of 537 biopsy-proven myositis patients in Australia (1981-95)
  - DM: 36/85 had cancer (42%); SIR 6.2
  - PM: 58/321 had cancer (18%); SIR 2.0

*Buchbinder, R et al. Ann Intern Med  
134; 2001*

# Risk Factors Associated with Malignancy in Patients with Myositis

- DM (including amyopathic?) > PM > IBM
- Older age at onset
  - No increased risk in PM patients age 15-44
- Rapid onset of symptoms
- Capillary damage on muscle biopsy
- Cutaneous necrosis or vasculitis
- Poor response to treatment
- Protective: Presence of interstitial lung disease

*Sparsa A et al. Arch Dermatol 138(7); 2002*

*Ponyi A et al. Ann Ny Acad Sci 1051; 2005*

# Myositis Autoantibodies and Cancer

- Chinoy et al (2007)
- 109 polymyositis – none with cancer
- 103 dermatomyositis – 15 with cancer
- 70 with myositis/CTD – 1 with cancer
  - Those with certain autoantibodies were “protected” from cancer
    - Jo-1, PM-Scl, U1-RNP, U3-RNP, Ku
  - Those with anti-155/140 had an increased risk of cancer
    - 8/16 cancer-associated myositis patients had 155/140 Ab

*Chinoy et al, Ann Rheum Dis (2007)*

# Usefulness of tumor markers in predicting cancer

- Amoura et al. assessed values of CEA, CA-125, CA-19-9, CA-15-3 in 102 DM and PM patients
- All patients underwent H&P, CXR, Echo, CT, GI endoscopy, Gyn exam, mammogram
- Over 5 yrs of f/u, 10/102 developed a tumor
  - CA-125 and CA-19-9 at baseline was associated with an increased cancer risk ( $p=0.0001$ , OR 29.7, 95% CI 8.2-106.6)
  - Risk of cancer is high during the first year following increased CA-125/CA-19-9 levels

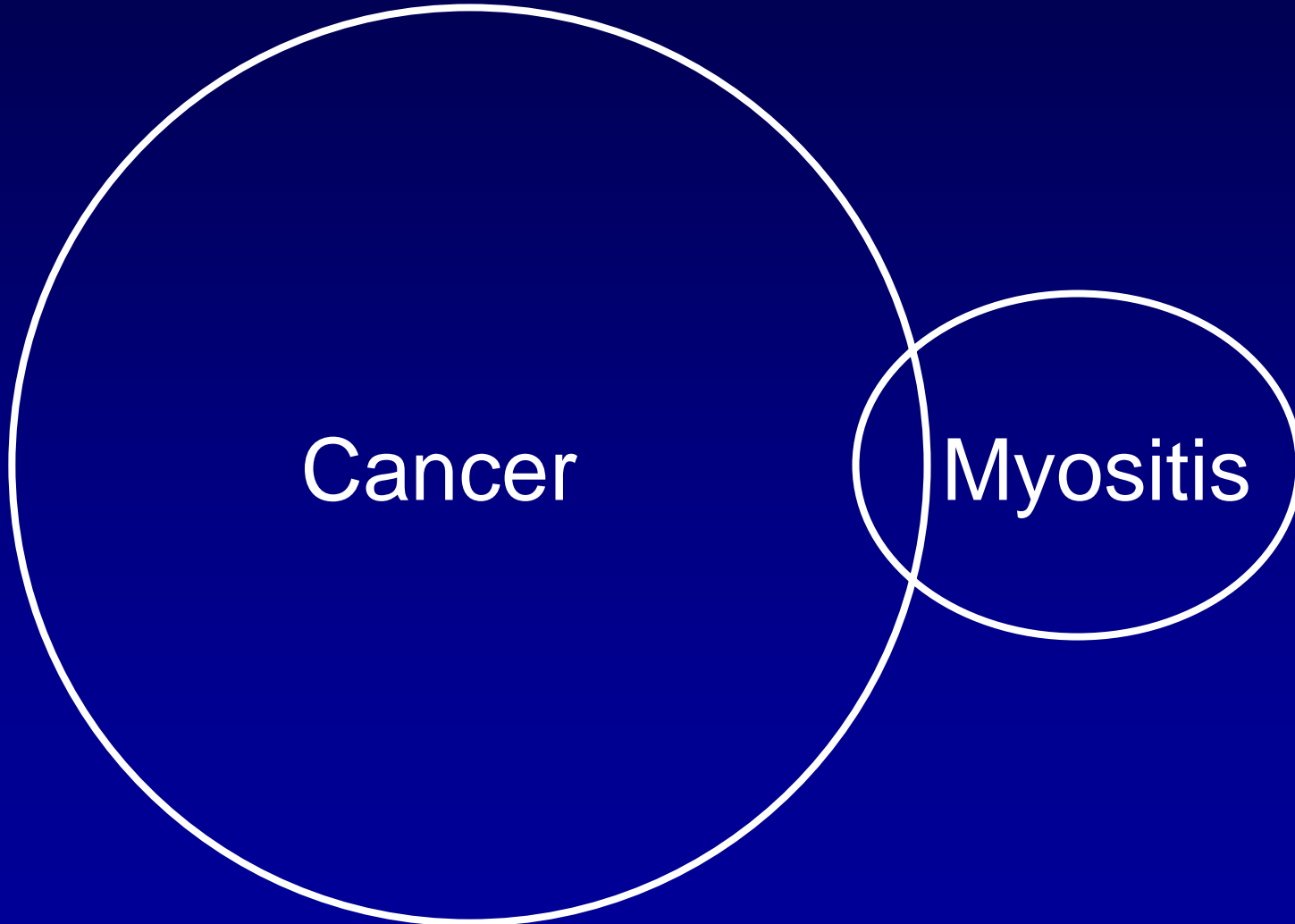
# Cancer Screening Recommendations

- A matter of debate
- Approach #1
  - Complete history and physical exam
  - Few routine blood and urine tests
  - Fecal occult blood
  - Chest x-ray
  - Additional tests in case of specific signs and symptoms
- Approach #2: Look really hard for cancer!

# Aggressive Approach

- Routine laboratory evaluation (CBC, ESR, CMP, U/A), serum and urine immunofixation, tumor markers (CA-125 and CEA)
- Chest/abdomen/pelvis CT
- Women: Pap smear, pelvic exam, transvaginal U/S, mammogram
- Men: Digital rectal exam, PSA (over 50 years of age)
- Colonoscopy in older adults
- Screen yearly for up to 5 years
- Select patients (e.g., refractory to treatment): PET scan

# Why do some patients have myositis and cancer?



# Antibodies vs. Autoantibodies

## Antigens vs. Autoantigens



Antibody – circulates in blood  
(anti-hepatitis B)

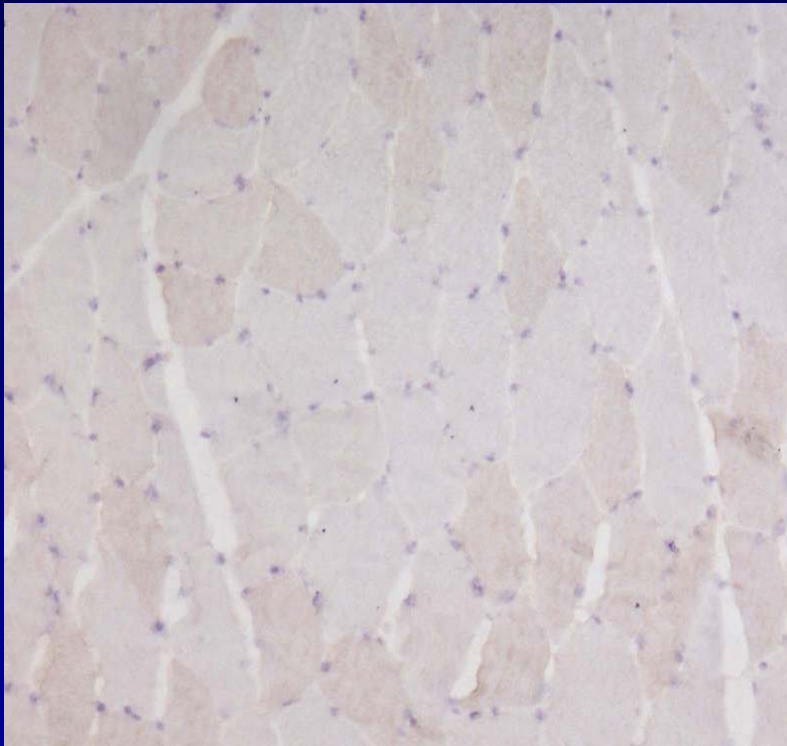
Antigen – foreign body  
(hepatitis B virus)



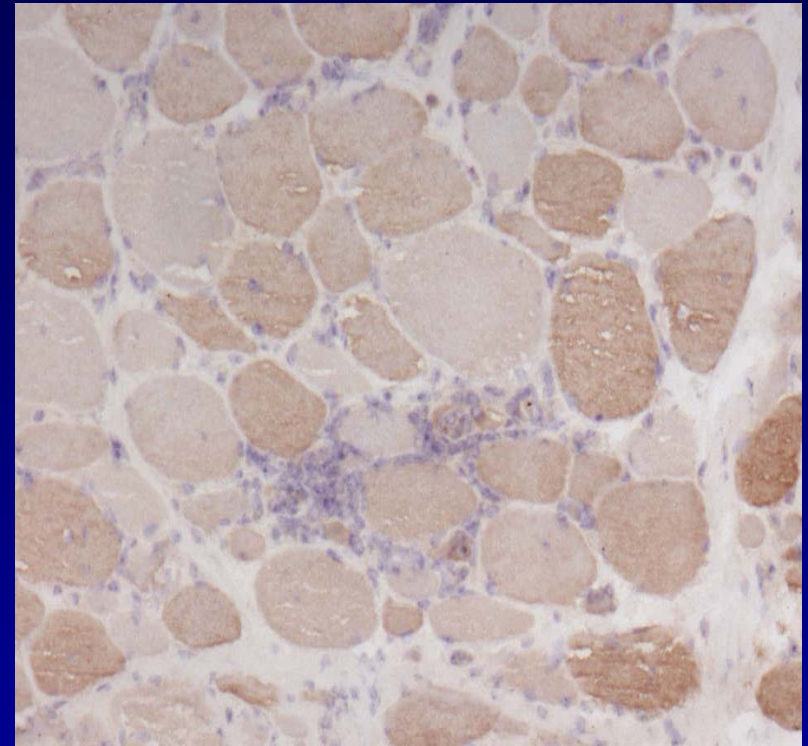
Autoantibody – circulates in blood  
(anti-Jo1)

Autoantigen – found in patient tissues  
(histidyl-tRNA synthetase)

# Myositis autoantigen expression high in myositis muscle



Normal muscle



Polymyositis muscle

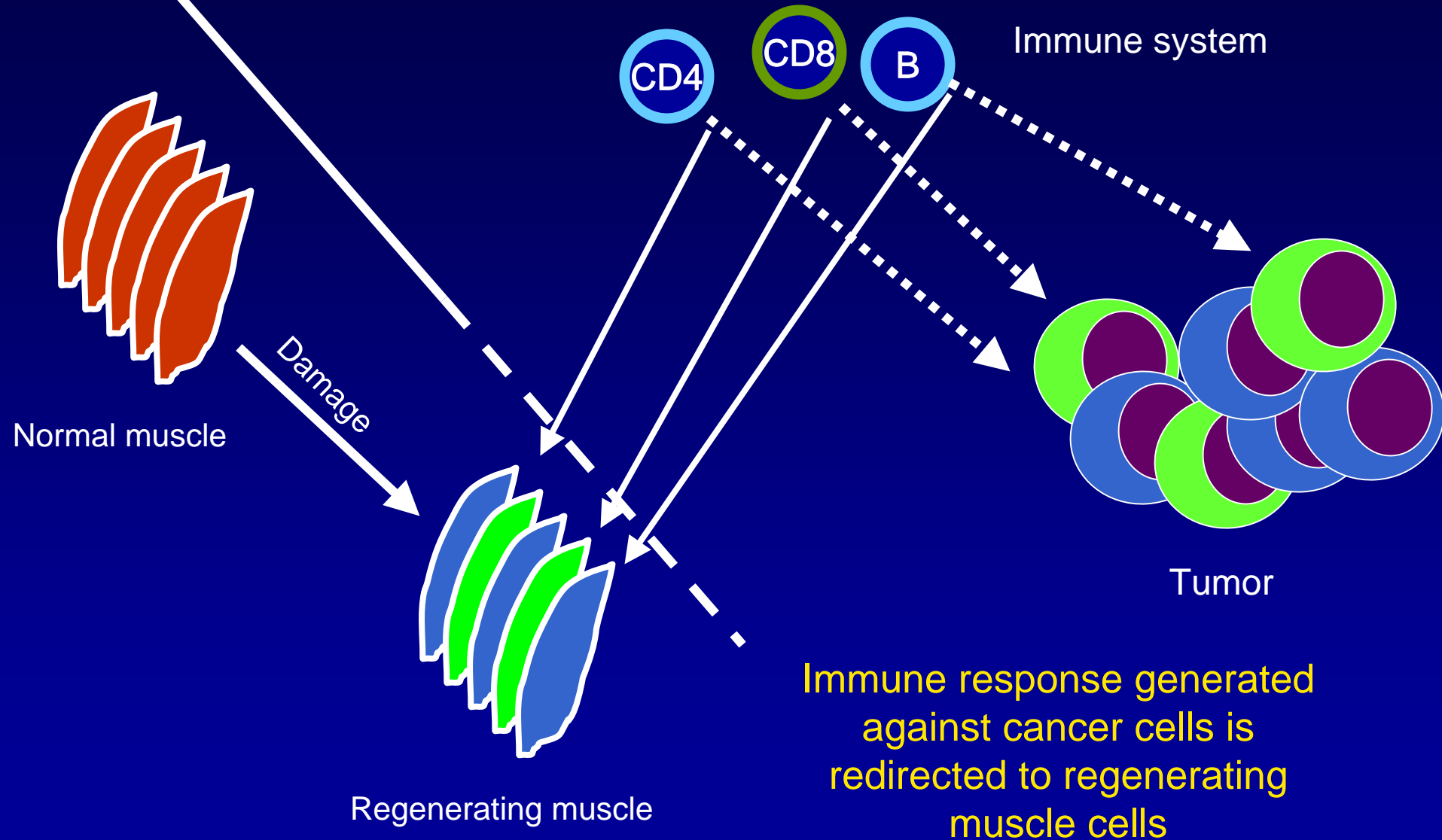
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Jo-1 staining

# Three observations about autoantigen levels

- An example: The Mi-2 autoantigen
  1. Expression increased 10-fold in DM muscle compared to control muscle
  2. Expression increased >10 fold in regenerating mouse muscle (unpublished observation)
  3. Expression increased 53-fold in breast tumors and 11-fold in lung tumors compared to normal breast and lung tissues

Growing tumors express high levels of myositis autoantigens



Immune system

CD4

CD8

B

Damage

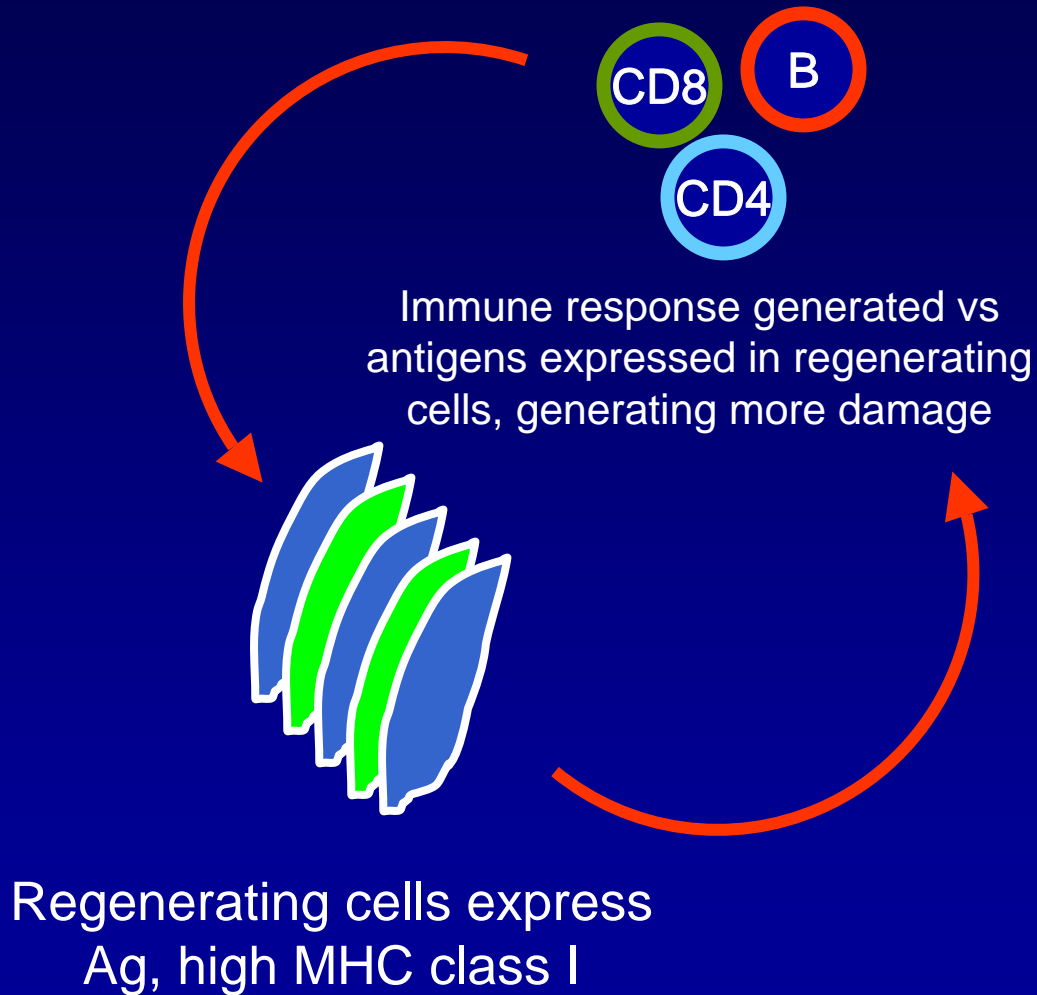
Normal muscle

Regenerating muscle

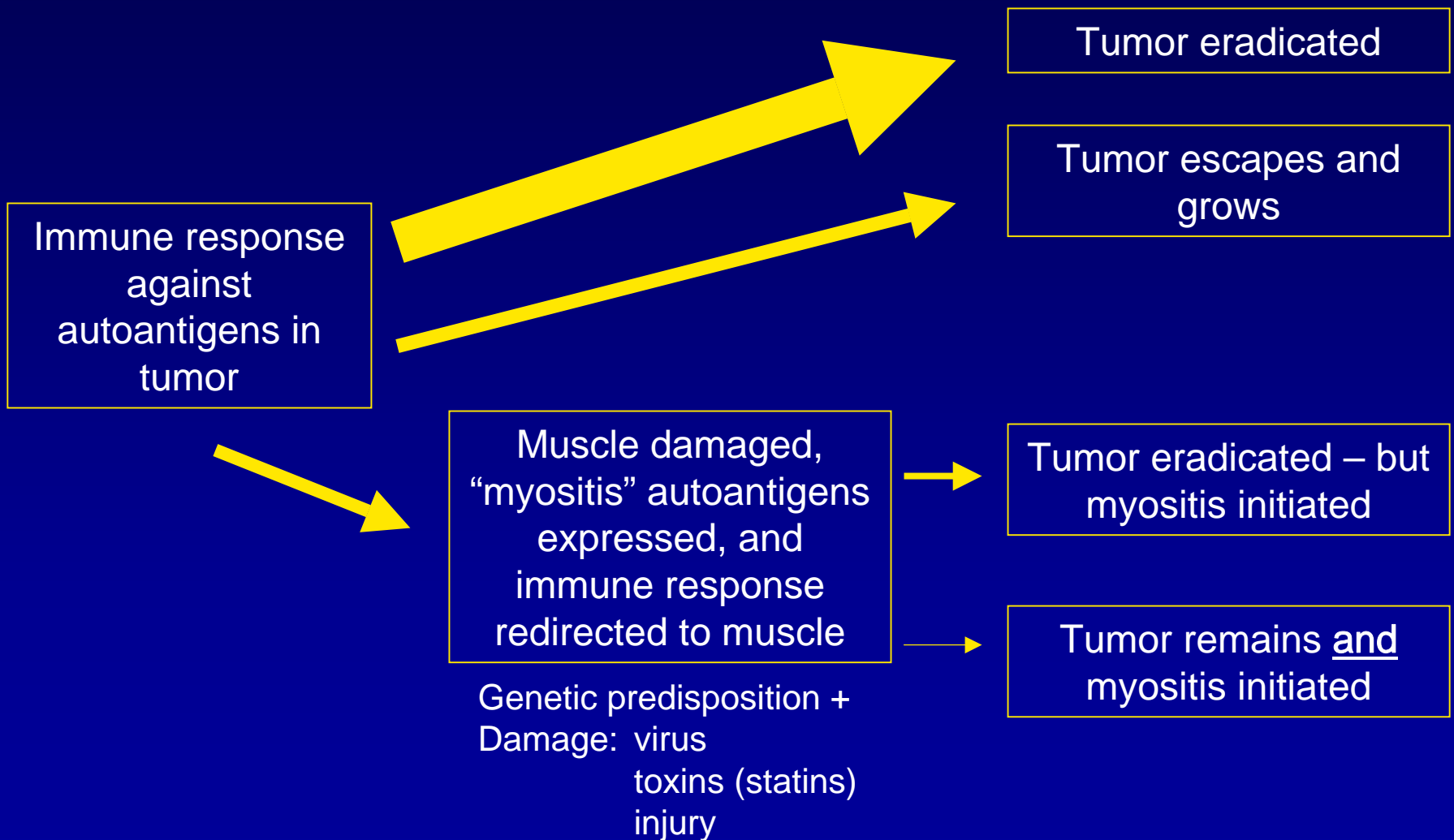
Tumor

Immune response generated against cancer cells is redirected to regenerating muscle cells

# Muscle-specific maintenance of immune response



# Possible Outcomes of Immune Response Against Tumor



# Summary

- Both DM and PM patients are at risk for developing cancer
- Cancer risk persists long after the diagnosis
- Appropriate cancer screening is controversial
- Perhaps autoantibody status can help guide screening strategies
- The cross-expression of similar antigens in tumors and regenerating muscle may help explain the relation of cancer to myositis